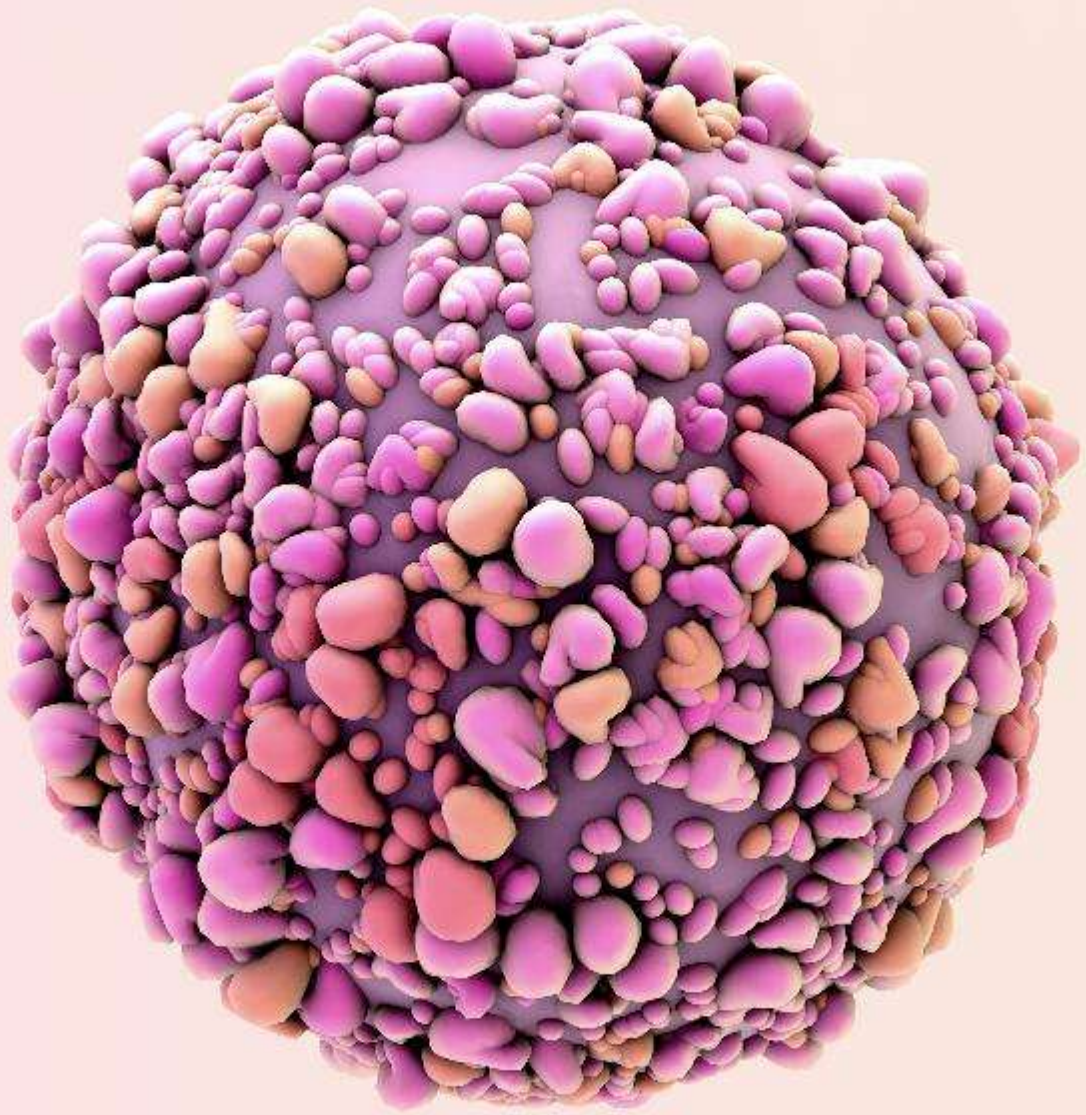
STIFEL | Healthcare

Breast Cancer:

History and Outlook



October 28, 2025

By Tim Opler (Managing Director, Stifel)

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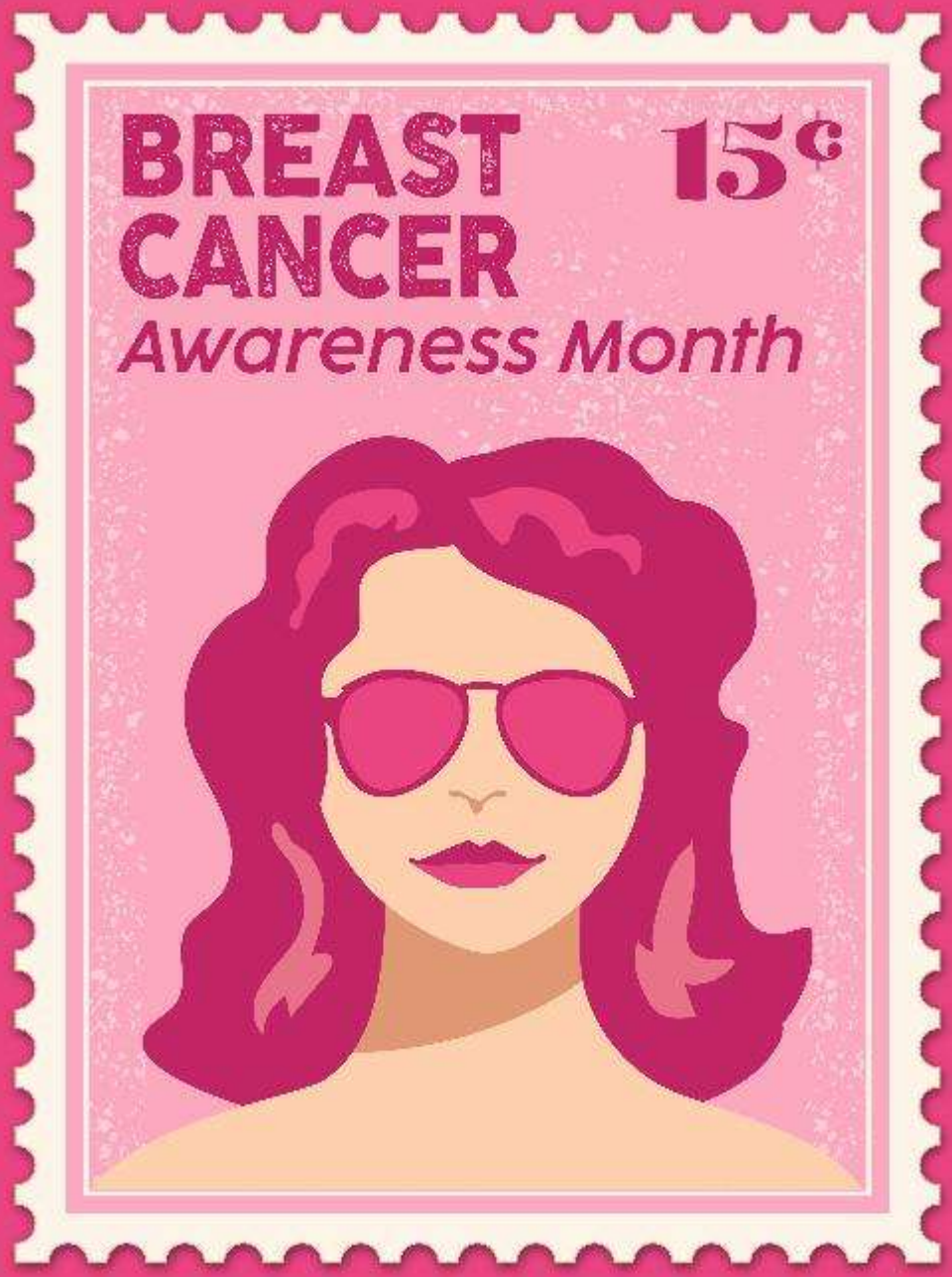


1. Introduction

A Survey of Breast Cancer Research

Early portrayal of breast cancer surgery.
16th Century
Wellcome Collection

A Survey of Breast Cancer Research

This month I write about an important topic: humanity's quest to overcome the scourge of breast cancer.

It is a particularly opportune moment for this review.

First, it's Breast Cancer Awareness Month. There is no better time to review how far we have come with this disease – but also how far we have yet to travel. I welcome your attention and thoughts on the topic of what we can all do in our society to accelerate the end of death from cancer.

Second, we are seeing *unprecedented innovation* in novel efforts to deal with breast cancer. Last week's ESMO conference in Berlin featured impressive data from Daiichi-Sankyo/AZ's Datroway® (a TROP2 ADC) in triple negative breast cancer. Not to be outdone, Gilead reported nice survival data for Trodelvy®, its TROP2 ADC. There are countless other stories of innovation hitting the journals and conferences this year – which give us encouragement that more lives will be saved in the years ahead.

This survey traces the development of our understanding of breast cancer, highlighting historical milestones, influential publications and the progress that has shaped the field.

Every year over 2 million women are diagnosed with breast cancer

More than 600,000 will die of the disease

In America, a woman has a 1 in 8 chance of getting breast cancer in her lifetime.

A Reader's Guide

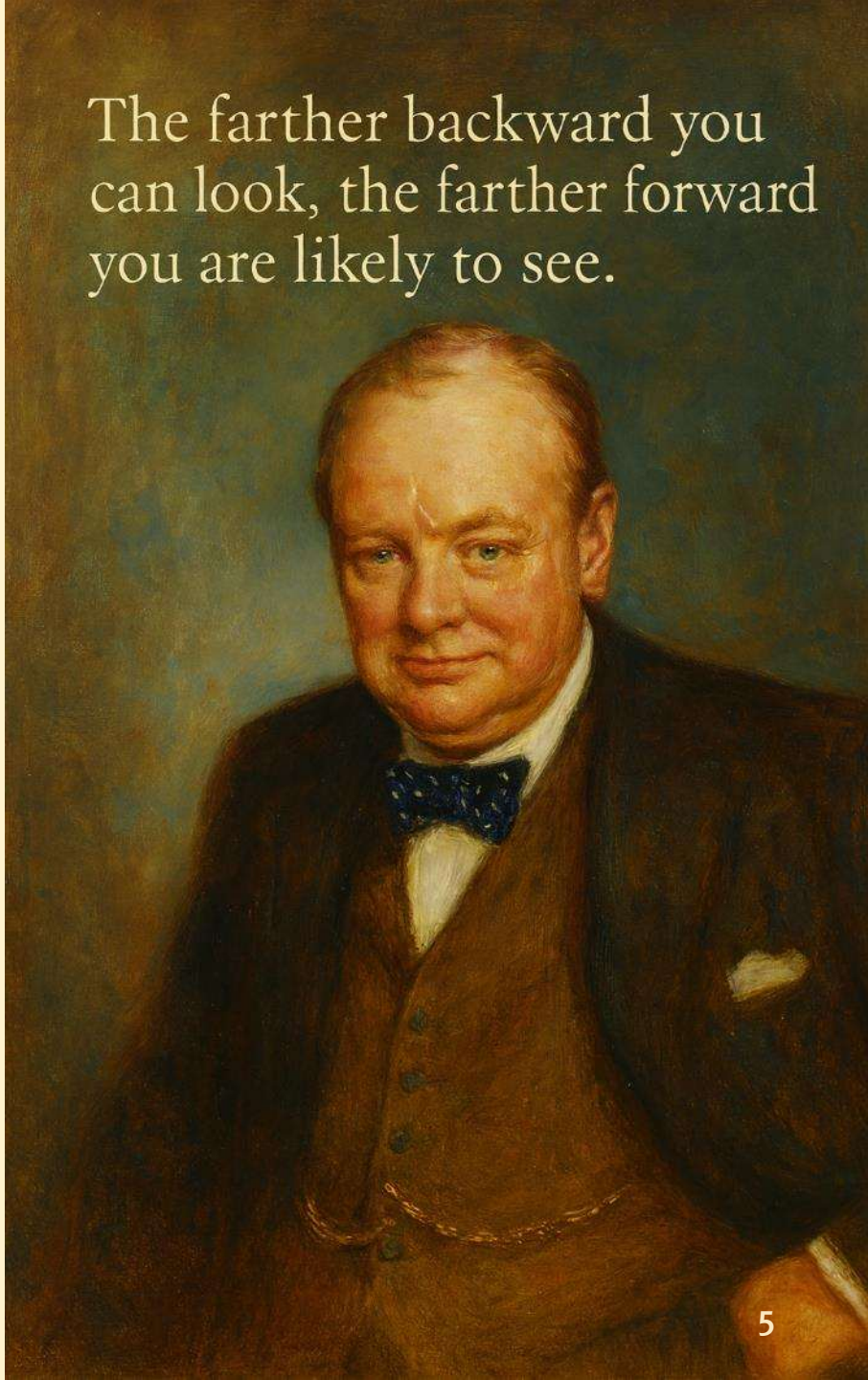
In total, I highlight and describe roughly 100 influential and important publications on cancer etiology and breast cancer going from 1700BC to 2025.

This survey has two parts. First, I provide an intellectual progress report from the past to the present. Second, I analyze today's translational science and discuss a dozen promising organizations developing new approaches.

There is a *ton* of historical content in this report, and I know it's not for everyone. For those of you that want to get to today's translational science, you can do so by jumping to the present. Go straight to page 121 and navigate forward from there. For those of you, in contrast, that like learning the history, we have more of a summary in the report for the antiquity to 1950 period with Appendix 1 holding much more detail on publications from that time (feel free to review that as reference). We do a deep dive on the last 75 years starting on p. 39 because they are so relevant for what is happening today in breast cancer therapy.

This said, one might ask the obvious question. Why bother at all looking at the history? Why not just focus on where we are with breast cancer now and contemplate where we might go next?

I think the exercise of reviewing the history is useful as it shows the context of current accomplishments, the progress of thought, the questions that have been asked and answered and, just as importantly, the questions that have not been answered. Winston Churchill, in our view, said it best in a 1944 speech (at right).



Humanity’s Oldest Cancer

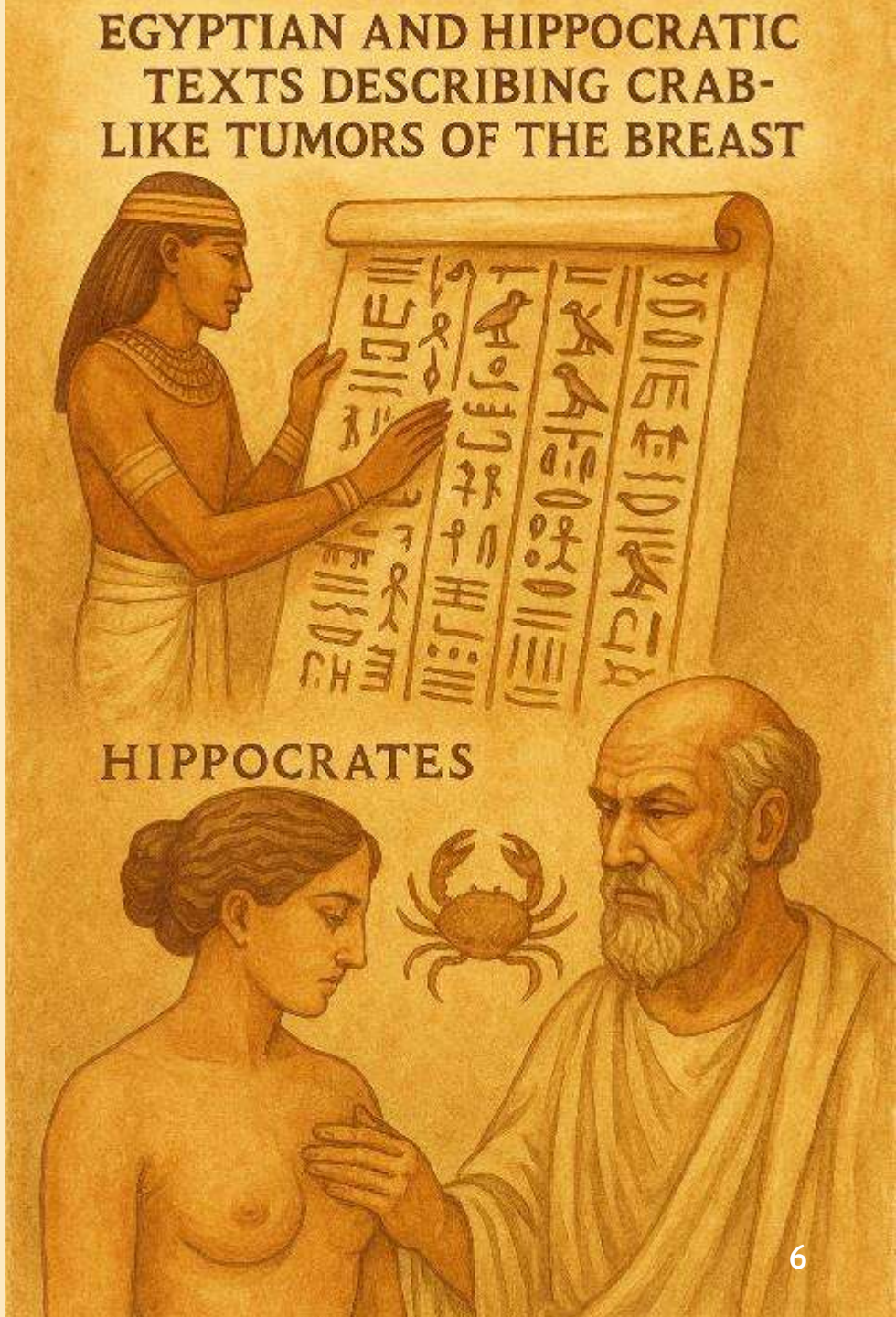
Indeed, breast cancer is the oldest recorded malignancy in human history and one of the most revealing mirrors of how medicine itself has evolved.

From the earliest Egyptian and Hippocratic texts describing “crab-like” tumors of the breast to the genomic precision of 21st-century oncology, every stage in its history reflects a fundamental transformation in medical thought, technology and social awareness.

Over twenty-five centuries, physicians have explained breast cancer through humors, lymph, cells and genes; treated it with prayer, cautery and cytotoxins; and debated whether it was a local lesion, a systemic disease, or a molecular disorder.

Its story is not just a chronicle of discoveries but a record of how science, culture and compassion converged to shape modern cancer care.

Perhaps, most interestingly, we have gone full circle in our thinking. The ancients saw cancer as a systemic disease. By the late 1800’s we had convinced ourselves it was local, leading to widespread use of mastectomy. Today, we have abandoned all of this and have come back to the view that cancer is very much a systemic disease. A bloody complicated one at that.



A Grim History

In a previous survey of the aging literature, I found striking parallels between the ideas of Aristotle 2500 years ago, Robert Boyle in the 17th century and modern theories of aging. Boyle somehow could see what was to come.

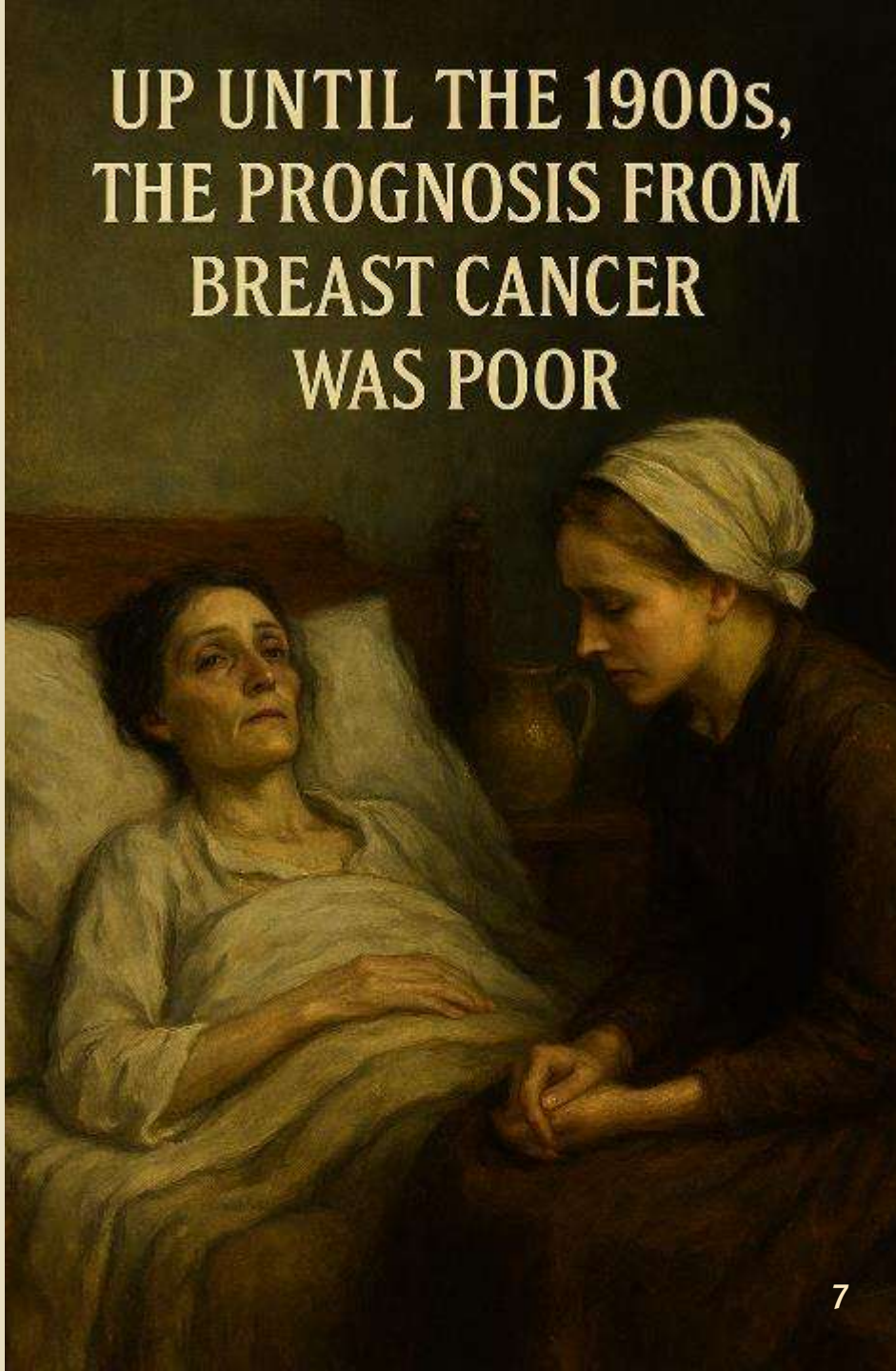
I find no similar parallels in our survey of breast cancer research. No deep intuition. No brilliant insights. Just deep frustration borne from helplessness. I have spent the last four weeks surveying dozens of historical books on breast cancer, many from my own medical library.

There are no glimmers of hope to be found in the period running up to 1900. Breast cancer has been a formidable enemy. Uniformly, writings on breast cancer up until the mid-1800s give no cause for optimism. Up to 1900, writers universally felt that there was little to do curatively for early disease.

The reality is that medicine had little, if anything, to reverse the inevitable consequences of advanced breast cancer until at least 1930.

There was a long-standing obsession with the idea that if one could excise enough, that the spread of a breast tumor could be halted through surgery. More recent work has done a very good job of disproving this idea.

And many of the more introspective writers acknowledged the abject desperation experienced by countless women stricken with breast cancer from the beginning of time.



Some Progress Made in Early Days

This is not to say that progress has eluded us entirely. There was some progress made in the early days of the study of breast disease.

Starting from untenable and indefensible positions to increasingly empiric observations made as the scientific revolution took hold after the 17th century. Between antiquity and 1500, the disease was interpreted through Hippocratic and Galenic humoralism—an excess of black bile, often tied to female melancholy or moral imbalance.

From 1500 to 1875, the anatomical revolution transformed breast cancer from an invisible fluid to a tangible lesion, while early surgeons like Le Dran and Petit began to describe lymphatic spread and surgical removal.

The period from 1875 to 1975 brought the birth of scientific oncology: Halsted's radical mastectomy, Virchow's cellular pathology, Beatson's hormonal therapy and Bernie Fisher's systemic model reframed cancer as a biological and clinical continuum.

Steady Progress Since the 1900's

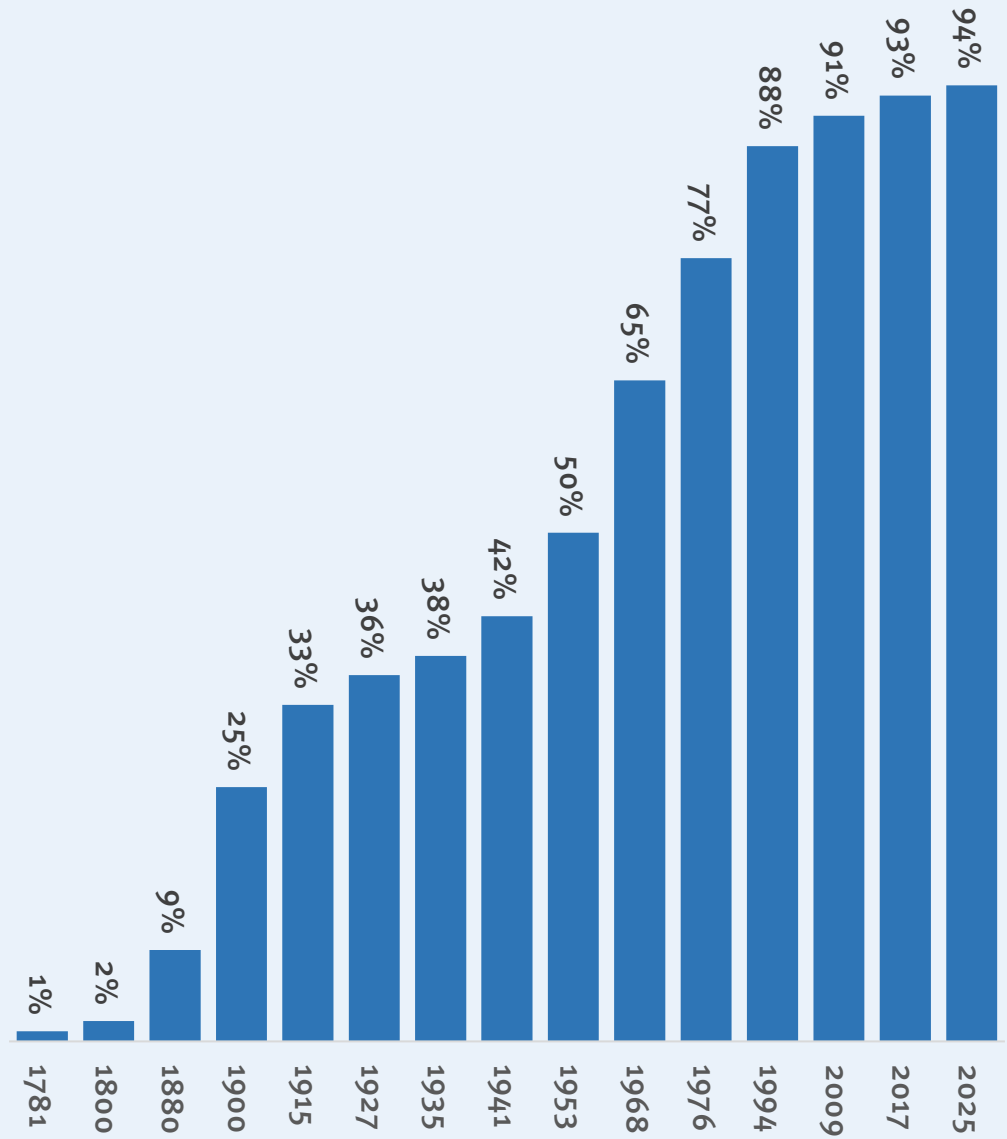
The chart at right shows five-year survival rates from breast cancer over the last 235 years.

In the period from antiquity to around 1850 the odds of surviving more than five years from breast cancer were two percent or less.

The issue is that if you didn't get surgery, you would face certain death and that if you did get surgery, you would still run the risk of infection, bleeding to death from hemorrhage and trauma from extreme pain.

With the advent of antisepsis and anesthesia in the 1850s, survival began to improve. By 1880, Samuel W. Gross was seeing post-surgery five-year survival rates in the high single digits. Results improved further with the spread of Halsted's radical operation. Things got better with the introduction of radiation therapy in the 1920s. Then, we saw the introduction of chemotherapies in the 1950 to 1975 period. After that, the modern era began with precision therapies – resulting in dramatic improvements in survival. By the early 1990s, survival rates well exceeded 85% in the United States. Today, five-year U.S. survival from breast cancer stands at 94%.

Five-Year Survival Rates from Breast Cancer, US and UK, 1781 to 2025



Source: Stifel Investment Banking.

Survival and Sample Heterogeneity

We should hasten to add that the chart on the previous page compares apples and oranges. In the old days breast cancer wasn't so well recognized and it's quite likely that patients showed up to see a physician quite late in the course of the disease. Not surprisingly, survival was quite low.

In contrast, tumors are increasingly caught early today thanks to mammography.

To compare apples to apples then, lets look at 5-year survival data for patients who are diagnosed with metastatic breast cancer.

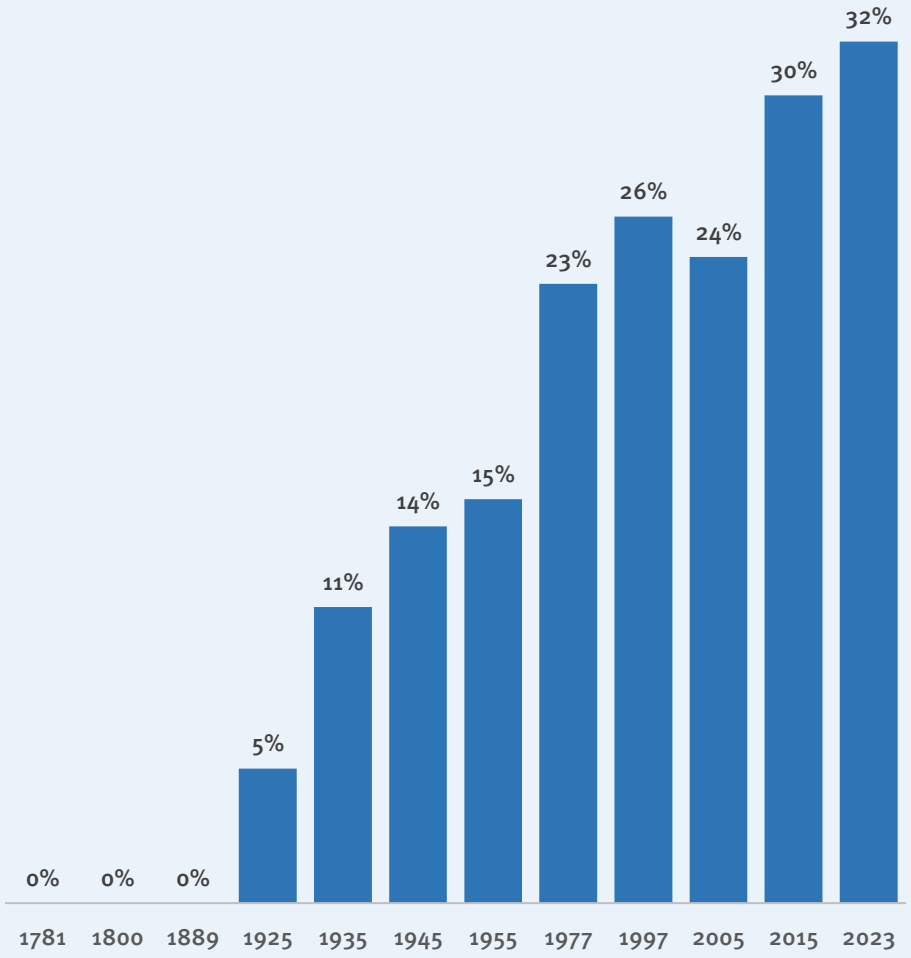
You can see the trend at right for this condition.

Survival for metastatic breast cancer has jumped six times in the last century. However, if there is a takeaway, it's that breast cancer needs to be caught early. Metastatic breast cancer still has a bad ending most of the time.

A key source of progress in our society is that we have ramped up efforts to screen for breast cancer early – helping to avoid situations where patients first find their cancer when it is metastatic.

Today, only six percent of breast cancer cases are diagnosed *de novo* as metastatic. This is way down from levels as high as 50% in the 1800s.

Five-Year Survival, Stage 4 / Metastatic Breast Cancer, 1781 to 2023



Source: Stifel Investment Banking. Data for 1791 from Monro (du Moulin p. 56). Data for 1800 from Shadle and Olson. Data for 1889 from Stephen Paget's analysis of fatal breast cancer cases. Data for 1925 to 1955 are from Todd et.al. (2016). Data since are from SEER (distal disease) and the NBCF.

A Medical Success Story

What emerges is one of the better success stories that medicine has ever recorded. While it is far too early for society to run a victory lap against breast cancer (as five-year survival doesn't necessarily correspond to full cure and too many die of metastatic disease), the progress has, nonetheless, been tangible, real and gratifying.

Over millennia, at least 200 million women have perished from this disease.* With today's tools, women are far less likely to face history's grim prognosis.

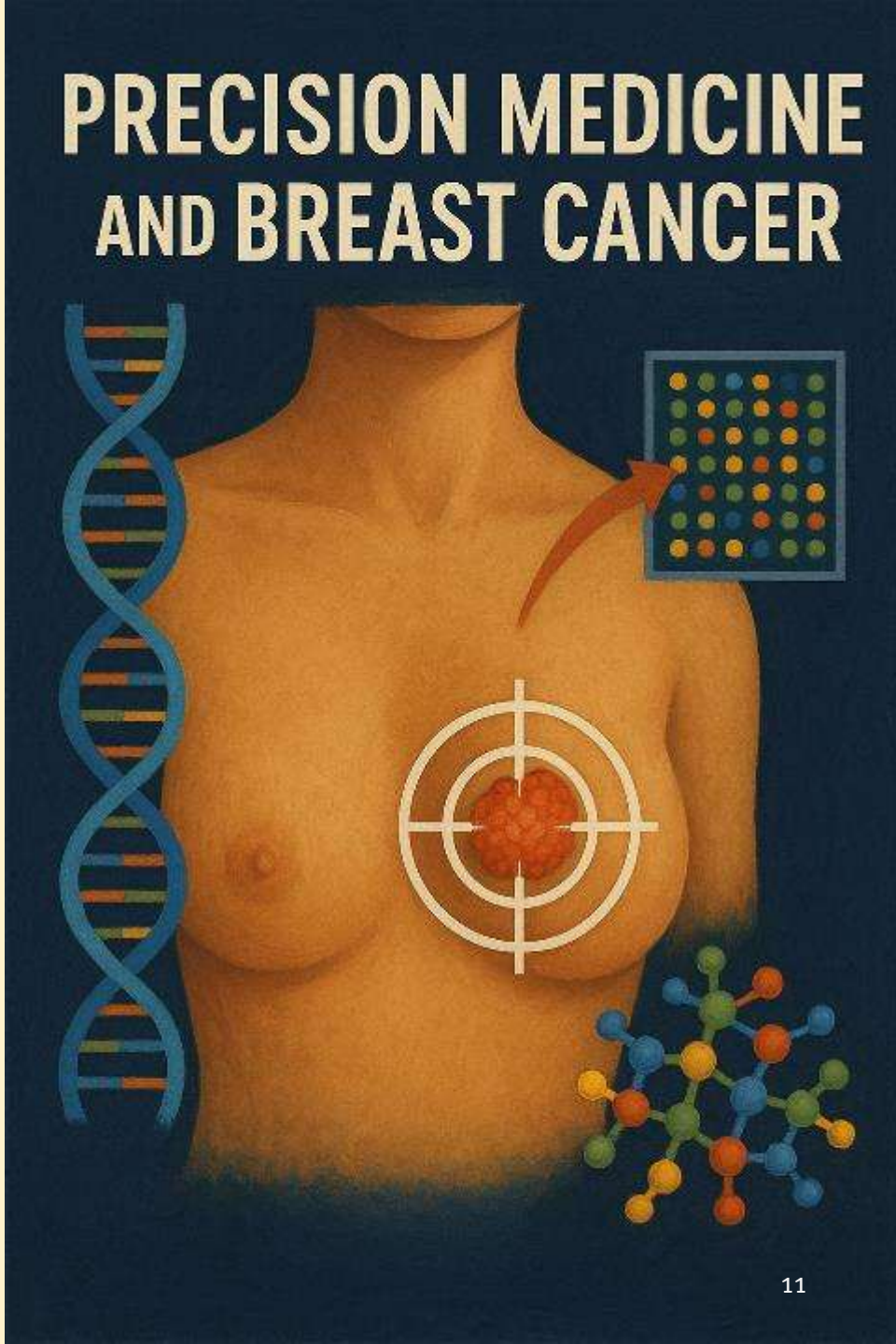
The success in beating back breast cancer mortality reflects:

1. Passion and a concerted effort to do something about the disease by countless people,
2. Substantial societal investment of resources and
3. Tremendous medical and scientific progress on many fronts.

I will dig into these various factors throughout this report.

Most importantly, breast cancer has become the paradigmatic example of precision disease management of our times.

The condition has gone from a monolithic disaster for patients to a disease that has been sliced and diced into at least ten treatable sub conditions.



* This estimate comes from number of lives ever lived x incidence of breast cancer in ancient times x percent female x fatality rate. We estimate that at least 100 billion humans have lived. See https://www.prb.org/articles/how-many-people-have-ever-lived-on-earth/. We estimate that incidence of breast cancer before 1900 was 0.5% because few women lived long enough to get it. See Bissell and Haas (1980) and Porter (1997). The mortality rate was 100%. See Long (1976). The percent female is assumed to be 50%. Thus, 100bn x 0.005 x 0.5 x 1 = 250 million.

The Potential of Precision Medicine

If we could enjoy such success in other cancers and, for that matter, other complex phenotypic diseases, society would be so much better for it.

One could imagine the potential of precision medicine methods to transform any number of common conditions such as atherosclerosis, depression, autism, inflammatory bowel disease and the like.

As I have perused many historic books, there is a clear refinement over the centuries in terminology that reflects ever better definition of what disease is.

Gone are conditions such as “dropsy”, “palsy” and “scirrhous disease”.

One need not dig too deep to note that the successes in breast cancer have been largely driven by better life science research tools. Microscopy was helpful in the 1800s in driving tissue analysis but the key advances of the 1990s came from a host of breakthroughs in tools like western blotting, gene sequencing, high throughput screening and the like. The advent of single cell analysis, RNA analysis, adaptive Bayesian clinical trials, proteomics and cryo-EM offers even more potential to make future advances.

Some of the most interesting reading for us has been going through the stories of tamoxifen (the first selective estrogen receptor modulator (SERM) and Palbociclib (the first CDK4/6 inhibitor). In neither case, did these drugs progress down a straightforward path.

The Tamoxifen Story

Imperial Chemical Industries (ICI) in Alderley Park first synthesized tamoxifen in the early 1960s, very early on in the era of rational drug design.

Depressingly, the person who synthesized the drug, Dora Richardson, was left off the first publication on the drug by her male colleagues (a practice that, hopefully, would not happen today).

Richardson developed the drug using early techniques involving screening for stereoisomers.

Dora Richardson and Tamoxifen

ICI wasn't particularly interested in the drug and lab director Arthur Walpole passed away early on – but not before encouraging Craig Jordan, a friend, to pursue the drug.

Jordan, indeed, marched tamoxifen all the way through to approval and the drug went on to save countless lives – despite numerous efforts to have the drug killed.

Walpole threatened to resign in 1972 when ICI (now AstraZeneca) tried to shut down the program – which, at the time, was focused on developing a better hormonal contraceptive.

Jordan is now widely credited as the "father of tamoxifen" and Dora Richardson's name has largely been lost.

Dora Richardson died in 1998 but not before writing a paper documenting the history of tamoxifen development. The paper remains unpublished today in the archives.

The website "lost women of science" has developed a nice podcast about her – that shares the story of her important contribution and has a link to her paper.

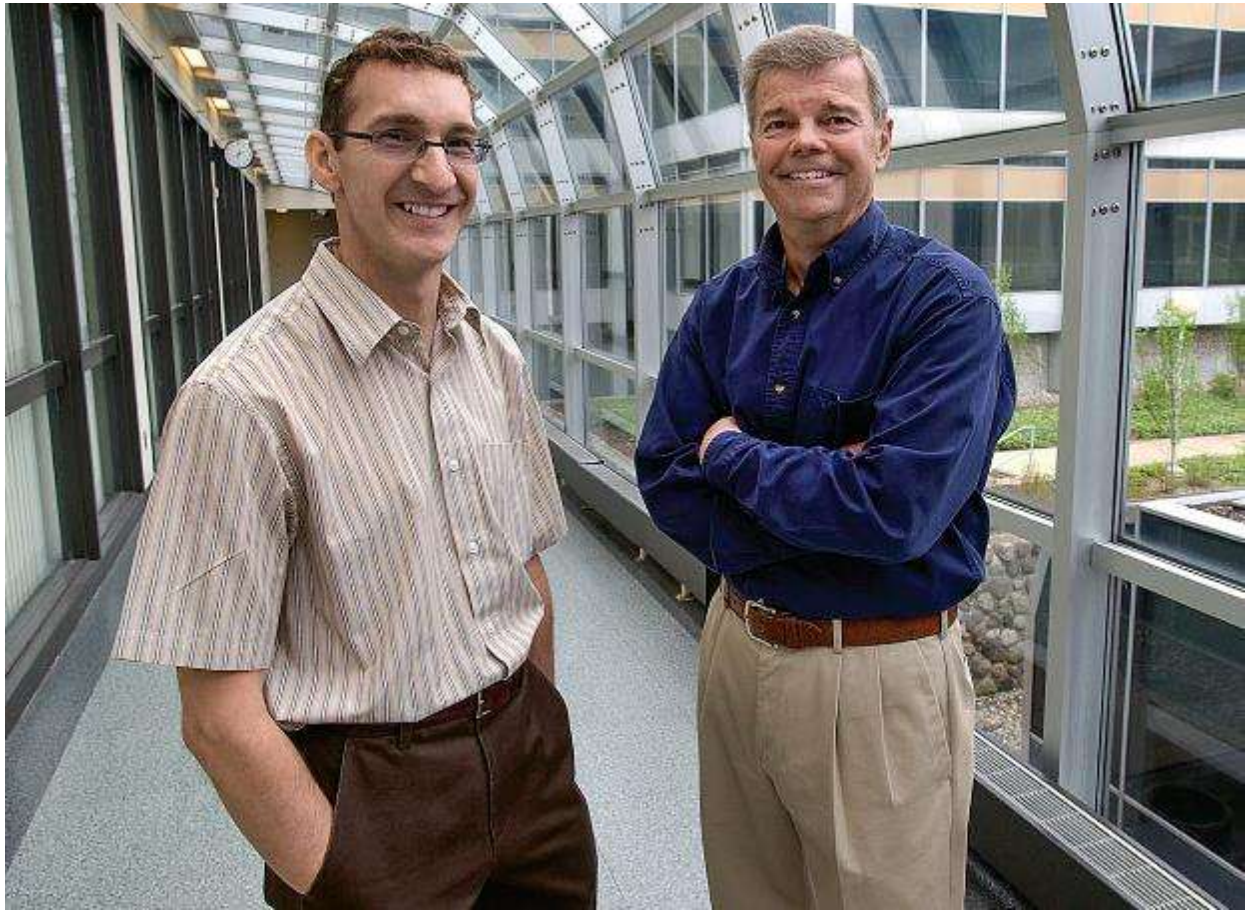
The Palbociclib Story

In 2016 UCLA oncologists Richard Finn and Dennis Slamon reported that Palbociclib (Pfizer's IBRANCE®) doubled progression-free survival in metastatic breast cancer.

This was the first meaningful trial result for a CDK inhibitor and heralded a new era where cell cycle inhibition drugs have become a mainstay of breast cancer treatment.

Like tamoxifen, Palbociclib's road to market was a long one. Synthesized by Parke-Davis scientists Dave Fry and Peter Toogood in 2001, Palbociclib (then called PD-0332991) ended up at Pfizer after an acquisition.

Pfizer shelved the drug. Following two large acquisitions in rapid succession (Warner Lambert and Pharmacia), Pfizer simply didn't have the resources to develop all the drug candidates in its portfolio. Dick Leopold, who led cancer drug discovery at Parke-Davis said: "Certainly there were some politics going on. Also, just some logistics with new management and reprioritization again and again."



Dave Fry (left) and Peter Toogood (right)
Parke-Davis Scientists who discovered Palbociclib.

IBRANCE® Becomes a Blockbuster

In late 2004, Selina Chen-Kiang, a molecular biologist at Weill Cornell Medical College, obtained PD-0332991 from Pfizer as a research tool for studying the cell cycle in normal immune cells. Convinced of the drug's potential in blood cancers, she persuaded Pfizer to sponsor a 17-patient phase I clinical trial in mantle cell lymphoma that began in 2007. In that trial, about one-fifth of patients had significant tumor shrinkage.

This raised interest and, in 2007, Dennis Slamon of UCLA found that PD-0332991 was associated with 30% tumor shrinkage among three women in ER-positive metastatic breast cancer.

These two trials got Pfizer interested and the rest is history. Pfizer invested in a Phase III program and IBRANCE® was approved by the FDA in 2015 – the first cell cycle inhibitor to get to patients.

Today, over 250,000 patients have been treated, and Pfizer has racked up more than $40 billion in sales of this drug.

Selina Chen-Kiang
Weill Cornell

Dennis Slamon
UCLA

Pfizer's IBRANCE became a $40+ billion drug saving countless lives thanks to the efforts of two very determined academic investigators.

The tamoxifen and palbociclib stories are just a few of the many regarding breast cancer innovation that you will find in the pages that follow.

The valiant, although largely fruitless, early efforts of physicians to better understand the nature of breast cancer in the 1700s and 1800s are impressive.

And the work (and battles) of researchers like Marie Curie, Geoffrey Keynes, Mary-Claire King, Vera Peters, Umberto Veronesi and countless others is inspiring, informative and worth learning.

Perhaps, the most exciting news lies ahead in the opportunities to address the most important unmet needs facing patients, including:

1. Improving survival in triple negative breast cancer,
2. Dealing with resistance to targeted drugs, particularly cell cycle inhibitors and hormonal therapies,
3. Improving survival in metastatic disease, and
4. Working to intercept more cancer early by improving on screening techniques.

We thank you for the time you are taking to peruse and consider the material herein. I hope that you can share some of the same pleasure that I have gained from contemplating our species' progress against the very first cancer to appear in the literature.

Breast cancer has terrified women for centuries and for many years progress was far too slow.

The convergence of advances in cell biology, genomics and clinical trial methods have helped immensely to reduce the burden of this disease.

This progress is a testament to humanity's enduring curiosity, determination and ingenuity.

Tim Opler
New York
October 2025

Acknowledgements

In preparing this survey I have benefitted from the advice and comments of many and am grateful for excellent suggestions along the way. I would particularly like to thank Guoqing Cao of Minghui Pharmaceuticals for a thoughtful conversation about the evolution of ADC landscape and the case for moving to frontline with TROP2; Gloria Olivier, of the Mayo Clinic for introducing me to new thinkers about breast cancer strategy; Carlo Rizutto, Versant Ventures, who shared opinions and insights on breaking science in the breast cancer field; Arlene Shaner, Historical Collections Reference Librarian, of the New York Academy of Medicine; Jim Tanenbaum of Foresite Capital, David Wolf, medical historian and Clinical Professor of Medicine at Weill Cornell and Leena-Das Young, former leader in late-stage oncology development at Pfizer (worked on getting five drugs approved for breast cancer).

I am particularly indebted to Andrew J. Dannenberg, former Head of Cornell's Cancer Center, for extensive conversations and reviews of the document; Masaki Doi, who run's Stifel's Japan practice; Stephanie Leouzon who not only read every page of this document but helped to restructure it to make it easier on the reader; Stifel's healthcare M&A head, Neal Karnovsky, an amateur history buff, who helped tighten the narrative quite a bit; my wife, Susan Lewis, who made countless helpful suggestions for improvement and Ernest Li of Emerald BioVentures, who had a series of valuable ideas for improving the material here.

I have learned much about breast cancer biology from academic investigators and would like to acknowledge particularly helpful conversations with Jenny Chang of Houston Methodist, Laura Esserman of UCSF; and Matt Goetz of the Mayo Clinic.

This survey has further benefitted from work on the history of breast cancer prepared by those that have come before me, and I have included a section of bibliographic references at the end. Daniel De Moulin's 1993 book *A Short History of Breast Cancer* is particularly good and, frankly, my survey would be superfluous given how thorough his work is – except he stops tracking the literature about 75 years ago – just when things started to get super interesting. Another particularly good book-length history of breast cancer is Olson's 2002 book *Bathsheba's Breast: Women, Cancer and History*. His history is constructed from the personal stories of many women throughout history and was helpful in identifying landmark publications. Journal resources of the most value were Robinson, J. O., 1986, "Treatment of breast cancer through the ages." and a series of articles on the history of cancer written by Steven Hajdu. Concerned that I might be missing a particularly important recent paper, I reviewed Ahmet Sanli's 2022 article: "Update of the 100 Most Cited Articles on Breast Cancer" on more than one occasion.

Two very interesting books that I enjoyed reading and using as resources were Jennet Conant's 2020 book *The Great Secret: The Classified World War II Disaster That Launched the War on Cancer* and Sid Mukherjee's history of cancer entitled *The Emperor of All Maladies*. Even though my section on patient advocacy is short I spent a fair bit of time reading about the efforts of Shirley Temple Black, Nancy Brinker, Betty Ford, Rose Kushner and Evelyn Lauder. Two great books in this area include Rachel Pearson's *Radical Sisters: Dawn of the Breast Cancer Movement* (out last month) and Barron Lerner's *Breast Cancer Wars* from 2001.

Finally, the work here was built from studying my own library of printed works in medicine, starting at around 1480. I would particularly like to acknowledge Catherine Smith who spends many hours each week acquiring new items for the library from around the world and Annabelle Seeliger, who has become quite the book cataloguer and is a budding rare book librarian. Neither realized what they were signing up for until the job started! Both now know their way well around dusty tomes, customs/tariff rules, grouchy book dealers and various ministries that touch rare books. Thank you both for working so hard every day!

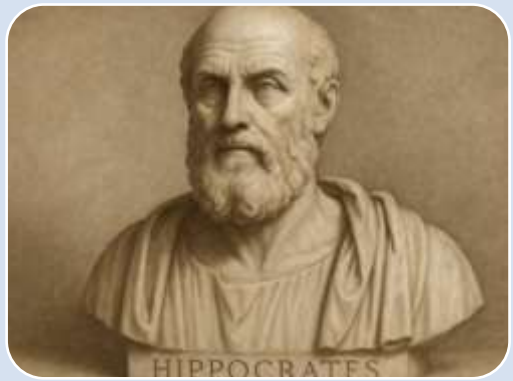
Section 2:

Landmarks in Breast Cancer Research

Twenty-Four Landmark Publications that Have Shaped Breast Cancer Research Over the Last 2500 Years

Twenty-Four Landmark Publications in Breast Cancer Research

#1



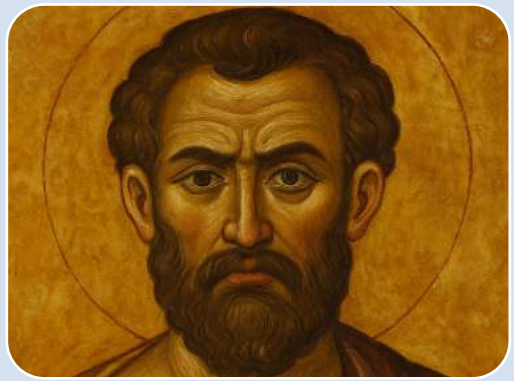
Hippocrates

400 B.C.E.

Viewed breast cancer as a humoral disorder caused by an excess of black bile.

He coined the term karkinos (“crab”) to describe tumors, observing that their radiating veins resembled crab legs.

#2



Leonidas

250 C.E.

First written description of an anatomy for breast cancer.

To avoid hemorrhage, he removed the breast slowly and with cauterization in what must have been an excruciating process.

#3

Joseph Récamier

1829

The first to describe cancer metastasis in a precise way.

He also described the invasion of the veins by a cancer.

Introduced a “multiple compression” technique to treat cancer.

#4

Rudolph Virchow

1863

Described cancer as a disease of cell biology.

Said “Omnis cellula e cellula” (every cell from a cell”)

Associated cancer development with inflammation.

Twenty-Four Landmark Publications in Breast Cancer Research

#5

William Halsted

1894

Refined and perfected the radical mastectomy.

While his work later became controversial Halsted is perhaps the most known historic figure in breast cancer research. Good evidence that he saved lives.

#6

George Beatson

1896

Found that oophorectomy (removal of ovaries) could cure breast cancer.

While Beatson did not understand sex hormones, his insight triggered hormonal therapies years later.

#7

Marie Curie

1899

Discovered polonium and then radium which was to transform breast cancer treatment.

Radiation therapy was the first good option beyond mastectomy to treat breast cancer.

#8

Paul Ehrlich and S. Hata

1910

Theorized about chemotherapy for the first time.

Imagined a “magic bullet” that could conquer cancer, presaging rational drug design.

This concept reshaped medicine.

Twenty-Four Landmark Publications in Breast Cancer Research

#9

Geoffrey Keynes

1932

Was the first to show that radiation could be just as effective in treating breast cancer as the radical mastectomy.

Brother of John Maynard Keynes, he led a distinguished career in medicine and the humanities.

#10

Alexander Haddow

1944

Showed that synthetic estrogens can cause regression of breast cancer.

Along with Huggins who did similar work in prostate cancer in 1941, Haddow laid the groundwork for hormonal therapy in breast cancer.

#11

Harry Shay

1953

Treated breast cancer with chemotherapy for the first time and saw clinical response.

Used an analogue of nitrogen mustard (Thio-TEPA) which had emerged from post-WW2 work.

#12

Federico Arcamone

1969

Lead member of the team at Farmitalia that discovered Adriamycin.

Farmitalia supplied this chemo drug to Bonadonna who showed it had transformational effect on breast cancer survival in the 1970s.

Twenty-Four Landmark Publications in Breast Cancer Research

#13

Lee Hartwell

1970

In 1970 published a key paper that outlined points of vulnerability in the yeast cell cycle.

Was awarded Nobel Prize for cell cycle work in 2001 along with Tim Hunt and Paul Nurse for work on cell cycle.

#14

Elwood Jensen

1973

Discovered the mammalian estrogen receptor. The implications were profound. His discovery of the estrogen receptor laid the foundation for the modern era of targeted hormonal breast cancer drugs.

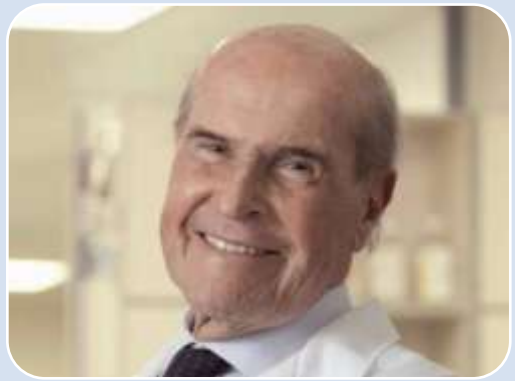
#15

Gianni Bonadonna

1976

Ran the initial trials in 1969 validating the activity of Adriamycin. By 1976 published a major paper showing that adjuvant chemotherapy could substantially extend expected survival for post-operative breast cancer.

#16



Umberto Veronesi

1981

Published a paper in 1981 that showed that patients who received a lumpectomy did not have worse survival outcomes than radical mastectomy.

This work was influential in the eventual rise of lumpectomy.

Twenty-Four Landmark Publications in Breast Cancer Research

#17

Dennis Slamon

1987

Slamon and colleagues analyzed DNA from breast cancer tissue samples and found that a substantial minority overexpressed HER2. This led to a new classificatory scheme for breast cancer and Herceptin.

#18

Mary-Claire King

1990

After a very long hunt for the gene associated with familial patterns of breast cancer inheritance, Mary-Claire King found that BRCA1 was a key risk gene. Later she found BRCA2 and helped to develop a gene test with Myriad.

#19

Tasuku Honjo

1992

Honjo and his team at Kyoto University discovered programmed cell death protein 1 (PD-1) and later found that it was a key checkpoint slowing immune response to cancer. He shared the Nobel Prize with Allison for this work.

#20

Charles Perou

2000

Lead author on a 2000 paper which used genetic sequencing analysis to show the genetic diversity of breast cancers. This highly cited paper led to a precision classification scheme for the disease.

Twenty-Four Landmark Publications in Breast Cancer Research

#21

Jim Allison

2006

Jim Allison identified CTLA4 as a brake on the immune system surrounding tumors.

He helped convert this idea to a therapy for patients and co-authored a key paper on this topic in 2006 with Alan Korman and Karl Peggs.

#22

Richard Finn

2016

Richard Finn was lead author on a paper with Dennis Slamon in the *NEJM* in 2016 that reported the first definitive data for a CDK4/6 inhibitor in breast cancer. Palbociclib brought substantially longer progression-free survival than the control arm.

#23

Daiichi Sankyo ADC Team

2016

In 2016, a team from Daiichi Sankyo's research laboratories published a paper on ENHERTU®, a HER2 targeting ADC.

ENHERTU® has transformed breast cancer treatment.

#24

Peter Schmid

2020

Peter Schmid was the lead author / investigator on the clinical trial that showed that a PD-1 inhibitor, when used with chemotherapy, could achieve improvements in survival from triple-negative breast cancer.

Section 3:

Breast Cancer Progress: From Antiquity to 1950

2000 Years of Thinking About an Extremely Challenging Disease

(Details on publications from this period are found in Appendix I).

Greta Garbo was a Breast Cancer Patient in the 1930s

Breast Cancer in Antiquity

Ancient Egyptians Recognized Breast Cancer

Concepts of cancer and the identification of breast cancer as a danger have been with humanity from the very beginning. Egyptian records from 4,000 years ago discuss breast cancer. The Edwin Smith Surgical Papyrus, from 1,600 B.C.E. (arguably, much earlier) provides accounts of breast cancer. A case was deemed incurable if the disease was “cool to touch, bulging and spread all over the breast”.

The Assyrians, Babylonians, Chinese and Indians Saw Breast Cancer

Babylonian cuneiform tablets (ca. 2000–1000 B.C.E.) describe breast swellings, often in association with the goddess Gula or the influence of demons. These were treated through a mixture of ritual incantation and topical salves—including poultices of oils, herbs, or minerals—rather than surgery. The approach was palliative and symbolic: physical manifestations like breast tumors were seen as signs of divine displeasure or evil possession, not as organic disease. See Scurlock and Anderson (2005).

In ancient China, early medical texts such as the *Huangdi Neijing* (The Yellow Emperor’s Inner Canon, ca. 3rd–2nd century B.C.E.) refer to breast disorders under terms like “Ru Yan” (乳岩, literally “breast rock”), describing hard, immovable masses that could ulcerate and lead to death. See Yan (2013).

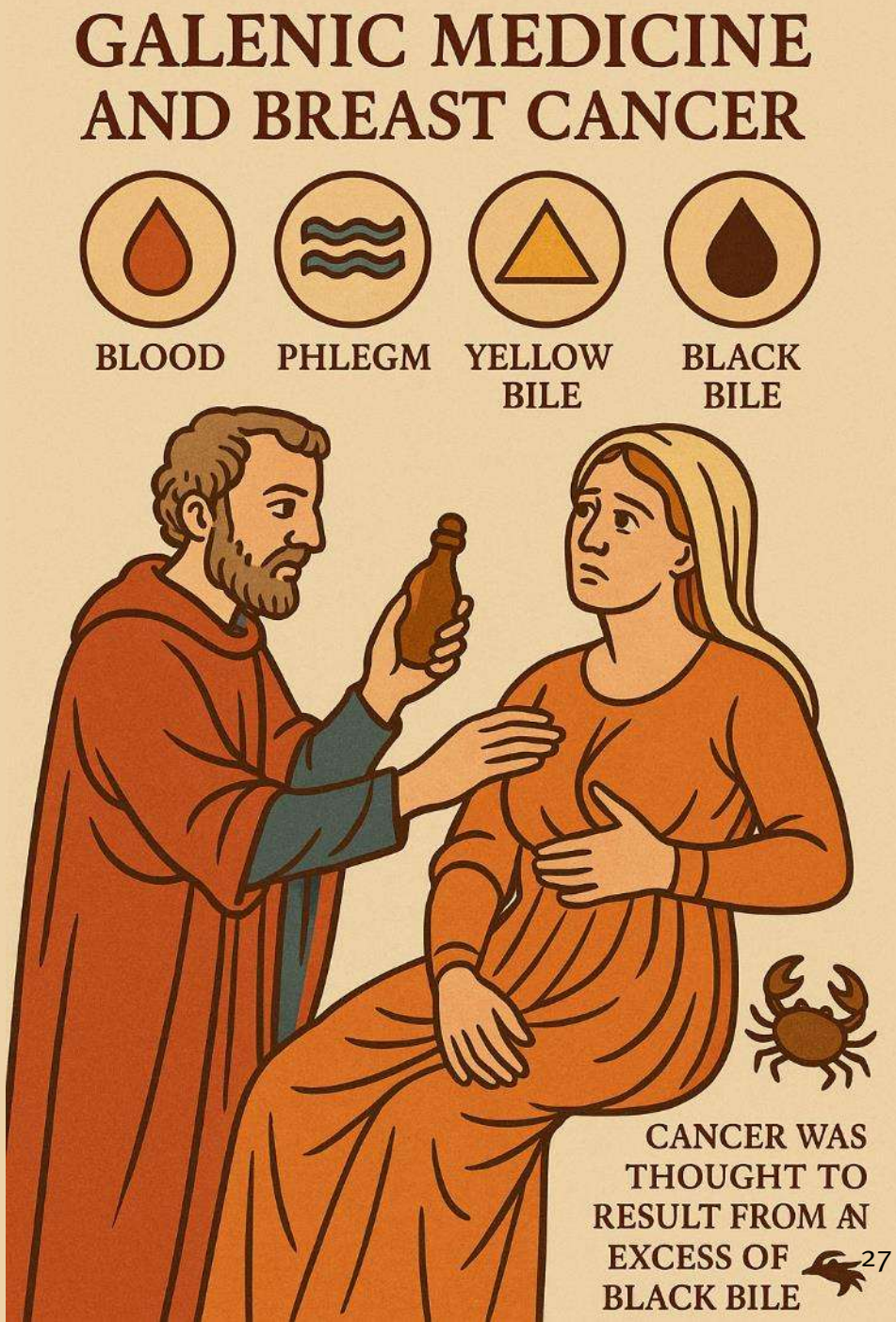
Ancient Indian (Ayurvedic) texts such as the *Sushruta Samhita* and *Charaka Samhita* (ca. 600–200 B.C.E.) also mention breast tumors under the name “Stana Arbuda”—a term for hard, slowly growing lumps of the breast.

Greeks and Romans Set the Humoral Foundations of Cancer

The cornerstone of ancient oncology was a systemic view of cancer that reflected humanity's abject absence of evidence as to what cancer was or where it came from—the humoral theory, developed by Hippocrates of Kos (460–370 B.C.E.) and elaborated by Galen of Pergamon (129–216 C.E.). Cancer, or karkinos (Greek for "crab"), was believed to result from an excess of black bile—one of the four humors (blood, phlegm, yellow bile, black bile). In breast cancer, this "cold and viscous humor" was thought to congeal in the soft female tissue, forming hard, immovable lumps with radiating "claws" hence the crab analogy. Hippocrates wrote of the earliest known case of breast cancer (Atossa's case noted by Herodotus). Hippocrates wisely advised non-intervention, claiming that surgical disturbance hastened death, while Galen recommended purges, diets and topical applications to rebalance humors. This model would dominate medicine for nearly two millennia.

Early Clinical Descriptions of Breast Cancer

Greek and Roman physicians such as Celsus (1st century C.E.) provided some of the earliest clinical descriptions of breast tumors—hard, fixed, painful masses that ulcerated and exuded dark fluid. Celsus distinguished between incipient and advanced cancers, noting that only early, localized growths might be surgically excised, while advanced "cancers of the breast" should be left untouched. Surgery in antiquity was rudimentary and brutal, performed with cautery or knife.



The Alexandrians & Early Pathology

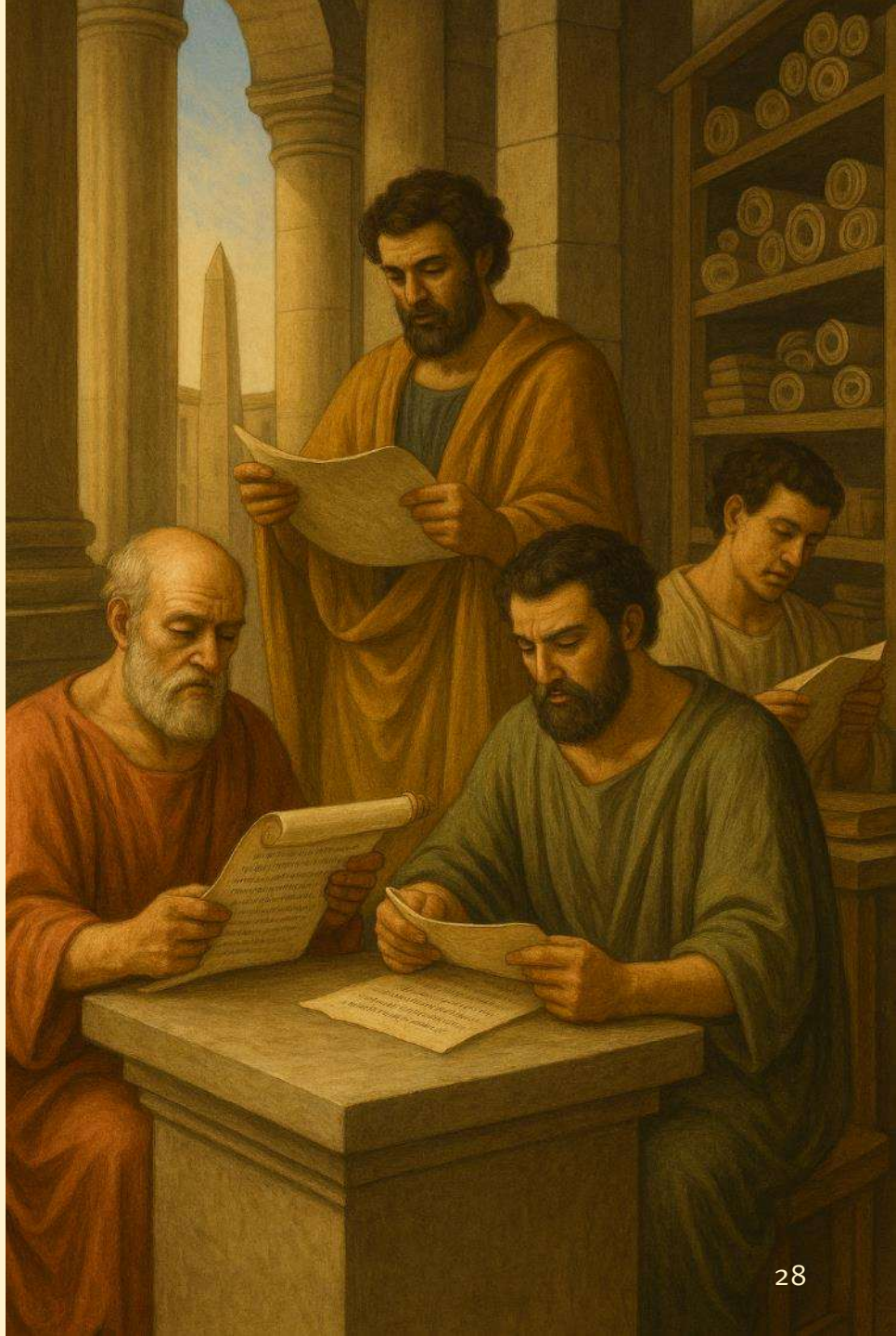
Leonidas of Alexandria, in the first century C.E., preserving the Greek traditions, boldly and skillfully detailed his approach of incision and cautery.

His stipulation of leaving a wide margin of excision and only removing tumours of limited extent, foreshadows the oncological principles of contemporary surgical practice.

In Alexandria, Herophilus and Erasistratus practiced human dissection and described breast structure with remarkable accuracy, identifying ducts, glands and lymph-like vessels. Though they did not abandon humoral theory, they initiated the idea that disease could be localized anatomically.

Later, Galen's dissections on animals reinforced this idea, laying groundwork for later "anatomical pathology." Their studies introduced the notion that certain organs—especially the breast and liver—were predisposed to cancer because of their supposed role in bile filtration.

Galen, attributing breast cancer in C.E. 200 to the accumulation of black bile in the blood, concluded that it was a systemic disease. These ancient physicians postulated that the cessation of menstruation was somehow linked to cancer; in fact, it probably had to do with the association of cancer with old age. In line with this theory, Galen allowed surgical wounds to bleed freely to get rid of the black bile and frowned on the use of ligatures.



The Golden Age of Islamic Medicine

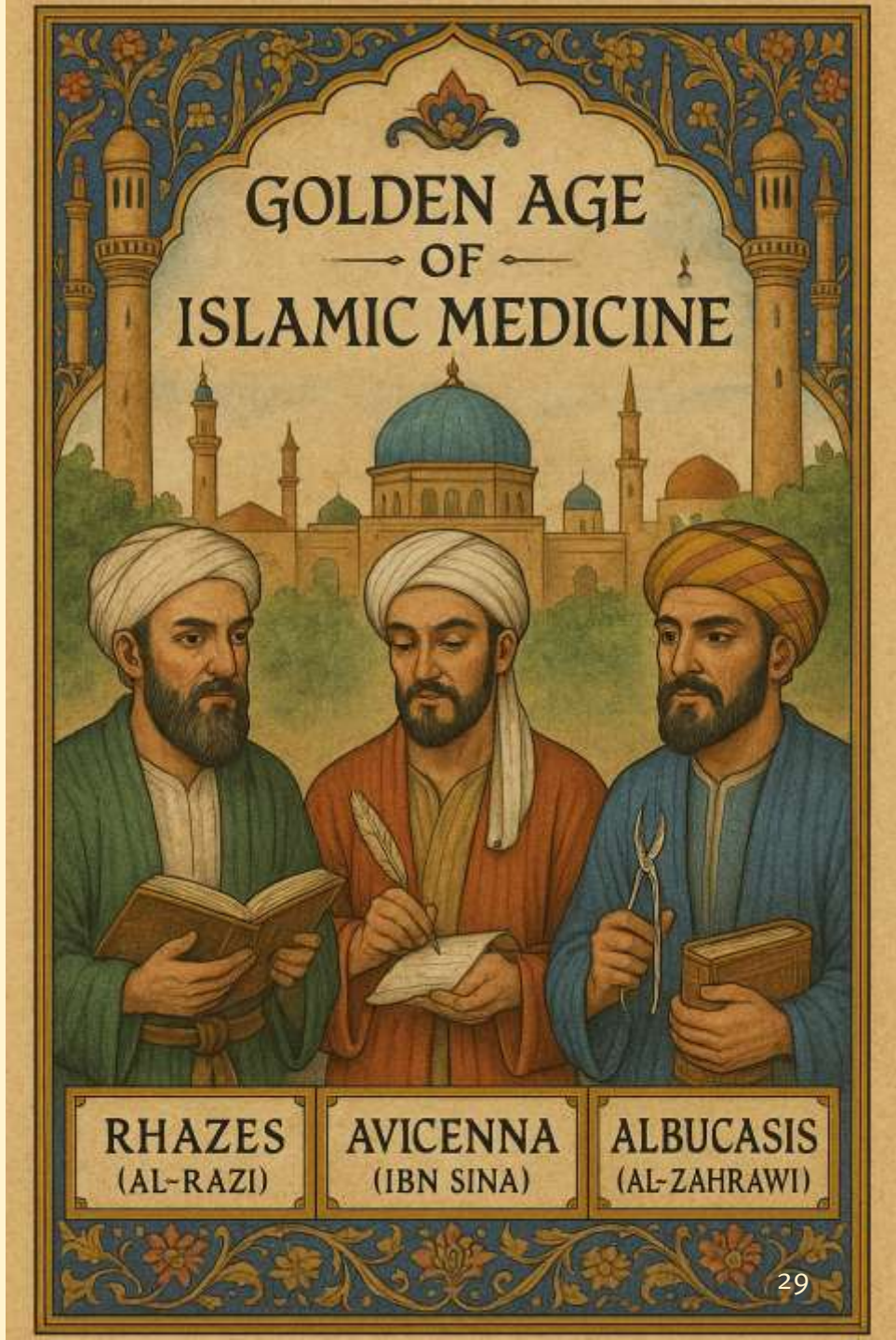
The translation of Greek medical texts into Arabic under the Abbasid caliphs revived and expanded oncologic thought in the 8th to 13th centuries.

Rhazes (Al-Razi), Avicenna (Ibn Sina) and Albucasis (Al-Zahrawi) all wrote about breast cancer in clinical detail. Albucasis recommended early surgical excision with cautery, foreshadowing later surgical oncology. The Islamic physicians combined Greek theory with practical surgery, preserving anatomical reasoning during Europe's intellectual stagnation.

The Scholastic Systematization of Disease (12th–15th Centuries)

In Medieval Europe, the revival of medical learning at Salerno, Bologna and Montpellier reintroduced Galen and Avicenna through Latin translation. Figures like Constantine the African and Lanfranc of Milan systematized cancer within the scholastic framework of humoral medicine. Their treatises described breast cancer as a "scirrhus" or hard tumor with black bile as its cause and prescribed dietary moderation, leeching and topical lead or arsenic preparations.

Surgery was generally discouraged unless the tumor was small and non-ulcerated, since bleeding was thought to "stir the bile." These texts codified centuries of humoral wisdom into academic orthodoxy.



The Early Renaissance (1300 to 1500)

By the late medieval and early Renaissance periods, surgeons such as Guy de Chauliac (c. 1300–1368), Henri de Mondeville and John of Arderne began to describe practical surgical management of breast tumors. Guy de Chauliac's *Chirurgia Magna* (1363) classified cancers by stage and recommended excision of the tumor "to the healthy tissue" when possible, followed by cauterization. He echoed Celsus in warning that complete removal was seldom curative. Nevertheless, the detailed surgical manuals of this era—often written in vernacular languages—reflected an emerging empiricism, emphasizing observation and manual skill over humoral abstraction.

Cancer as a Moral and Mystical Disease

Throughout antiquity and the Middle Ages, cancer carried powerful moral, religious and symbolic connotations. It was described as a punishment for sin, a visible mark of divine displeasure, or a corruption of feminine virtue. The "crab" metaphor extended beyond anatomy to represent malignancy as moral decay, its claws emblematic of evil's inescapable grasp.

Pilgrimages, relics and prayer were often prescribed alongside purges and potions. This duality—spiritual affliction and physical pathology—characterized pre-Renaissance thinking about breast cancer and persisted into early modern Europe.

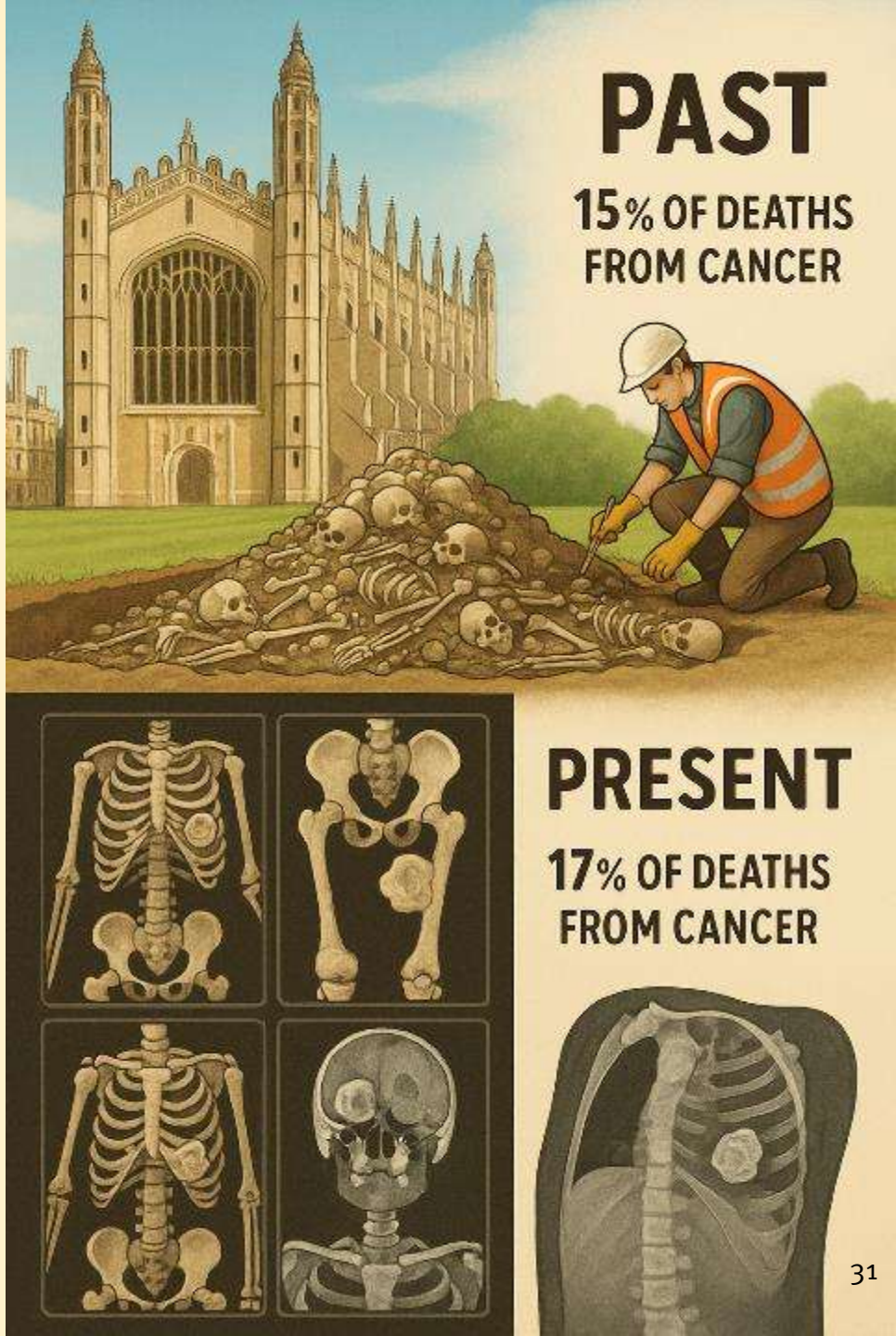
The More Things Change The More They Stay the Same

Perhaps one of the more interesting tidbits I ran into was a study on the incidence of cancer in England in the period from 500 C.E. to 1600 C.E. Piers Mitchell and colleagues from the Department of Archaeology at Cambridge University decided to analyze 143 skeletons from six cemeteries in England (6th to 16th Centuries).

Visual inspection coupled with screening using both plain radiographs and computed tomography scans was used to detect malignant lesions. They estimate that approximately 15% of deaths in this era were caused by malignant or metastatic cancer. See Mitchell et al. (2021).

Interestingly, today, it is estimated that 17% of deaths are caused by cancer. The main difference, however, was that the average English lifespan in the Medieval period was 30 years of age whereas today it is close to 80.

This is, in part, a reflection of changes in childhood mortality but I am quite struck by the basic sense that cancer has been with us since time immemorial and that its impact on our society may not have changed that much.



The 1500 to 1875 Period: The Scientific Revolution Arrives

At the dawn of the sixteenth century, European medicine remained largely tied to Galen's system of the four humors: blood, phlegm, yellow bile and black bile. Breast cancer was attributed to an excess of black bile – whatever that might have been.

Disease—particularly cancer—was explained as an imbalance of these bodily fluids, an idea that was obviously at complete variance with any sense of today's scientific understanding.

The Renaissance revival of anatomy did not immediately overturn humoralism but began to provide it with a material vocabulary.

Dissection, previously taboo, was practiced systematically in Italy—by Vesalius, Falloppio and their students—and slowly extended to pathological anatomy. Surgeons gained a clearer understanding of breast structure: ducts, glands and fibrous tissue. Yet they still interpreted these discoveries through the lens of fluid imbalance and moral symbolism (black bile signifying sorrow, aging and the waning of fertility).

What changed most during this era was not the theory but the sensibility: a new faith in observation, case description and illustration. Books such as Scultetus's *Armamentarium Chirurgicum* (1655) turned surgery into an empirical craft rather than a derivative of ancient authority. Pain, mortality and deformity remained omnipresent, but the surgeon's identity evolved—from artisan to proto-scientist. The Renaissance thus marks the moment when cancer began to be seen and described, even if not yet understood.

Enlightenment Medicine and the Birth of the Local Disease Model (1650–1775)

The Enlightenment's hallmark was confidence in reason and mechanism. By the late seventeenth century, the notion that disease could arise from localized structural change, rather than invisible humors, was gaining acceptance. Dissection, autopsy and the microscope—though rudimentary—invited the study of lesions as tangible entities.

A crucial conceptual shift occurred: cancer came to be viewed

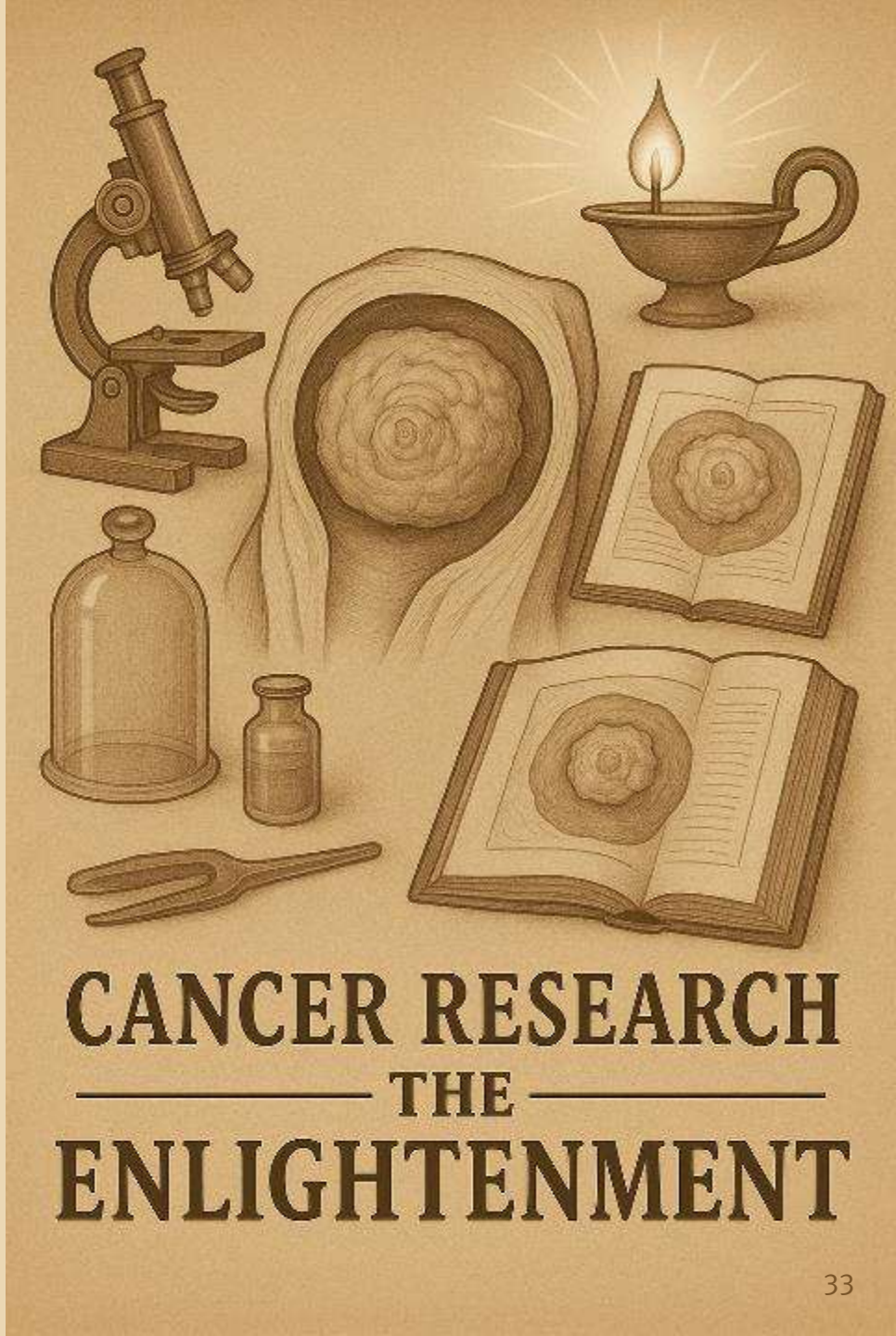
Taxonomy of Cancer Changes

as a *local* process that could spread through contiguous tissues or lymphatic channels. This idea replaced the Galenic vision of a *systemic* poison with a model of invasion. Surgeons began to argue that if a tumor originated locally, it might be cured by complete excision. Hence the logic of the mastectomy emerged long before anesthesia or antisepsis.

At the same time, Enlightenment rationalism fostered a new taxonomy of disease. Physicians classified cancers by stage, texture and appearance—scirrhous, medullary, ulcerated—prefiguring modern pathology. Yet this enthusiasm for classification coexisted with fatalism. Even as they learned to name and cut tumors, eighteenth-century practitioners recognized that recurrence was the rule, not the exception. Their increasing precision made cancer less magic but still, of course, tragic.

Parallel to this anatomical turn was an ethical and gendered transformation. The breast, symbolically tied to femininity, motherhood and virtue, became a privileged site for debates over pain, modesty and the limits of surgery.

Enlightenment case reports often dwelled on the courage of women who "submitted to the knife," turning the operation into a moral exercise that was reinforced both by scientific authority and gender ideals.



The Clinical Revolution (1800–1875)

The nineteenth century revolutionized the understanding of breast cancer through four intertwined developments: clinical observation, anesthesia, antisepsis and microscopic pathology.

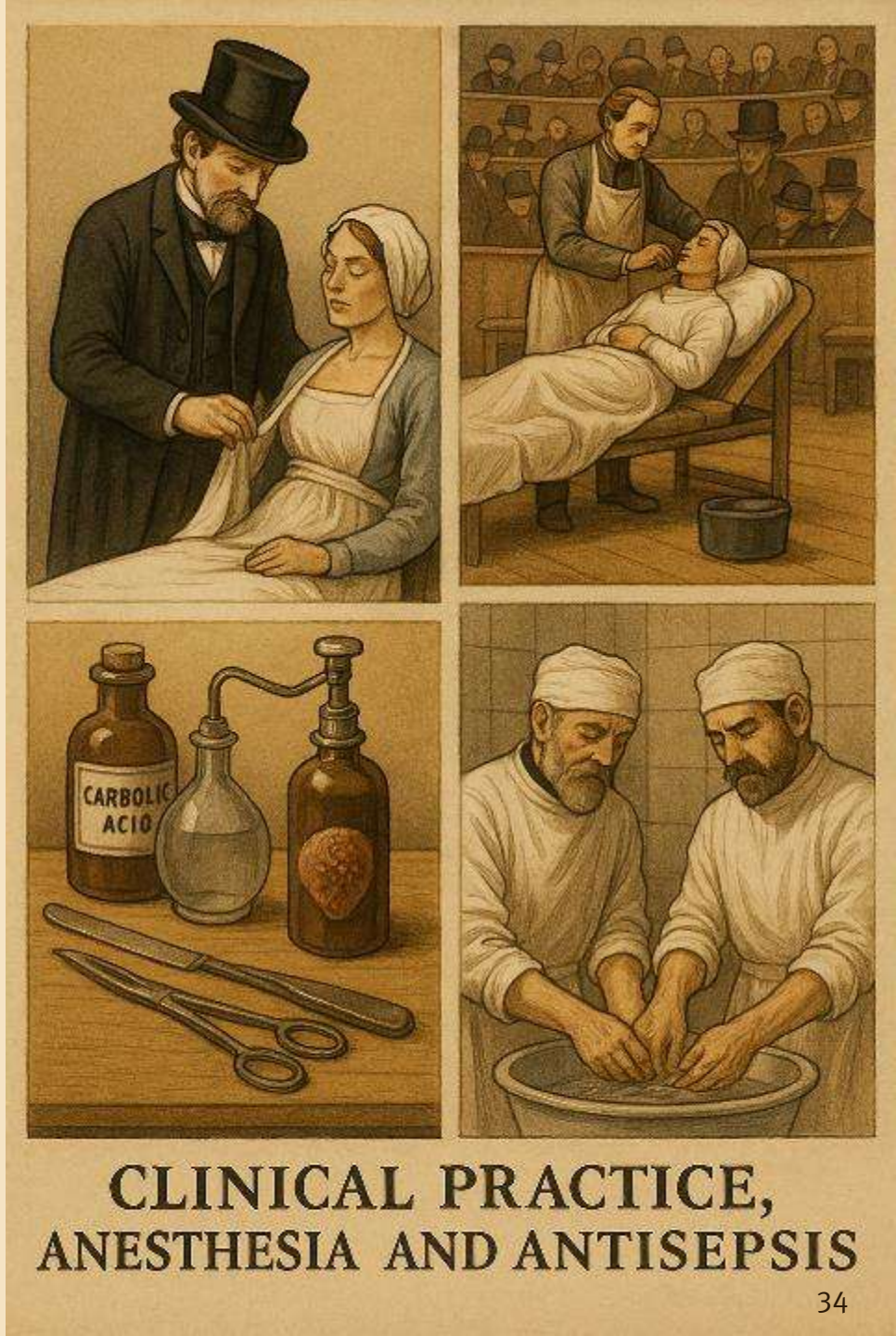
1. The Clinical Revolution

The hospital medicine of Paris and London—typified by the Hôtel-Dieu and St. Bartholomew's—transformed bedside observation into a systematic science.

Physicians compiled vast case records linking symptoms to autopsy findings. Cancer, once a metaphor for corruption, became a diagnosable lesion with predictable stages. This period witnessed the professionalization of surgery: specialized wards, surgical instruments and teaching hospitals institutionalized operative care. The mastectomy, though brutal, became standardized. Mortality remained high largely because of infection rather than surgical incompetence.

2. The Technological Revolution

Two inventions—anesthesia (1846) and antisepsis (1860s)—redefined what surgery could achieve. Ether and chloroform allowed antiseptic methods dramatically reduced postoperative infection. For the first time, surgeons could attempt wide excision of tumors and explore axillary glands.



The Mid-1800's: Cell Biology

These advances made breast cancer surgery a frontier for demonstrating scientific progress.

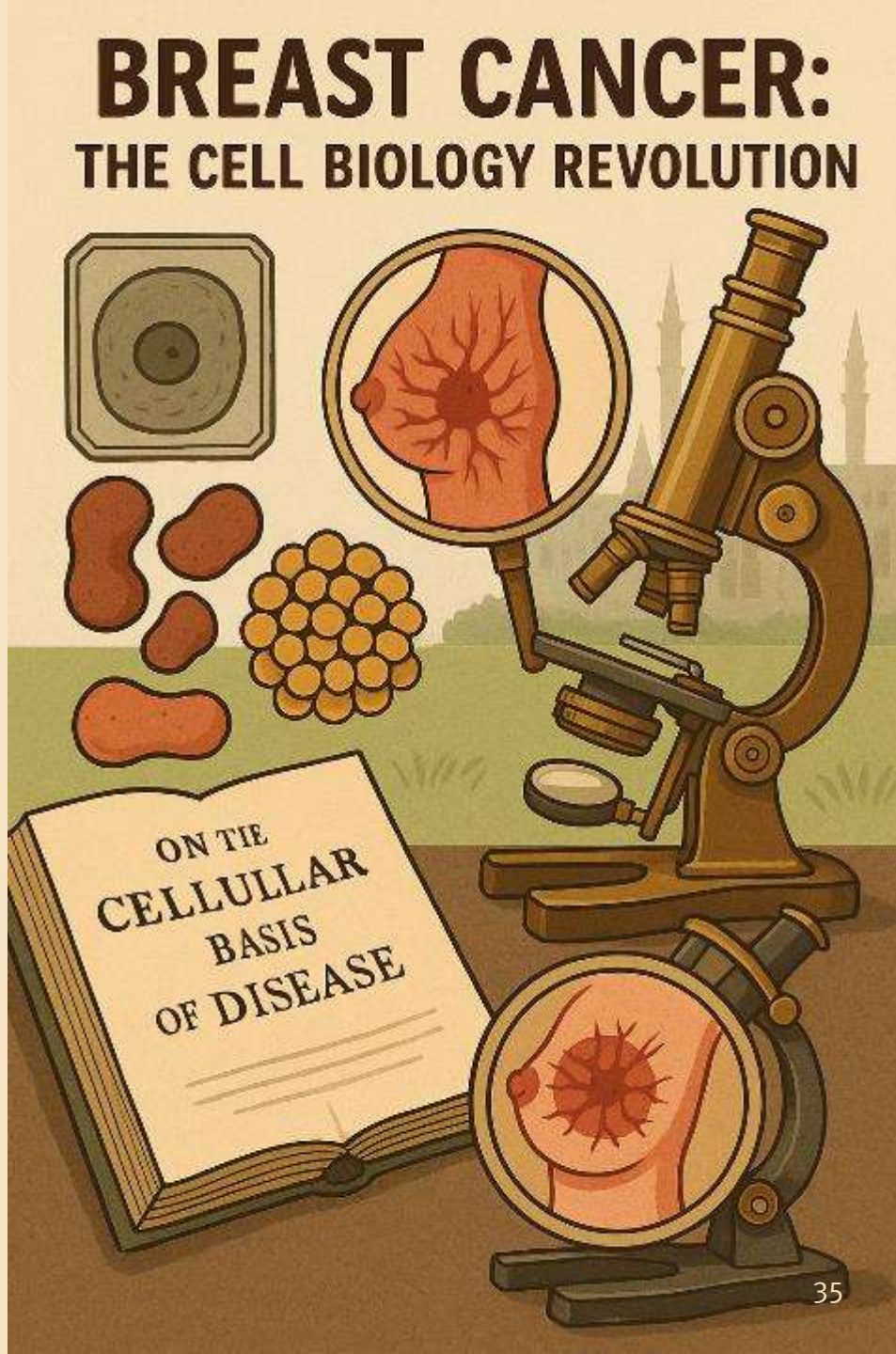
Yet recurrence persisted, keeping alive the debate between "local" and "constitutional" theories of disease.

3. The Revolution in Cellular Biology

The microscope finally displaced humoralism altogether. German histologists—Johannes Müller, Rudolf Virchow and others—showed that tumors were composed of abnormal proliferations of normal cells. Virchow's dictum *omnis cellula e cellula* ("every cell from a cell") established that cancer arose from within the body's tissues, not from foreign contamination or mystical humors. This cellular understanding created the foundation for modern pathology and oncology.

Breast cancer became the paradigmatic malignant epithelial tumor. Physicians could now correlate clinical course, histology and outcome.

Paget's later description of nipple carcinoma (1874) epitomized the union of clinic and microscope: the disease's surface manifestation was explained by an underlying histologic process.



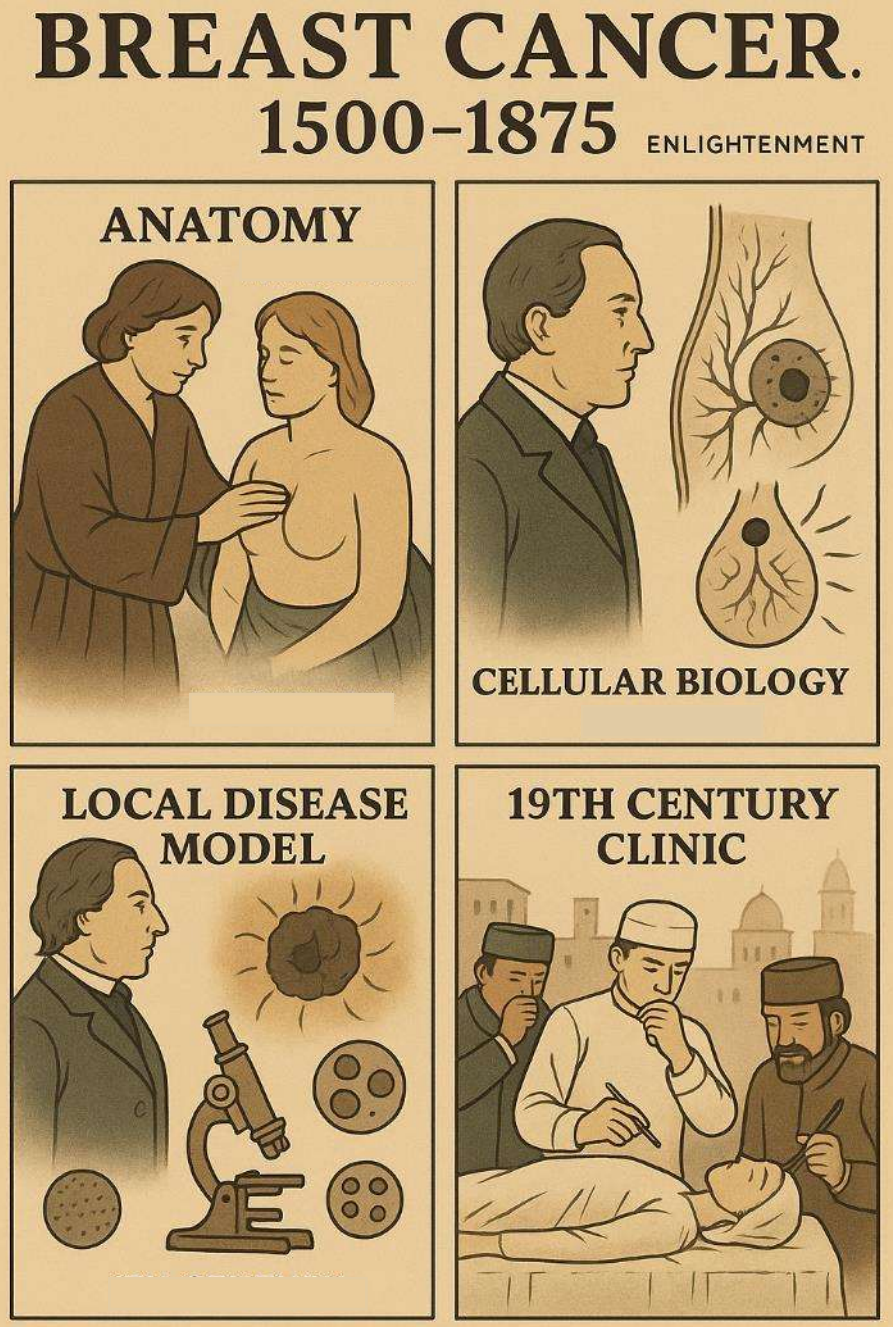
Where We Stood by 1875

Across the three centuries, the dominant transformation was the shift from systemic to local conceptions of disease. The Galenic model imagined cancer as a humor spread throughout the body; Enlightenment surgeons localized it in the breast; nineteenth-century pathologists located it in the cell. Each step compressed the scale of explanation—from the whole body to the organ, from the organ to the tissue and finally to the cell.

At the same time, surgery evolved from a despised manual trade to the leading expression of medical rationality. The cancer operation, with its drama and difficulty, symbolized the surgeon's new scientific legitimacy.

Yet this rise entailed paradox: as surgeons became more confident, operations became more radical and often more traumatic. Without anesthesia or antisepsis, cure rates remained minimal until the late 1800s, when Halsted's generation finally institutionalized "radical" resection with aseptic technique.

Perhaps most striking is the stability of outcome. From Renaissance to Victorian times, survival after mastectomy rarely exceeded a few years. The percentage of deaths attributable to cancer in skeletal remains or vital statistics changed little. Progress lay not in cure but in understanding—an intellectual conquest of meaning rather than mortality.



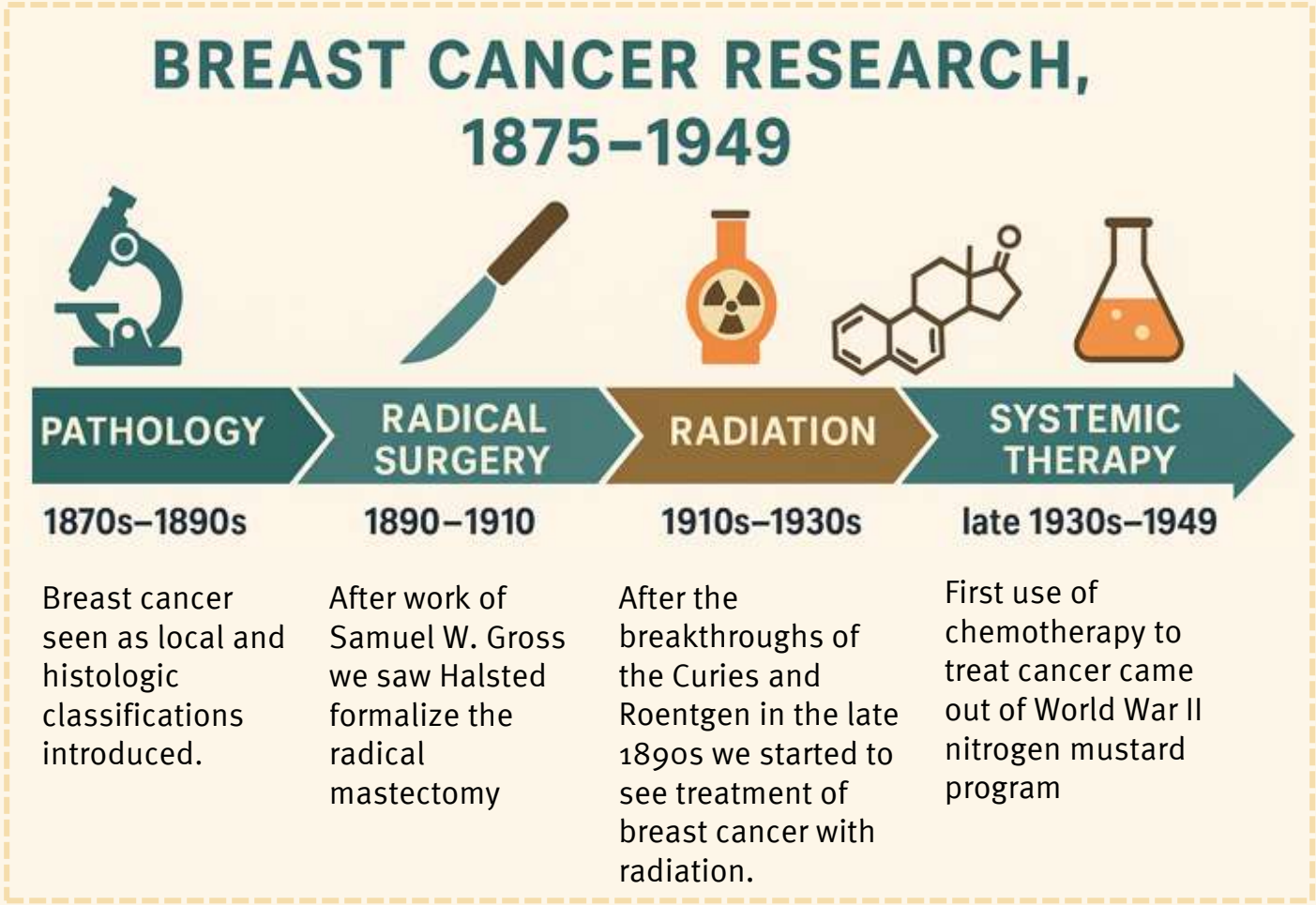
1875 to 1949: A Period of Transformation

The 19th century was a transformative period for biology, marked by major advances in our understanding of heredity, cell biology and evolution. These advances profoundly impacted the understanding of cancer biology and how we treat breast cancer.

You will recall from our earlier discussions that as late as 1890 the prognosis for breast cancer patients was nearly hopeless. Further, it had been this way for thousands of years. Despite medical innovation in many areas, presenting with breast cancer in 1890 would have a worse prognosis than the discovery of advanced pancreatic cancer today.

The only option to contemplate at the time was surgery – which had gotten better – perhaps best perfected by Samuel W. Gross.

Sometimes change in medicine can be rapid. This is exactly what happened in the 1890s. First, Halsted improved on the mastectomy. Radical or not, the Halsted mastectomy was associated with higher survival. Second, after Roentgen's discovery of X-rays, there was the first therapeutic application to breast cancer by Emil Grubbé in 1896. Third, Marie Curie discovered radioactivity in 1899 – which was to transform breast cancer care by the 1920s. Fourth, Beatson discovered that an oophorectomy (removal of ovaries) could be associated with a breast cancer cure.



Turn of the Century Brought Hope

Collectively, these turn of the century events brought the first real hope to breast cancer patients in history. And, importantly, the foundations built in the 19th century helped to buttress the amazing progress since. Advances in pathology and clinical institutionalization led to the rapid growth of capabilities at key hospitals like St. Bartholomew's in London, Charité in Berlin and Johns Hopkins and Memorial in the U.S.

Key points of progress came in the 1930s and the 1940s. The radiation dose that could be delivered to a patient went up substantially in the late 1920s so that radium treatment began to become more effective.

Geoffrey Keynes findings for radiation over surgery in 1932 were cause for substantial hope – even if they did not persuade his peers at the time.

The next big steps were publications in the 1940s on chemotherapy and hormonal therapy. Alexander Haddow's finding in 1944 that hormonal therapy could substantially improve outcomes in breast cancer was a bolt out of the blue for patient survival and began a period of major advances in this area that continues even today. Alfred Gilman's 1946 publication of secret WWII work at Yale on chemotherapy was also quite unexpected and presaged major breakthroughs to come from chemical therapy for breast cancer in the next sixty years.

1894

William Halsted

Perfected the radical mastectomy

1896

George Beatson

An oophorectomy could cure breast cancer

1912

Albert Salomon

Discovers that X-rays can find cancer in breasts

1932

Geoffrey Keynes

Radium can cure breast cancer

1944

Alexander Haddow

Finds life-saving potential of synthetic estrogen therapy

1946

Alfred Gilman

First publication on chemotherapy for cancer

Section 4:

The Last 75 Years:

An Explosion in Understanding and Treatment of Breast Cancer

(1950 to 2025)

Entry Way to Memorial Hospital for Cancer Treatment (Built in 1938)
MSK, New York, NY October 2025

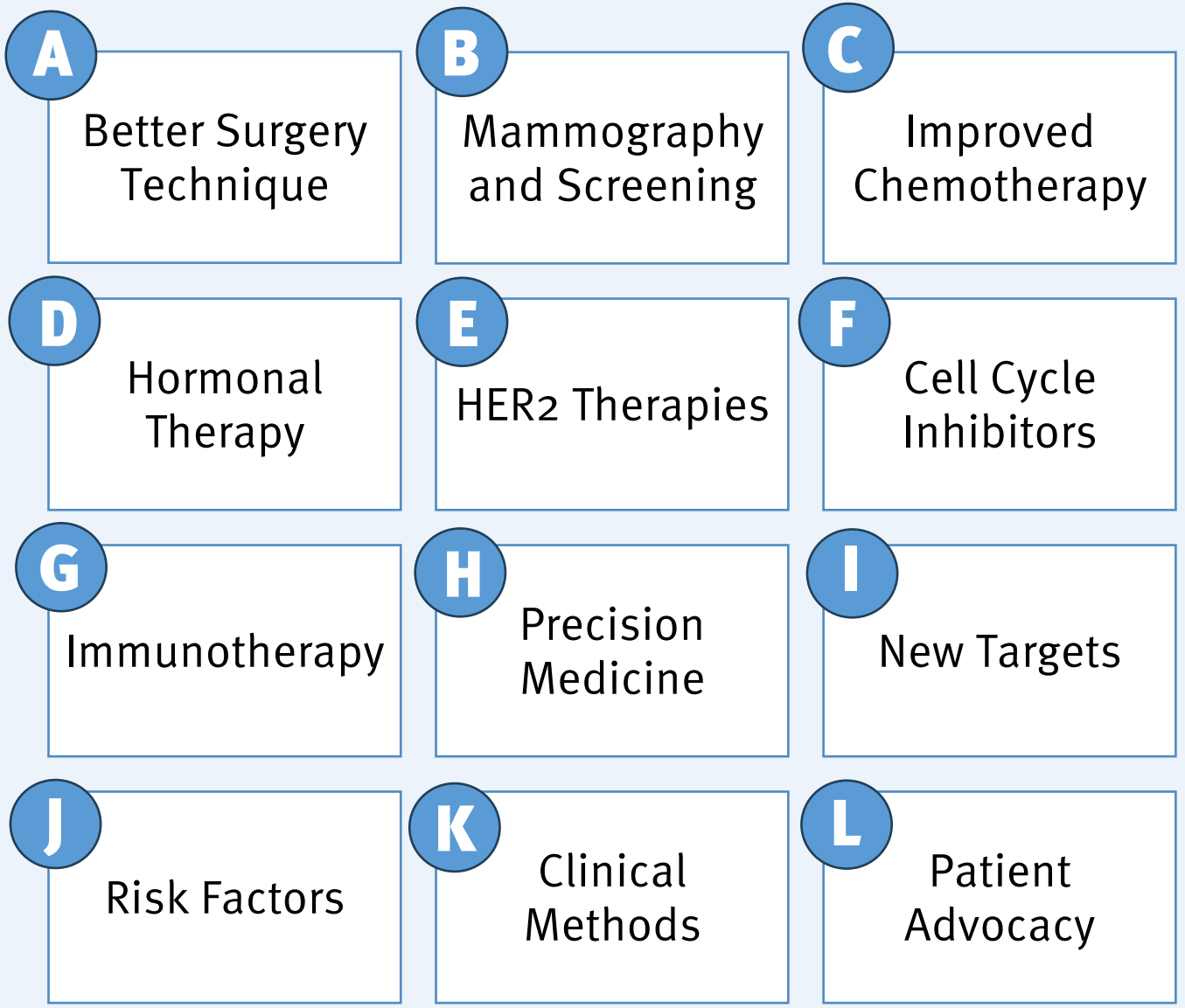
Key Areas of Breast Cancer Progress in Last 75 Years

The field of breast cancer research has been revolutionized in the last 75 years in ways that were unimaginable at the start of the 1950s.

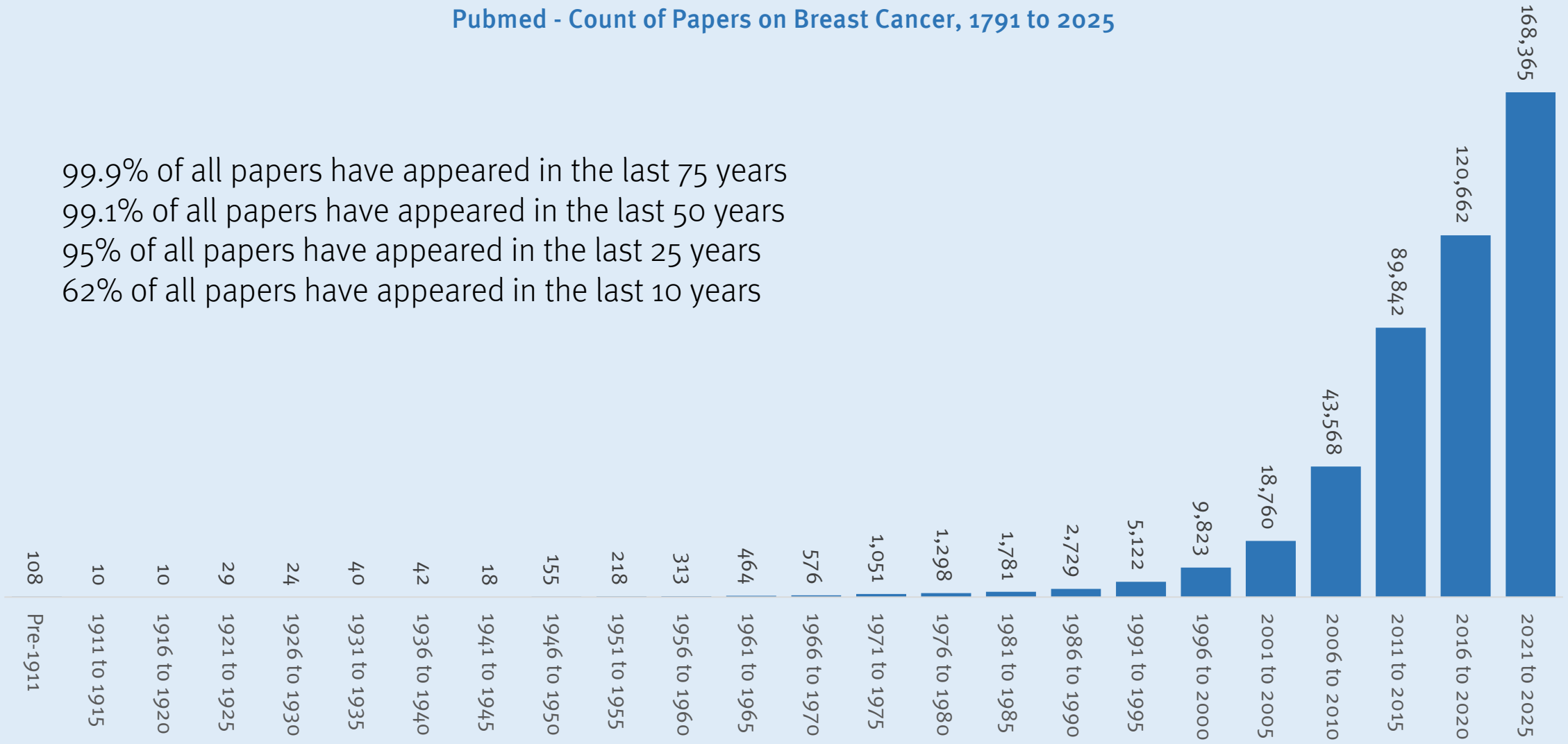
Breast cancer has gone from a disease with abysmal survival to one that can be usually overcome with appropriate therapy. The key has been precision therapy. Hippocrates once said “It is more important to know what sort of person has a disease than to know what sort of disease a person has.”

As illustrated on the next page, nearly all papers ever written on breast cancer have come in the last 75 years.

The research areas that have been most important scientifically, in our view, are shown at right:



Breast Cancer Research Has Taken Off Since 1950



Source: Pubmed. Counted papers that either referenced breast and cancer in title or breast and carcinoma in the title.

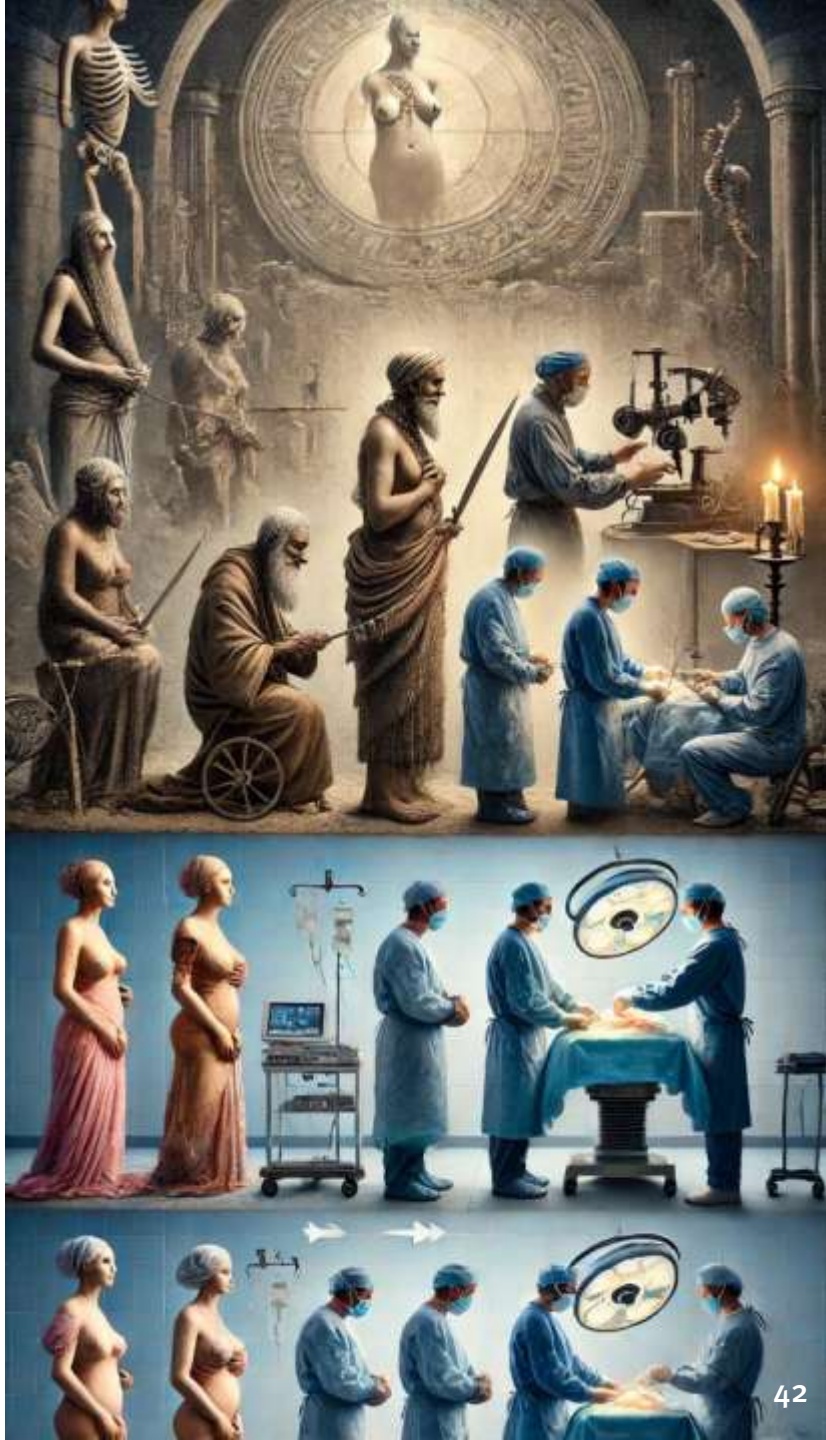
Section 4.A: Surgery Technique

Humanity's first instinct when spotting a cancer is to remove it with a knife. To cut it out. Get rid of it. Tumor - be gone.

Thus, we have records going back two thousand years showing that physicians attempted to excise breast tumors with mastectomy. As one peruses the pages in this report it becomes clear that it was understood early on that this could be a fruitless exercise in advanced cases. Importantly, the understanding of the lymphatic structure of breast tumors expanded in the 18th and 19th centuries which improved thinking on how to maximize the chance of survival – the basic message was the more you remove, the better.

Of course, the unfortunate effect of radical mastectomy can be devastating for a woman's bodily integrity and ability to function. The most important progress of the last century has been the retreat from the radical operation perfected by Halsted and the return to a less invasive surgery (lumpectomy) that could be accompanied by chemotherapy, radiation or both. This has become a mainstay of today's breast cancer surgical technique.

We saw a 60-year battle play out between advocates of radical mastectomy and less invasive surgery. Despite overwhelming evidence against it, the radical operation held on due to ingrained practices among surgeons until less than 50 years ago.



Milestones in Breast Cancer Surgery

~250 AD Leonidas – First description of breast cancer surgery

660 AD Aetius of Amida – Detailed description of mastectomy

1363 Guy de Chauliac – Only operate on small breast tumors

1600 Gabriele Falloppio – Caution on surgery

1656 Scultetus– Enthusiastic practitioner of mastectomy

1697 Helvetius – First recorded examples of success in mastectomy

1831 James Syme – Detailed instructions on mastectomy

1845 Carpentier-Mericourt – Managed hemorrhage and infection

1867 Charles Moore – Showed full tumor removal needed to avoid recurrence

1880 Samuel W. Gross – Advocated radical mastectomy

1894 William Halsted – Perfected and taught the radical mastectomy

1923 Geoffrey Keynes – Showed radiation had lower recurrence than mastectomy

Milestones in Breast Cancer Surgery (continued)

1948 McWhirter – Continued to show radiation better than mastectomy

1959 Diana Brinkley – Showed that mastectomy not better than radiation

1961 George Crile – For Stage I cancer lumpectomy had better survival than radical mastectomy

1967 Vera Peters – Lumpectomy associated with survival similar to mastectomy

1972 John Madden – Preservation of pectoral muscles still worked in mastectomy

1981 Veronesi – First clinical trial results to show survival similar with lumpectomy and radiation vs radical

1985 Bernard Fisher – Second large trial to show that lumpectomy results similar to full mastectomy

1997 Veronesi – Lymph node biopsy can help avoid axillary dissection

2002 Bernard Fisher– 20-year data from initial trial definitively supported lumpectomy

2011 Giuliano – Sentinel node dissection similar in survival as conducting an axillary dissection

What is so striking in this timeline is that lumpectomy did not become the standard of care in routine breast cancer surgery in the U.S. until around 1990. Practitioners of the radical mastectomy were slow to change and care guidelines did not shift until Fisher's large scale trial results in 1985 were published in the *New England Journal of Medicine*.

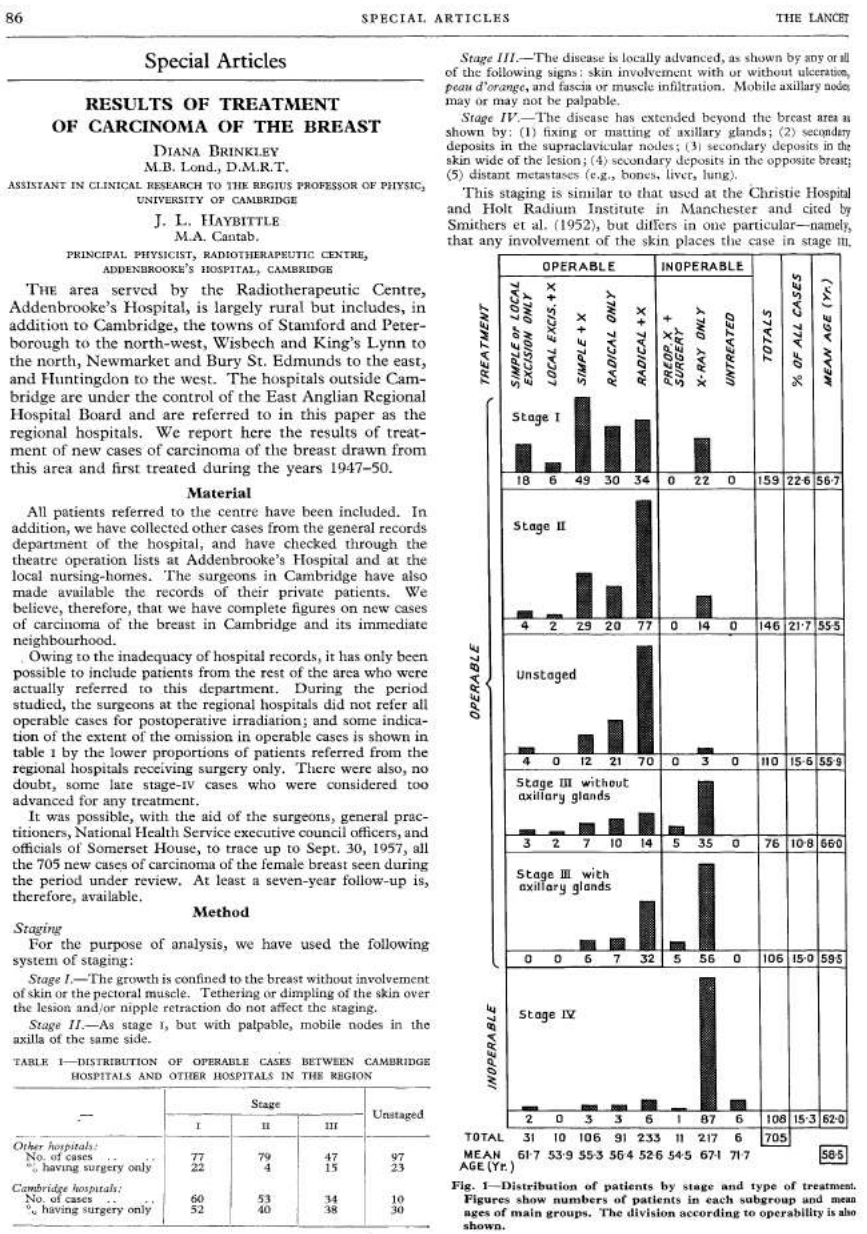
1959: Diana Brinkley

Showed that radiotherapy was associated with similar survival outcomes as surgery, casting doubt on radical mastectomy.

Diana Brinkley's 1959 paper, "Results of Treatment of Carcinoma of the Breast," published in *The Lancet*, brought rigorous statistical analysis and clinical follow-up to bear on a question that had long divided the surgical and radiotherapeutic communities: what treatment provided the best long-term outcomes for women with operable breast cancer.

Working within Britain's evolving National Health Service and drawing on large institutional data, Brinkley compared the results of radical mastectomy, simple mastectomy with postoperative radiotherapy and primary radiotherapy alone, focusing on survival, recurrence rates and quality of life. Her results demonstrated that radiotherapy, when appropriately administered, could achieve survival outcomes comparable to those of surgery, especially for early-stage cancers, while sparing many women from the physical and psychological trauma of radical operations.

Brinkley's broader contributions to breast cancer extended beyond this single paper. As one of the early female leaders in British oncology and radiotherapy, she played a critical role in integrating radiation therapy into mainstream breast cancer treatment, emphasizing precision, dosage planning and the importance of long-term clinical follow-up. Her work helped validate the approach pioneered by earlier figures such as Robert McWhirter, reinforcing that radiotherapy could serve not merely as palliation but as a curative modality. Brinkley's careful outcome studies influenced treatment planning in the 1960s and 1970s, paving the way for the combined-modality strategies that became standard practice later in the century.



86 SPECIAL ARTICLES THE LANCET

Special Articles

RESULTS OF TREATMENT OF CARCINOMA OF THE BREAST

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THE area served by the Radiotherapeutic Centre, Addenbrooke's Hospital, is largely rural but includes, in addition to Cambridge, the towns of Stamford and Peterborough to the north-west, Wisbech and King's Lynn to the north, Newmarket and Bury St. Edmunds to the east, and Huntingdon to the west. The hospitals outside Cambridge are under the control of the East Anglian Regional Hospital Board and are referred to in this paper as the regional hospitals. We report here the results of treatment of new cases of carcinoma of the breast drawn from this area and first treated during the years 1947–50.

Material

All patients referred to the centre have been included. In addition, we have collected other cases from the general records department of the hospital, and have checked through the theatre operation lists at Addenbrooke's Hospital and at the local nursing-homes. The surgeons in Cambridge have also made available the records of their private patients. We believe, therefore, that we have complete figures on new cases of carcinoma of the breast in Cambridge and its immediate neighbourhood.

Owing to the inadequacy of hospital records, it has only been possible to include patients from the rest of the area who were actually referred to this department. During the period studied, the surgeons at the regional hospitals did not refer all operable cases for postoperative irradiation; and some indication of the extent of the omission in operable cases is shown in table I by the lower proportions of patients referred from the regional hospitals receiving surgery only. There were also, no doubt, some late stage-IV cases who were considered too advanced for any treatment.

It was possible, with the aid of the surgeons, general practitioners, National Health Service executive council officers, and officials of Somerset House, to trace up to Sept. 30, 1957, all the 705 new cases of carcinoma of the female breast seen during the period under review. At least a seven-year follow-up is, therefore, available.

Method

Staging

For the purpose of analysis, we have used the following system of staging:

Stage I.—The growth is confined to the breast without involvement of skin or the pectoral muscle. Tethering or dimpling of the skin over the lesion and/or nipple retraction do not affect the staging.

Stage II.—As stage I, but with palpable, mobile nodes in the axilla of the same side.

Stage III.—The disease is locally advanced, as shown by any or all of the following signs: skin involvement with or without ulceration, *peau d'orange*, and fascia or muscle infiltration. Mobile axillary nodes may or may not be palpable.

Stage IV.—The disease has extended beyond the breast area as shown by: (1) fixing or matting of axillary glands; (2) secondary deposits in the supraclavicular nodes; (3) secondary deposits in the skin wide of the lesion; (4) secondary deposits in the opposite breast; (5) distant metastases (e.g., bones, liver, lung).

This staging is similar to that used at the Christie Hospital and Holt Radium Institute in Manchester and cited by Smithers et al. (1952), but differs in one particular—namely, that any involvement of the skin places the case in stage III.

TABLE I—DISTRIBUTION OF OPERABLE CASES BETWEEN CAMBRIDGE HOSPITALS AND OTHER HOSPITALS IN THE REGION

	Stage			Unstaged
	I	II	III	
Other hospitals:				
No. of cases	77	79	47	97
% having surgery only	22	4	15	23
Cambridge hospitals:				
No. of cases	60	53	34	10
% having surgery only	52	40	38	30

TREATMENT	OPERABLE					INOPERABLE					
	SIMPLE or LOCAL EXCISION ONLY	LOCAL EXCIS. + X	SIMPLE + X	RADICAL ONLY	RADICAL + X	PREOP. X + SURGERY	X-RAY ONLY	UNTREATED	TOTALS	% OF ALL CASES	MEAN AGE (Yr.)
OPERABLE — Stage I	18	6	49	30	34	0	22	0	159	22·6	56·7
OPERABLE — Stage II	4	2	29	20	77	0	14	0	146	21·7	55·5
OPERABLE — Unstaged	4	0	12	21	70	0	3	0	110	15·6	55·9
OPERABLE — Stage III without axillary glands	3	2	7	10	14	5	35	0	76	10·8	660
OPERABLE — Stage III with axillary glands	0	0	6	7	32	5	56	0	106	15·0	595
INOPERABLE — Stage IV	2	0	3	3	6	1	87	6	108	15·3	62·0
TOTAL	31	10	106	91	233	11	217	6	705		
MEAN AGE (Yr.)	61·7	53·9	55·3	56·4	52·6	54·5	67·1	71·7			585

Fig. 1—Distribution of patients by stage and type of treatment. Figures show numbers of patients in each subgroup and mean ages of main groups. The division according to operability is also shown.

Diana Brinkley, 1959, "Results of Treatment of Carcinoma of the Breast," (with John Haybittle), Lancet, January 10, 1959, Volume 273, pp. 86-90.
From the author's medical library.

1961: George Crile, Jr.

Showed clinical benefit of breast conserving surgery.

George Crile Jr.'s 1961 paper in *Annals of Surgery* presented was a highly influential paper that made the case against the radical mastectomy tradition established by Halsted. Crile compared outcomes in women treated at the Cleveland Clinic between 1953 and 1957, contrasting simple mastectomy (with limited or no radiation) versus radical or modified-radical operations with routine radiation.

His data—covering over 300 cases—showed that for Stage I breast cancer, three- to five-year survival after simple mastectomy (≈ 80% at 3 years, ≈ 68% at 5 years) was at least as good as or slightly better than that following radical procedures (≈ 75% and 59%, respectively). Local recurrence rates were similar (≈ 7%), but postoperative morbidity such as arm edema and shoulder limitation was dramatically lower after simple surgery. Crile concluded that aggressive nodal dissections and postoperative radiation did not improve survival and might even impair it by destroying lymphocytes essential to the body's immunologic defense against metastatic spread—a remarkably prescient idea.

He proposed that breast cancer, even when apparently localized, behaves as a systemic disease, thus justifying less mutilating surgery followed by adjuvant therapy or careful surveillance. The paper's final call was for randomized "blind" clinical trials to determine the optimal balance between survival and quality of life. This study, together with Crile's earlier 1955 popular essay on "The Overtreatment of Cancer," anticipated the paradigm later proven by Bernard Fisher's NSABP trials in the 1970s, which demonstrated that breast-conserving surgery with radiation achieves survival outcomes equivalent to radical mastectomy.

References: Ekmektzoglou (2009), Olson (2002, p. 107).

Simplified Treatment of Cancer of the Breast: *

Early Results of a Clinical Study

GEORGE CRILE, JR., M.D.

From the Department of General Surgery, The Cleveland Clinic Foundation, and The Frank E. Bunts Educational Institute, Cleveland, Ohio

I. Introduction

THERE is mounting evidence that conventional radical operations combined with radiation increase the morbidity of patients with breast cancer without increasing their survival rate above that of simpler treatments. Paterson and Russell's [7] double blind study in Manchester showed that radiation after radical mastectomy had no effect on survival or local recurrence rates of patients whose axillary nodes were involved, and it seemed actually to diminish the survival rate of patients whose nodes were not involved. Smith and Meyer,[9] and Williams, Murley and Curwen [10] have shown that the survival rate of patients treated by simple mastectomy is similar to that following radical operations or may be slightly higher. The blind study of Kaae and Johansen [3] shows no difference in the three- and five-year survival rates of patients treated by ultraradical mastectomy with internal mammary and supraclavicular node dissection, and patients treated by simple mastectomy and radiation. Finally, Mustakallio [6] has shown that in 127 patients local excision of small cancers followed by radiation therapy resulted in an 84 per cent rate of survival at five years and 72 per cent at ten years.

The results of the following study suggest that in favorable stages of breast cancer the early (3 to 6 years) results of treatment are just as good following simple operations with radiation used in only one-fourth of the cases as they are following more radical operations with radiation used in one-half of the cases. In clinical stage 1 cases, it is even possible that there is a slightly higher survival rate in patients treated by simple operations, usually without radiation, as compared with radical ones, with or without radiation. If such a difference actually exists, it is further evidence that in certain types of systemically metastasizing cancer we must pay less attention to the possible involvement of lymph nodes by tumor and more to the possible immunologic role of the lymphocytes in the nodes as a defense against the cancer cells that are circulating in the blood.

II. Materials and Methods

A. Plan of Study

In January, 1955, I decided to use simple mastectomy, usually without radiation therapy, as the standard treatment of most patients with cancers that had no clinical evidence of cancer beyond the breast. At the same time my colleagues in the Cleveland Clinic, who together did approximately the same number of breast operations as I did, continued in most cases to do the conventional radical operations and often added postoperative radiation. The stages of the disease, the size of the tumors, and the ages of the patients were similar in the simple mastectomy and the radical

* Presented before the Southern Surgical Association, Boca Raton, Florida, December 6–8, 1960.

George Criles, Jr., 1961, "Simplified Treatment of Cancer of the Breast" *Annals of Surgery*, May 1961, From the author's medical library.

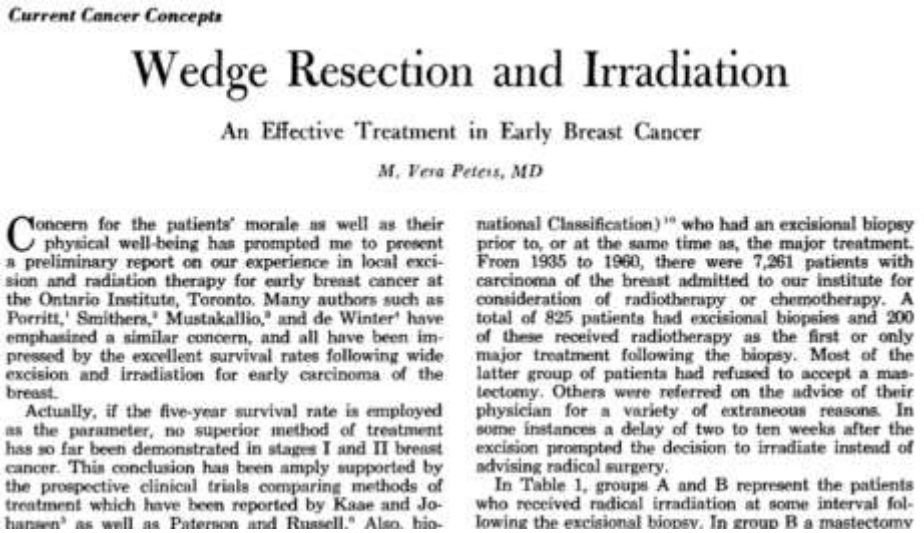
1967: Vera Peters

Showed that lumpectomy plus radiation was associated with similar survival as mastectomy plus radiation.

Mildred Vera Peters (1911–1993) was a pioneering Canadian oncologist and radiotherapist whose life and work profoundly reshaped the treatment of both Hodgkin lymphoma and breast cancer. Her mother's death from metastatic breast cancer in 1933 shaped her life's mission. Peters trained under Dr. Gordon Richards at Toronto General Hospital, a visionary radiologist who had treated her mother. Together, they began groundbreaking work in radiotherapy—culminating in Peters' landmark 1950 study demonstrating that Hodgkin lymphoma could be cured with radiation, a finding that revolutionized oncology. Through decades of meticulous clinical record-keeping at Toronto General and Princess Margaret Hospitals, she analyzed outcomes of thousands of women treated with simple mastectomy and radiotherapy, demonstrating survival rates equal to those of radical mastectomy but with far less disfigurement. Her seminal 1977 paper provided convincing evidence that breast-conserving surgery combined with radiation could cure early breast cancer. At a time when the Halsted radical mastectomy was considered untouchable surgical doctrine, Peters' data-driven research—later validated by Fisher and Veronesi—proved that compassion and science could coexist in cancer care. Her work laid the foundation for modern breast-conservation therapy, making her one of the most visionary figures in the history of radiation oncology and women's health.

References: Cowan (2010), Olson (2002, p. 107).

While her contributions were generally unheralded in the literature at the time, Peters substantial contribution to oncology research were commemorated in a 2020 Canadian postage stamp. Canada Post created a nice video worth watching on her life and contributions.



Current Cancer Concepts

Wedge Resection and Irradiation

An Effective Treatment in Early Breast Cancer

M. Vera Peters, MD

Concern for the patients' morale as well as their physical well-being has prompted me to present a preliminary report on our experience in local excision and radiation therapy for early breast cancer at the Ontario Institute, Toronto. Many authors such as Porritt,[1] Smithers,[2] Mustakallio,[3] and de Winter[4] have emphasized a similar concern, and all have been impressed by the excellent survival rates following wide excision and irradiation for early carcinoma of the breast.

Actually, if the five-year survival rate is employed as the parameter, no superior method of treatment has so far been demonstrated in stages I and II breast cancer. This conclusion has been amply supported by the prospective clinical trials comparing methods of treatment which have been reported by Kaae and Johansen[5] as well as Paterson and Russell.[6] Also, bio-

national Classification)[10] who had an excisional biopsy prior to, or at the same time as, the major treatment. From 1935 to 1960, there were 7,261 patients with carcinoma of the breast admitted to our institute for consideration of radiotherapy or chemotherapy. A total of 825 patients had excisional biopsies and 200 of these received radiotherapy as the first or only major treatment following the biopsy. Most of the latter group of patients had refused to accept a mastectomy. Others were referred on the advice of their physician for a variety of extraneous reasons. In some instances a delay of two to ten weeks after the excision prompted the decision to irradiate instead of advising radical surgery.

In Table 1, groups A and B represent the patients who received radical irradiation at some interval following the excisional biopsy. In group B a mastectomy

Vera Peters, 1967, "Wedge Resection and Irradiation," JAMA, 200(2): pp. 144-145.

1972: John Madden

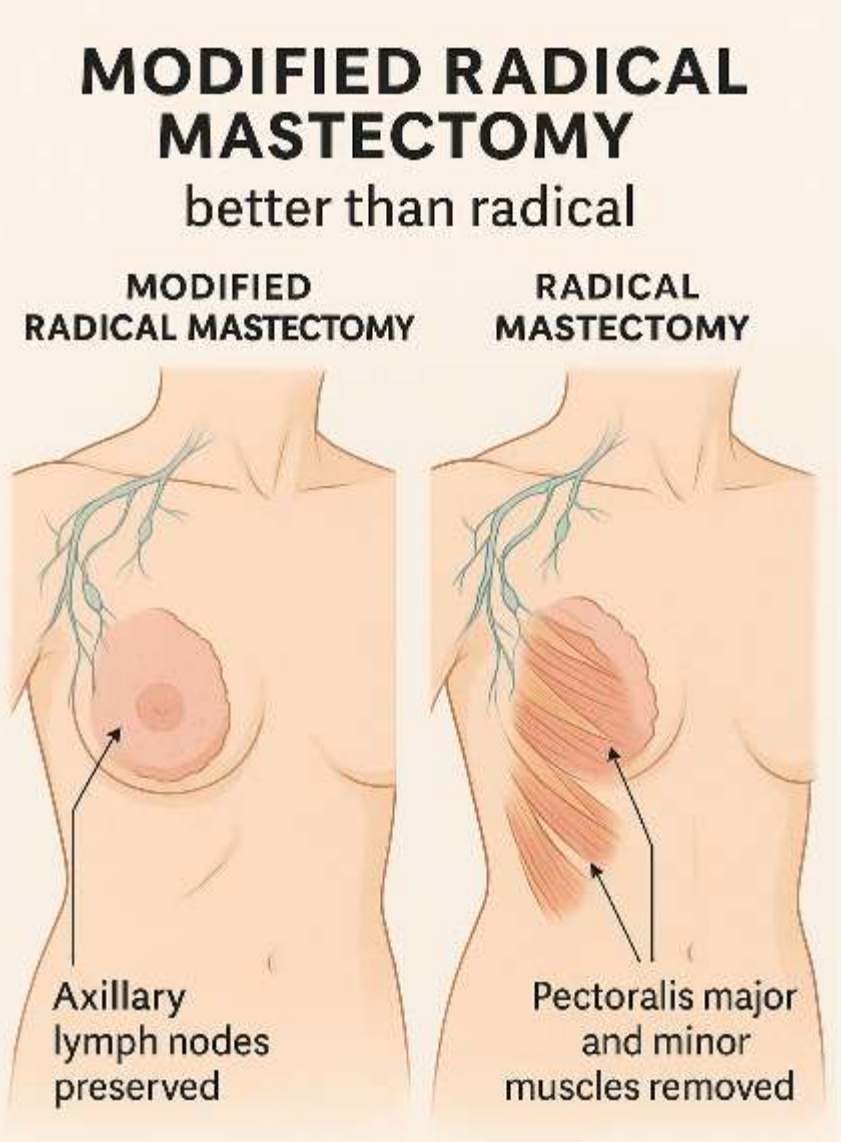
Showed that a less invasive mastectomy, like Patey's operation, worked just as well as a full mastectomy.

John L. Madden made a significant contribution to breast-cancer surgery with his 1972 paper "Modified Radical Mastectomy" (*Annals of Surgery*, 175(5):624-634) in which he described a more conservative surgical approach for operable breast cancer.

In this paper, Madden reported on his series of patients undergoing a modified radical mastectomy in which the breast and axillary lymph nodes were removed but with preservation of both the pectoralis major and minor muscles, rather than the traditional radical mastectomy with removal of chest wall musculature. He emphasized that this approach allowed adequate oncologic clearance of the axilla while reducing morbidity — namely less chest-wall deformity, better shoulder function and improved cosmetic outcomes.

The implications of Madden's work were substantial for breast-cancer treatment. By demonstrating that a less disfiguring operation could achieve local control of axillary disease while preserving chest musculature, he helped shift surgical practice away from the more radical, debilitating operations of earlier eras (such as those by William Halsted) toward more function-preserving approaches. Over time, the principle of balancing oncologic safety with preservation of form and function paved the way for further de-escalation of surgery—including breast-conserving therapy, sentinel-node biopsy and less extensive axillary surgery. As a result, Madden is frequently credited with helping to define the "current standard" for radical mastectomy in cases where mastectomy (rather than conservative surgery) remains necessary.

While Madden's new approach was widely adopted in Europe, Halsted's radical mastectomy held sway in the U.S. for many years to come.



John Madden, Modified Radical Mastectomy, *Annals of Surgery*, May 1972, Volume 175, pp. 624-634. From the author's medical library.

1981: Umberto Veronesi

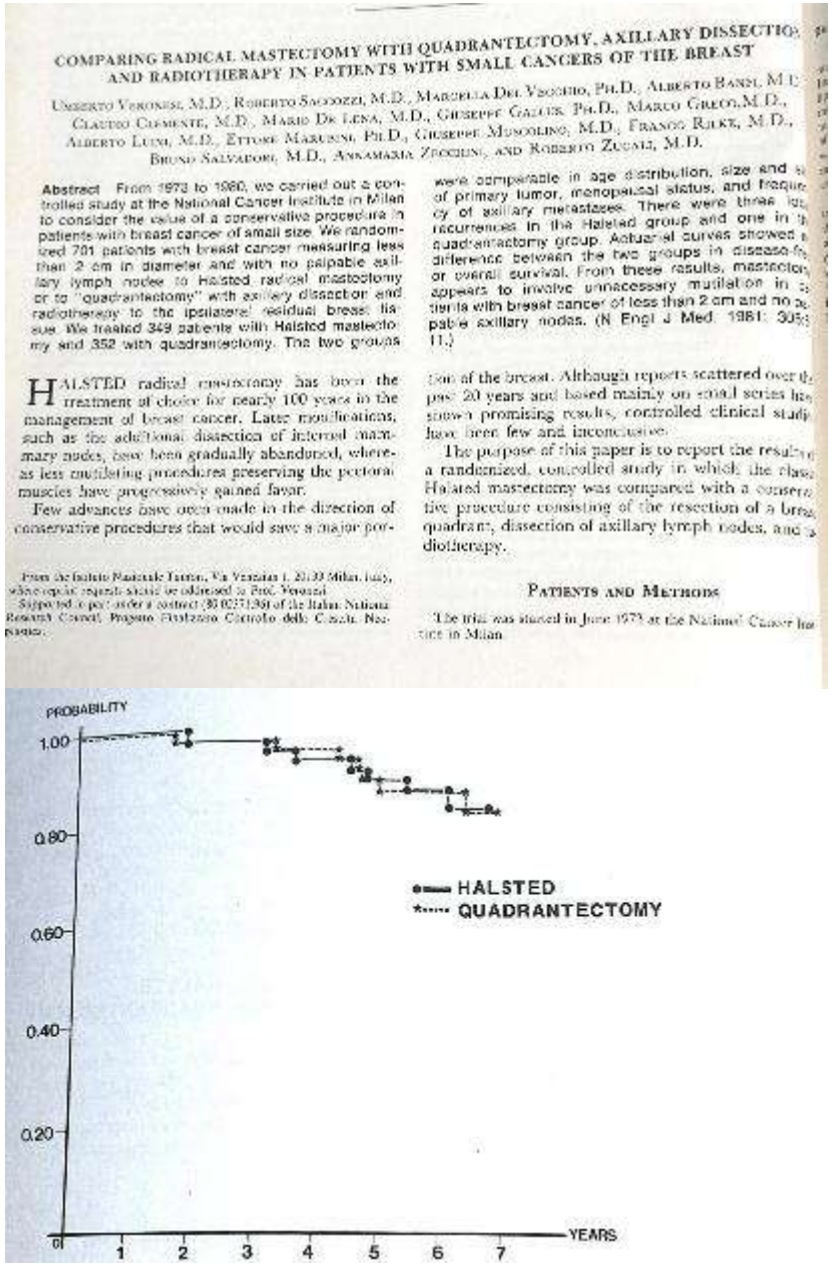
Showed no difference in survival among patients receiving a lumpectomy, when properly followed by radiation, relative to total mastectomy.

Umberto Veronesi (1925–2016) was an Italian surgical oncologist whose work fundamentally changed the management of early-stage breast cancer. His landmark 1981 paper in the *New England Journal of Medicine*, titled "Comparing Radical Mastectomy with Quadrantectomy, Axillary Dissection and Radiotherapy in Early Breast Cancer," reported the results of a randomized clinical trial involving over 700 women. Veronesi demonstrated that breast-conserving surgery (quadrantectomy, essentially a lumpectomy) followed by radiation was as effective as radical mastectomy in terms of overall survival and local recurrence. This study provided the first rigorous, prospective, long-term data showing that less mutilating surgery did not compromise cure rates, definitively overturning the century-old Halstedian paradigm of radical mastectomy. The *NEJM* paper established the foundation for breast-conserving therapy as the new standard of care, influencing treatment guidelines worldwide.

Veronesi's European work coincided with that of Bernie Fisher in the U.S. on the same topic. Both authors found that lumpectomy could achieve the same results in survival as a mastectomy. Fisher went on to show that post-operative radiation was not necessary.

Beyond this pivotal publication, Veronesi's broader contributions to breast cancer encompassed decades of innovation in surgical minimalism, multidisciplinary care and patient-centered oncology. As founder of the European Institute of Oncology (IEO) in Milan, he advanced research on sentinel lymph node biopsy, intraoperative radiotherapy and the biology of breast cancer subtypes. Veronesi was also a champion of ethics and quality of life in cancer care, emphasizing that effective treatment must preserve both survival and dignity.

References: Ades (2017), Ekmektzoglou (2009).



COMPARING RADICAL MASTECTOMY WITH QUADRANTECTOMY, AXILLARY DISSECTION AND RADIOTHERAPY IN PATIENTS WITH SMALL CANCERS OF THE BREAST

UMBERTO VERONESI, M.D., ROBERTO SACCOZZI, M.D., MARCELLA DEL VECCHIO, PH.D., ALBERTO BANFI, M.D., CLAUDIO CLEMENTE, M.D., MARIO DE LENA, M.D., GIUSEPPE GALLUS, PH.D., MARCO GRECO, M.D., ALBERTO LUINI, M.D., ETTORE MARUBINI, PH.D., GIUSEPPE MUSCOLINO, M.D., FRANCO RILKE, M.D., BRUNO SALVADORI, M.D., ANNAMARIA ZECCHINI, AND ROBERTO ZUCALI, M.D.

Abstract From 1973 to 1980, we carried out a controlled study at the National Cancer Institute in Milan to consider the value of a conservative procedure in patients with breast cancer of small size. We randomized 701 patients with breast cancer measuring less than 2 cm in diameter and with no palpable axillary lymph nodes to Halsted radical mastectomy or to "quadrantectomy" with axillary dissection and radiotherapy to the ipsilateral residual breast tissue. We treated 349 patients with Halsted mastectomy and 352 with quadrantectomy. The two groups were comparable in age distribution, size and site of primary tumor, menopausal status, and frequency of axillary metastases. There were three local recurrences in the Halsted group and one in the quadrantectomy group. Actuarial curves showed no difference between the two groups in disease-free or overall survival. From these results, mastectomy appears to involve unnecessary mutilation in patients with breast cancer of less than 2 cm and no palpable axillary nodes. (N Engl J Med 1981; 305: 6-11.)

HALSTED radical mastectomy has been the treatment of choice for nearly 100 years in the management of breast cancer. Later modifications, such as the additional dissection of internal mammary nodes, have been gradually abandoned, whereas less mutilating procedures preserving the pectoral muscles have progressively gained favor.

Few advances have been made in the direction of conservative procedures that would save a major portion of the breast. Although reports scattered over the past 20 years and based mainly on small series have shown promising results, controlled clinical studies have been few and inconclusive.

The purpose of this paper is to report the results of a randomized, controlled study in which the classic Halsted mastectomy was compared with a conservative procedure consisting of the resection of a breast quadrant, dissection of axillary lymph nodes, and radiotherapy.

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Supported in part under a contract (83.00771.56) of the Italian National Research Council, Progetto Finalizzato Controllo delle Cisti, Neoplasie.

PATIENTS AND METHODS

The trial was started in June 1973 at the National Cancer Institute in Milan.

Umberto Veronesi et al., 1982, "Comparing Radical Mastectomy with Quadrantectomy, Axillary Dissection and Radiotherapy in Patients with Small Cancers of the Breast," NEJM, July 2, 1981, Volume 305, pp. 6-11. From the author's medical library.

1985: Bernard Fisher

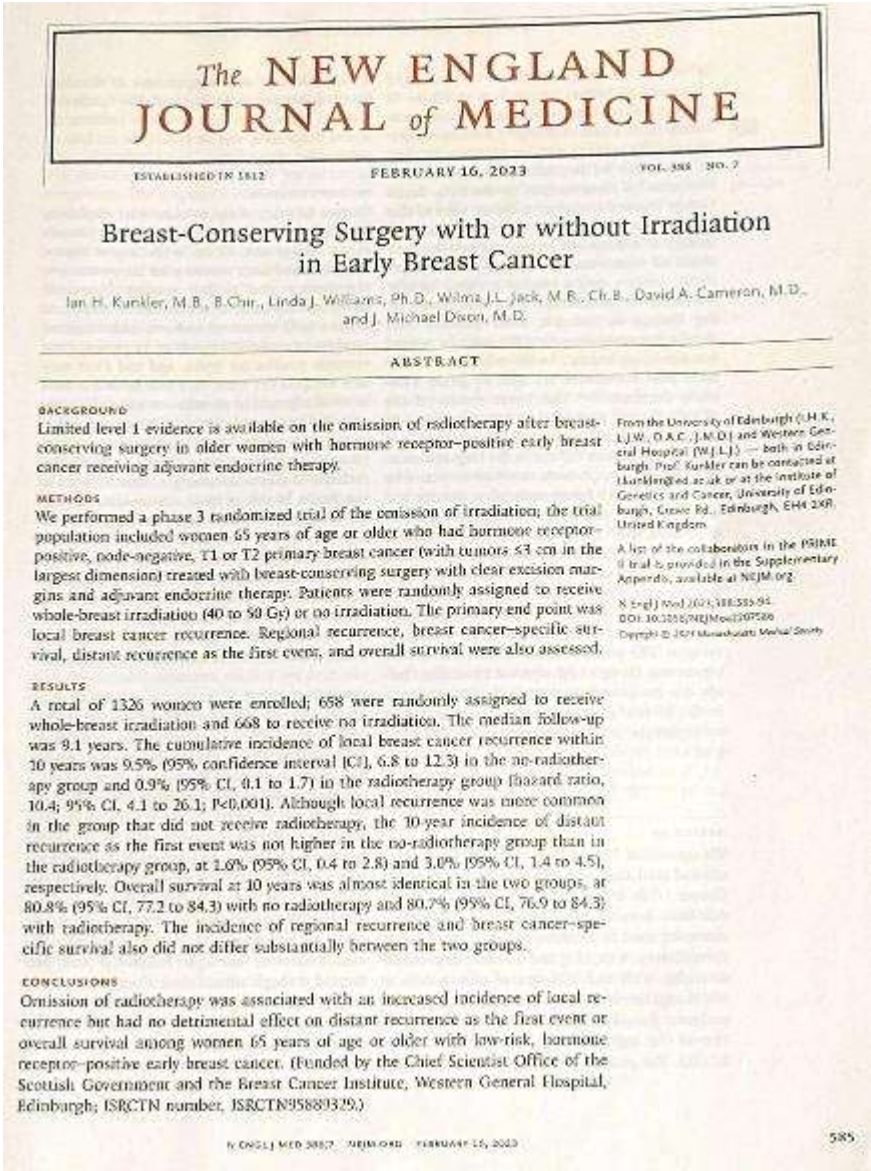
Showed no difference in overall survival among patients receiving breast-conserving surgery, when properly followed by radiation, relative to total mastectomy.

In this landmark 1985 *New England Journal of Medicine* paper, Bernard Fisher and colleagues from the National Surgical Adjuvant Breast and Bowel Project (NSABP B-06 trial) reported the five-year outcomes of a randomized clinical study comparing three surgical approaches for women with stage I or II breast cancer: (1) total mastectomy, (2) lumpectomy alone and (3) lumpectomy followed by whole-breast radiation.

The results demonstrated that overall survival and disease-free survival were statistically equivalent among all three groups after five years of follow-up. However, local recurrence rates were significantly lower in patients who received lumpectomy plus radiation compared to lumpectomy alone, confirming the local control benefit of adjuvant radiotherapy. Importantly, there was no evidence that less extensive surgery increased the risk of distant metastasis or reduced long-term survival.

Fisher's findings fundamentally challenged the Halstedian doctrine that radical mastectomy was necessary to cure breast cancer. The study provided definitive clinical proof that breast-conserving surgery combined with radiation was as safe and effective as total mastectomy for early-stage disease. This pivotal trial laid the foundation for the modern standard of breast-conserving therapy (BCT) and marked a paradigm shift in oncologic surgery—from aggressive local eradication to integrated local and systemic treatment guided by tumor biology rather than surgical extent.

References: Ben-Dror (2022), DeVita and Rosenberg (2012), Lukong (2017), Olson (2002), Sanli (2022).



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 16, 2023 VOL. 388 NO. 7

Breast-Conserving Surgery with or without Irradiation in Early Breast Cancer

Ian H. Kunkler, M.B., B.Chir., Linda J. Williams, Ph.D., Wilma J.L. Jack, M.B., Ch.B., David A. Cameron, M.D., and J. Michael Dixon, M.D.

ABSTRACT

BACKGROUND
Limited level 1 evidence is available on the omission of radiotherapy after breast-conserving surgery in older women with hormone receptor–positive early breast cancer receiving adjuvant endocrine therapy.

METHODS
We performed a phase 3 randomized trial of the omission of irradiation; the trial population included women 65 years of age or older who had hormone receptor–positive, node-negative, T1 or T2 primary breast cancer (with tumors ≤3 cm in the largest dimension) treated with breast-conserving surgery with clear excision margins and adjuvant endocrine therapy. Patients were randomly assigned to receive whole-breast irradiation (40 to 50 Gy) or no irradiation. The primary end point was local breast cancer recurrence. Regional recurrence, breast cancer–specific survival, distant recurrence as the first event, and overall survival were also assessed.

RESULTS
A total of 1326 women were enrolled; 658 were randomly assigned to receive whole-breast irradiation and 668 to receive no irradiation. The median follow-up was 9.1 years. The cumulative incidence of local breast cancer recurrence within 10 years was 9.5% (95% confidence interval [CI], 6.8 to 12.3) in the no-radiotherapy group and 0.9% (95% CI, 0.1 to 1.7) in the radiotherapy group (hazard ratio, 10.4; 95% CI, 4.1 to 26.1; P<0.001). Although local recurrence was more common in the group that did not receive radiotherapy, the 10-year incidence of distant recurrence as the first event was not higher in the no-radiotherapy group than in the radiotherapy group, at 1.6% (95% CI, 0.4 to 2.8) and 3.0% (95% CI, 1.4 to 4.5), respectively. Overall survival at 10 years was almost identical in the two groups, at 80.8% (95% CI, 77.2 to 84.3) with no radiotherapy and 80.7% (95% CI, 76.9 to 84.3) with radiotherapy. The incidence of regional recurrence and breast cancer–specific survival also did not differ substantially between the two groups.

CONCLUSIONS
Omission of radiotherapy was associated with an increased incidence of local recurrence but had no detrimental effect on distant recurrence as the first event or overall survival among women 65 years of age or older with low-risk, hormone receptor–positive early breast cancer. (Funded by the Chief Scientist Office of the Scottish Government and the Breast Cancer Institute, Western General Hospital, Edinburgh; ISRCTN number, ISRCTN95889329.)

From the University of Edinburgh (I.H.K., L.J.W., D.A.C., J.M.D.) and Western General Hospital (W.J.L.J.) — both in Edinburgh. Prof. Kunkler can be contacted at i.kunkler@ed.ac.uk or at the Institute of Genetics and Cancer, University of Edinburgh, Crewe Rd., Edinburgh, EH4 2XR, United Kingdom.

A list of the collaborators in the PRIME II trial is provided in the Supplementary Appendix, available at NEJM.org.

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N ENGL J MED 388;7 NEJM.ORG FEBRUARY 16, 2023

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Bernard Fisher, 1985, "Five-year results of a randomized clinical trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer," *New England Journal of Medicine*, March 14, 1985, Volume 312, pp. 665-673. Boston: Massachusetts Medical Society, First edition. From the author's medical library.

1997: Umberto Veronesi

Showed that lymph node biopsy can help to avoid axillary dissection in breast cancer.

In this study the authors evaluated the feasibility of using the “sentinel-node” concept in women with early breast cancer who had clinically node-negative axillae. They used lymphoscintigraphy plus gamma-probe–guided surgery to locate the first (“sentinel”) lymph node draining the breast tumor, removed that node and assessed whether a full axillary lymph node dissection might be avoided if the sentinel node was free of metastasis.
The paper reported that the sentinel node could be identified in a high proportion of patients and that when the sentinel node was negative, the likelihood was high that the remainder of the axilla was also free of metastatic disease.

The authors further argued that in patients with clinically negative axillae (i.e., no palpable nodes), if the sentinel node is negative, a full axillary dissection might be safely omitted, thereby sparing the patient the morbidity associated with full axillary surgery.

This paper marked a pivotal shift in the surgical management of early breast cancer. At the time, standard of care involved full axillary lymph-node dissection for staging and regional control — a procedure associated with substantial morbidity (lymphedema, shoulder dysfunction, pain, nerve injury). The Veronesi et al. 1997 work provided proof of concept that a much less invasive approach (sentinel-node biopsy) could achieve accurate staging while avoiding the adverse consequences of full axillary surgery when the sentinel node is negative. Over time this contributed to the widespread adoption of sentinel-node biopsy as standard practice in clinically node-negative breast cancer.

References: Ekmektzoglou (2009), Sanli (2022).

THE LANCET

Sentinel-node biopsy to avoid axillary dissection in breast cancer with clinically negative lymph-nodes

Umberto Veronesi, Giovanni Paganelli, Viviana Galimberti, Giuseppe Viale, Stefano Zurrida, Marilia Bedoni, Alberto Costa, Concetta de Cicco, James G Geraghty, Alberto Luini, Virgilio Sacchini, Paolo Veronesi

Summary

Background Axillary lymph-node dissection is an important staging procedure in the surgical treatment of breast cancer. However, early diagnosis has led to increasing numbers of dissections in which axillary nodes are free of disease. This raises questions about the need for the procedure. We carried out a study to assess, first, whether a single axillary lymph node (sentinel node) initially receives malignant cells from a breast carcinoma and, second, whether a clear sentinel node reliably forecasts a disease-free axilla.

Methods In a consecutive series of 165 women with operable breast carcinoma, we injected microcolloid particles of human serum albumin labelled with technetium-99m. This tracer was injected subdermally, close to the tumour site, on the day before surgery, and scintigraphic images of the axilla and breast were taken 10 min, 30 min, and 3 h later. A mark was placed on the skin over the site of the radioactive node (sentinel node). During breast surgery, a handheld γ-ray detector probe was used to locate the sentinel node, and make possible its separate removal via a small axillary incision. Complete axillary lymphadenectomy was then done. The sentinel node was tagged separately from other nodes. Permanent sections of all removed nodes were prepared for pathological examination.

Findings From the sentinel node, we could accurately predict axillary lymph-node status in 138 (97·5%) of the 160 patients in whom a sentinel node was identified, and in all cases (45 patients) with tumours less than 1·5 cm in diameter. In 32 (38%) of the 85 cases with metastatic axillary nodes, the only positive node was the sentinel node.

Interpretation In the large majority of patients with breast cancer, lymphoscintigraphy and γ probe-guided surgery can be used to locate the sentinel node in the axilla, and thereby provide important information about the status of axillary nodes. Patients without clinical involvement of the axilla should undergo sentinel-node biopsy routinely, and may be spared complete axillary dissection when the sentinel node is disease-free.

Lancet 1997; 349: 1864–67

Introduction

Axillary lymph nodes are the commonest site of metastasis in breast carcinoma. Metastatic involvement of the axilla is known to progress regularly from the first, via the second, to the third axillary level; skip metastases are found in roughly 2% of cases only.[1,2]

Axillary-node status is one of the most important prognostic indicators in breast cancer, and of particular value in the choice of adjuvant therapy.[3,4] The prognostic information is gained from histological examination of all or most axillary nodes; the treatment of operable breast carcinoma almost always involves lymph-node dissection.[5] However, if a non-invasive or minimally invasive diagnostic procedure could provide accurate prognostic staging of the axilla, axillary dissection could be avoided in patients with no involved nodes. Sentinel-node biopsy has been developed for this purpose. The technique was first used by Morton and colleagues[6] with blue dye,[7] and later by van der Veen and colleagues[8] with lymphoscintigraphy to select melanoma patients for regional node dissection. These researchers showed that early metastasis of melanoma almost always occurs in the first node, or sentinel node, to receive lymph from the area containing the primary tumour. In breast cancer, cells that detach from the primary tumour are likely to arrive at, and be held by, the first node to receive lymph from the involved breast area. If the sentinel node can be reliably identified, and if careful examination reveals no cancer cells, the other axillary nodes should also be clear.

In most previous investigations of the sentinel node, blue dye was injected into the peritumoral area, and the coloured node was sought through axillary incision.[9] A few studies on small series of patients used the lymphoscintigraphic technique.[10,11] The validity of the sentinel-node strategy has thus been established in breast cancer.

We designed this study to assess the value of sentinel-node biopsy in breast cancer by means of a lymphoscintigraphic technique and, in particular, a γ-ray detection probe to facilitate identification and dissection of the lymph node. We had three objectives: first, to assess the reliability of external-body lymphoscintigraphy for identification of the node that receives lymph from the region of the primary carcinoma; second, to assess the usefulness of a γ-ray detection probe in identification and removal of the sentinel node during axillary surgery; and, third, to measure, by histological analysis of all axillary nodes, the extent to which the sentinel node is a predictor of axillary-node status.

Patients and methods

Patients

We studied 169 consecutive patients with operable breast carcinoma (T1–T3) scheduled to receive axillary dissection at the European Institute of Oncology, from March to [illegible] 1996. We excluded pregnant or lactating women, those who had

Division of Surgery (Prof U Veronesi, MD, V Galimberti, MD, S Zurrida, MD, A Costa, MD, J G Geraghty, FRCS, A Luini, MD, V Sacchini, MD, P Veronesi, MD), Division of Nuclear Medicine (G Paganelli, MD, C de Cicco, MD), Department of Pathology (G Viale, FRCPath), and Department of Anaesthesiology (M Bedoni, MD), European Institute of Oncology, via Ripamonti 435, 20141 Milan, Italy
Correspondence to: Prof Umberto Veronesi

Umberto Veronesi et al., 1997, "Sentinel-node biopsy to avoid axillary dissection in breast cancer with clinically negative lymph-nodes," *Lancet*, Volume 349, June 28, p. 1864-1867. From the author’s medical library.

2002: Bernard Fisher

Showed without doubt that lumpectomy followed by radiation could be as effective as mastectomy.

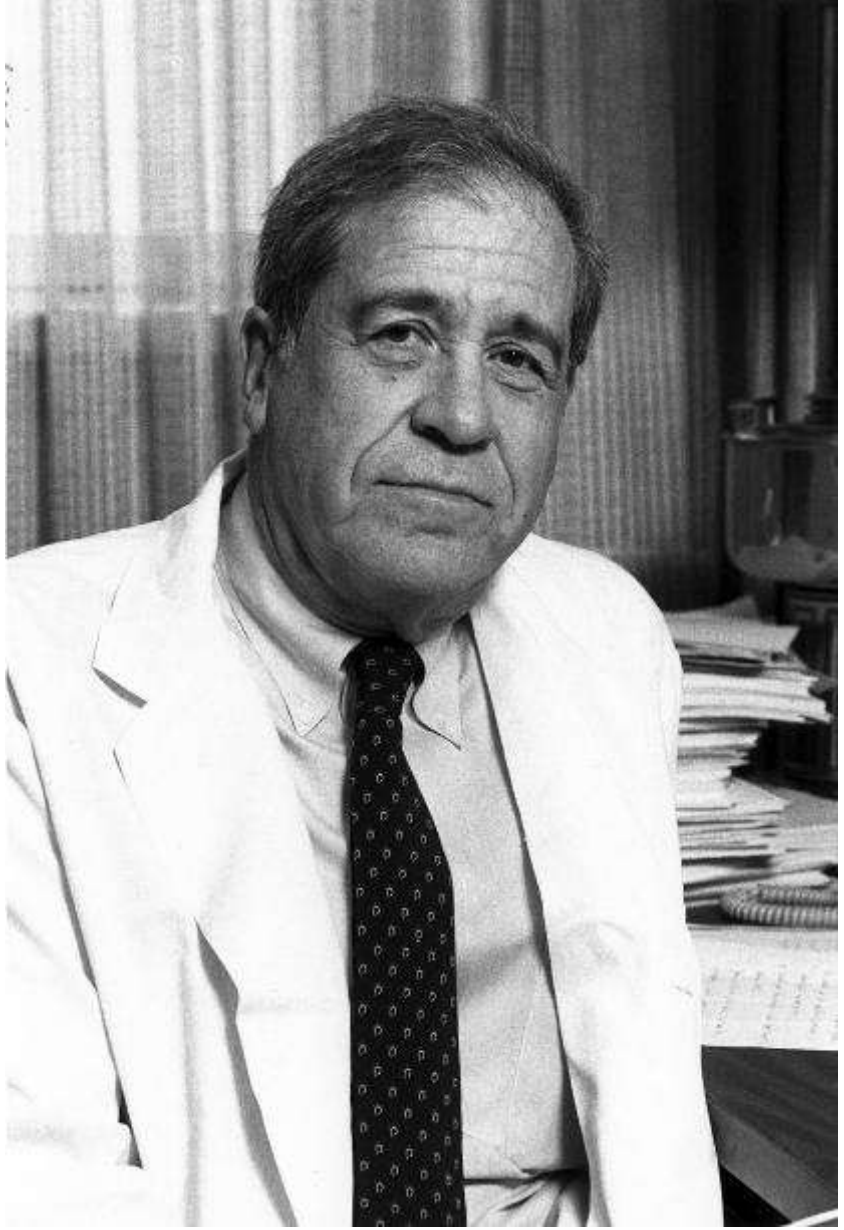
In this 2002 *New England Journal of Medicine* paper, Bernard Fisher and colleagues from the National Surgical Adjuvant Breast and Bowel Project (NSABP B-06 trial) reported the twenty-year outcomes of a randomized clinical study comparing three surgical approaches for breast cancer.

The study enrolled over 1,800 women with stage I or II invasive breast cancer and randomly assigned them to one of three treatment groups: total mastectomy, lumpectomy alone, or lumpectomy followed by radiation therapy. After two decades of follow-up, Fisher and colleagues found no significant difference in overall survival or disease-free survival among the three groups. Women who underwent lumpectomy plus irradiation had slightly lower local recurrence rates than those treated with lumpectomy alone, but survival outcomes were equivalent to those of total mastectomy.

This long-term analysis confirmed that breast-conserving surgery combined with radiation is as effective as mastectomy in treating early-stage breast cancer, fundamentally changing surgical oncology and patient care.

The oncology journal and website *OncLive* described Bernie Fisher's research as "launching the breast cancer community into the modern era" and honored him with a Giants of Cancer Care award for his work that ultimately ended the standard practice of performing the Halsted radical mastectomy, a treatment that had been in place for more than 75 years. Fisher also received a Lasker award in 1985. Thanks to Fisher, notes another major oncology journal, breast-cancer survival rates have improved worldwide.

References: Ben-Dror (2022), Lukong (2017), Olson (2002), Sanli (2022).



Bernard Fisher, 2002, “Twenty-Year Follow-up of a Randomized Trial Comparing Total Mastectomy, Lumpectomy and Lumpectomy plus Irradiation for the Treatment of Invasive Breast Cancer,” *New England Journal of Medicine*, 347:1233–1241. From the author’s medical library.

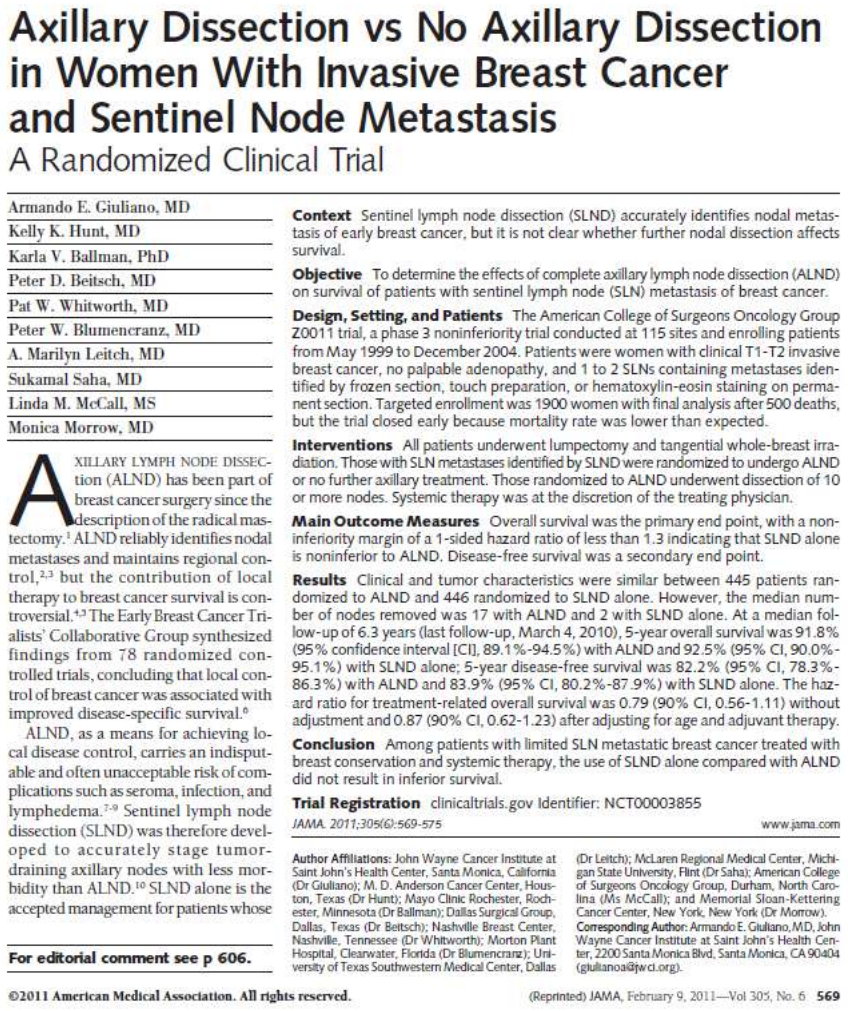
2011: Armando Giuliano

Showed that sentinel node dissection is similar in terms of survival as conducting an axillary dissection.

Giuliano and colleagues reported the results of the ACOSOG Z0011 Trial, a randomized clinical trial that enrolled women with early-stage invasive breast cancer (clinical T1–T2), no palpable axillary lymphadenopathy and one or two positive sentinel lymph nodes (SLNs). All participants had breast-conserving surgery, whole-breast irradiation (tangential fields) and appropriate adjuvant systemic therapy. Patients were randomized to either complete axillary lymph-node dissection (ALND) or no further axillary surgery beyond sentinel lymph-node dissection (SLND) alone. The trial's primary endpoint was overall survival, with noninferiority set by a hazard-ratio margin. After a median follow-up of approximately 6.3 years at the initial report, the authors found that survival and disease-free survival in the SLND-alone arm were not significantly worse than in the ALND arm. In other words, omitting ALND in this selected group of women did not lead to worse outcomes in the short to medium term.

The findings of this trial had major implications for surgical management of the axilla in early breast cancer. Historically, ALND had been a routine part of treatment for node-positive disease, but ALND carries risks including lymphedema, shoulder dysfunction and neuropathy. Giuliano's study provided strong evidence that in carefully selected patients (small primary tumor, clinically node-negative, 1-2 SLNs positive, treated with breast conservation + radiation + systemic therapy), omitting ALND was safe in terms of survival and recurrence. This supported a paradigm shift toward less invasive axillary surgery— reducing morbidity without compromising oncologic outcomes. Over time, the results have been incorporated into guidelines and have led to many patients avoiding full ALND when they meet similar criteria, thus improving quality of life for many women with early breast cancer.

References: Sanli (2022).



Axillary Dissection vs No Axillary Dissection in Women With Invasive Breast Cancer and Sentinel Node Metastasis

A Randomized Clinical Trial

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Context Sentinel lymph node dissection (SLND) accurately identifies nodal metastasis of early breast cancer, but it is not clear whether further nodal dissection affects survival.

Objective To determine the effects of complete axillary lymph node dissection (ALND) on survival of patients with sentinel lymph node (SLN) metastasis of breast cancer.

Design, Setting, and Patients The American College of Surgeons Oncology Group Z0011 trial, a phase 3 noninferiority trial conducted at 115 sites and enrolling patients from May 1999 to December 2004. Patients were women with clinical T1-T2 invasive breast cancer, no palpable adenopathy, and 1 to 2 SLNs containing metastases identified by frozen section, touch preparation, or hematoxylin-eosin staining of permanent section. Targeted enrollment was 1900 women with final analysis after 500 deaths, but the trial closed early because mortality rate was lower than expected.

Interventions All patients underwent lumpectomy and tangential whole-breast irradiation. Those with SLN metastases identified by SLND were randomized to undergo ALND or no further axillary treatment. Those randomized to ALND underwent dissection of 10 or more nodes. Systemic therapy was at the discretion of the treating physician.

Main Outcome Measures Overall survival was the primary end point, with a noninferiority margin of a 1-sided hazard ratio of less than 1.3 indicating that SLND alone is noninferior to ALND. Disease-free survival was a secondary end point.

Results Clinical and tumor characteristics were similar between 445 patients randomized to ALND and 446 randomized to SLND alone. However, the median number of nodes removed was 17 with ALND and 2 with SLND alone. At a median follow-up of 6.3 years (last follow-up, March 4, 2010), 5-year overall survival was 91.8% (95% confidence interval [CI], 89.1%-94.5%) with ALND and 92.5% (95% CI, 90.0%-95.1%) with SLND alone; 5-year disease-free survival was 82.2% (95% CI, 78.3%-86.3%) with ALND and 83.9% (95% CI, 80.2%-87.9%) with SLND alone. The hazard ratio for treatment-related overall survival was 0.79 (90% CI, 0.56-1.11) without adjustment and 0.87 (90% CI, 0.62-1.23) after adjusting for age and adjuvant therapy.

Conclusion Among patients with limited SLN metastatic breast cancer treated with breast conservation and systemic therapy, the use of SLND alone compared with ALND did not result in inferior survival.

Trial Registration clinicaltrials.gov Identifier: NCT00003855

JAMA. 2011;305(6):569-575 www.jama.com

ALND, as a means for achieving local disease control, carries an indisputable and often unacceptable risk of complications such as seroma, infection, and lymphedema.[7-9] Sentinel lymph node dissection (SLND) was therefore developed to accurately stage tumor-draining axillary nodes with less morbidity than ALND.[10] SLND alone is the accepted management for patients whose

For editorial comment see p 606.

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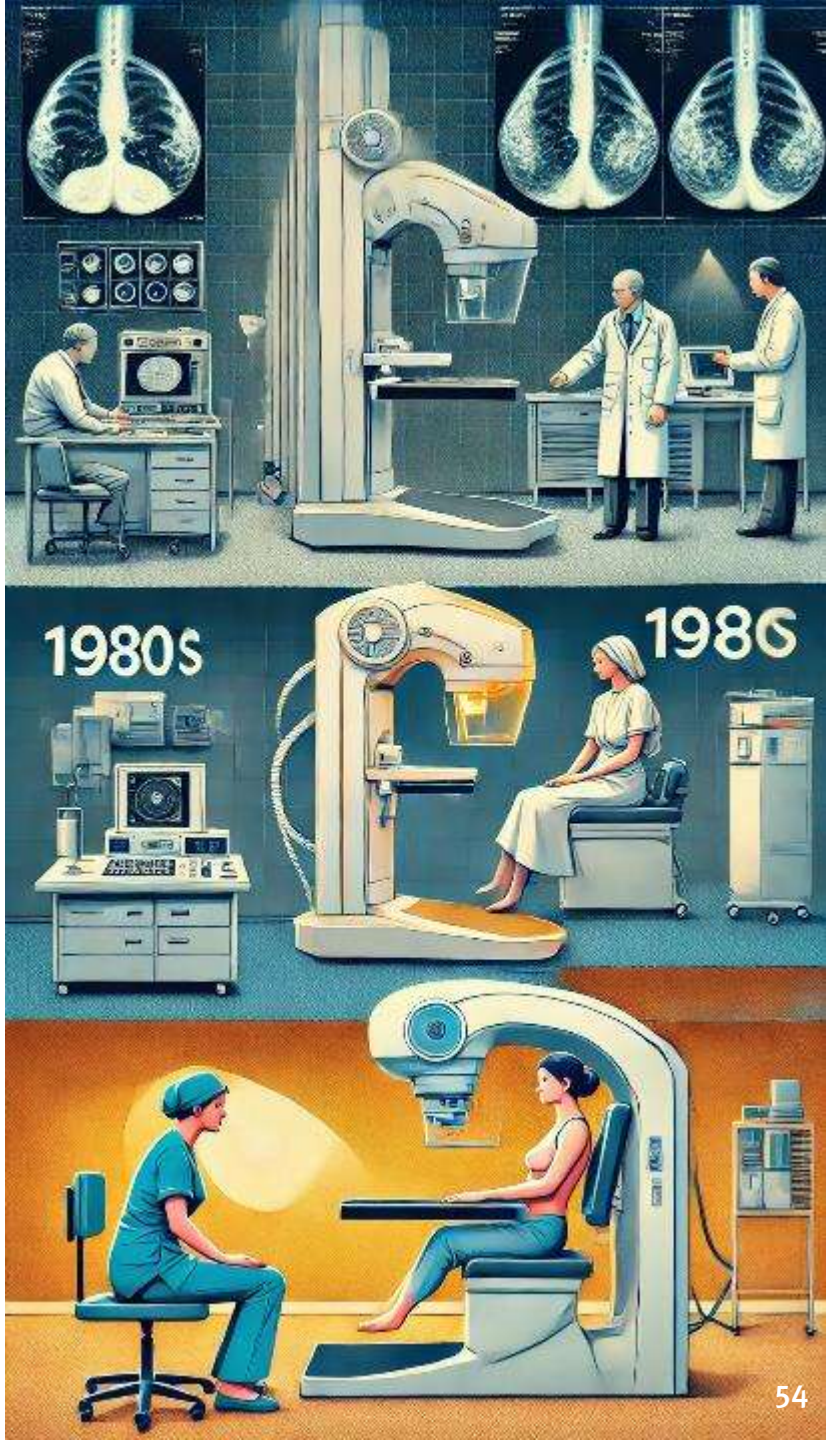
Armando Giuliano et al., "Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial," JAMA, Feb 9, 2011, Volume 305(6), pp. 569-75.

Section 4.B: Mammography

The history of mammography began in the early 20th century, when German surgeon Albert Salomon first used X-rays in 1913 to study mastectomy specimens, meticulously documenting how cancer altered breast tissue.

In the 1940s, the Uruguayan radiologist Raul Leborgne advanced the field by identifying microcalcifications as a key radiologic sign of carcinoma, but clinical use was limited by high radiation doses and poor imaging contrast. The breakthrough came in the 1950s when Robert Egan, who developed the “Egan technique”: a standardized, low-dose, high-contrast method that allowed clear imaging of soft breast tissue on industrial X-ray film. In parallel, French radiologist Charles Gros refined mammography in Europe by introducing specialized equipment—dedicated X-ray tubes, compression devices and film–screen combinations—designed specifically for breast imaging.

Building on these advances, Philip Strax, Louis Venet and Sam Shapiro conducted the HIP trial which proved that mammography screening reduced breast cancer mortality. From there, mammography evolved from an experimental imaging method into a life-saving cornerstone of women’s health. Today’s digital and 3D mammography trace their lineage directly to these mid-20th-century pioneers who proved that early detection could change the course of breast cancer.



Milestones in Development of Mammography

1913 Albert Salomon – In breast X-rays he realizes that cancer is marked by detectable calcifications

1951 Raul Leborgne – Set mammography as a practical tool implementing compression technique

1954 Charles Gros – Introduced low dose radiation and a machine to conduct mammography

1964 Robert Egan – Used fine grained film and low-dose radiation to show mammography works

1966 Philip Strax – Provides data for the first time that mammography saves lives.

1976 John Wolfe– Grading from mammograms could predict the incidence of breast cancer

2011 Lazlo Tabor – Large clinical trial in Sweden shows that mammography saves lives

2020 UK Age Trial – Largest clinical trial in history shows mammography saves lives

1951: Raul Alfredo Leborgne

Operationalized mammography as a practical diagnostic tool implementing breast compression technique for the first time.

Discovered in 1895, x-rays were all the rage in the early 1900s, dramatically illuminating the insides of the human body, showing bones in detail. There were even attempts to use x-ray machines to find cancer in breasts. Breast cancer certainly deserved attention, since it was and is one of the most common cancers, but differentiating soft tissue in the first x-ray machines was problematic. In 1930 Stafford Warren, a radiologist from New York, performed a study indicating x-rays might perform better than doctors at finding breast cancer, but his published article didn't excite too many and progress remained slow, with small advances occurring in fits and halts. The potential to use x-rays to find breast cancer was apparent. If cancer could be found before it spreads, it could more easily be treated and irradicated.

Raul Leborgne vitalized mammography with a key publication in 1951. He was a radiologist from Uruguay and one of his insights still makes patients cringe, yet was crucial to the development of mammograms. Leborgne devised an apparatus that would squeeze a patient's breast between a cone and a compression pad to hold it flat while an x-ray was taken. He introduced this technique in 1949 and reported his findings in a landmark publication in 1951. This compression enhanced the quality of the images. Using it, he was better able to see small structures and use spot/magnification. He was the first to report the significance of radiographically detectable microcalcifications, “which may be seen in extensive as well as incipient lesions.” Finding them in 30% of cancers, Leborgne gave radiologists something more to look for. His methods set the stage for our current techniques and for improved detection and diagnosis. Mammography became routine in the 1970s and has continued to improve. Since 1990 it has helped reduce breast cancer mortality 40%. (Science Heroes).

References: Lukong (2017).

This is a photo of one of Leborgne’s patients getting a mammograph in the early 1950’s. The X-Ray dosing was too high to be practical, and the procedure did not use any of today’s equipment to ease the burden of the procedure.

Raul Alfredo Leborgne, 1953, The Breast in Roentgen Diagnosis, Montivideo, Uraguay: Impresora Uruguaya S.A.; Constable. From the author’s medical library. This is the first English language version of Leborgne’s work.

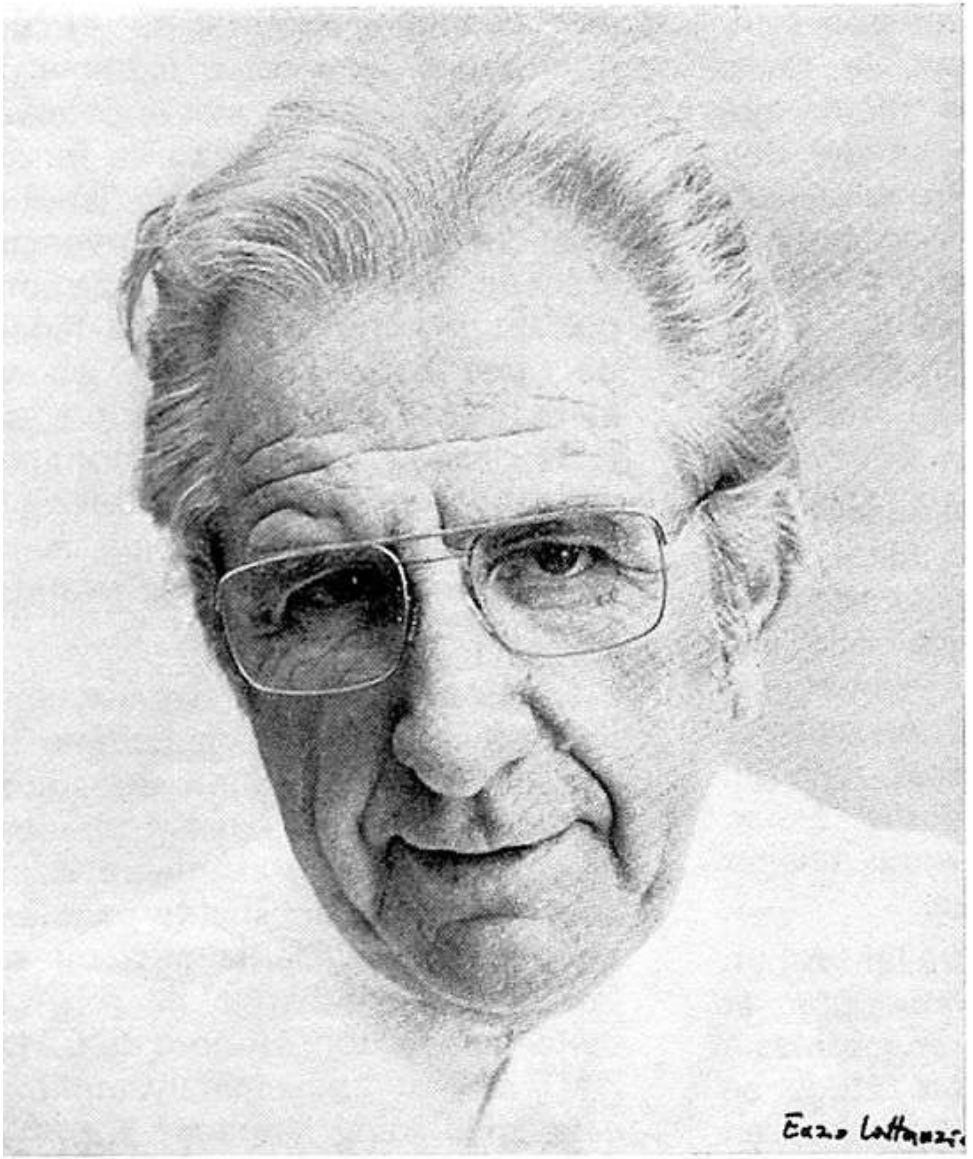
1954: Charles Gros

First to use low dose radiation in mammography and to create a commercial machine that could carry out the procedure.

Charles Henri Gros (1910–1977) was a French radiologist whose pioneering work in the 1950s and 1960s transformed mammography from a crude, high-radiation experiment into a precise and safe diagnostic technique. Working at the Hôpital de l'Hôtel-Dieu in Paris, he developed the first dedicated mammography unit, specifically designed for imaging the breast rather than adapting general x-ray machines. Gros optimized the use of low kilovoltage (20–30 kVp) radiation, fine-grain industrial film and controlled breast compression, creating clear, high-contrast images that allowed the visualization of small calcifications and soft-tissue detail at a fraction of the radiation dose used previously. In 1969, he invented the first mammography system the Senograph. This was commercialized in Europe and the Companies Generale de Radiology (CGR). CGR was acquired by GE in the 1980s allowing it to build the world's largest line of mammography equipment.

Beyond his technical achievements, Gros was among the first to demonstrate the clinical value of mammography for early detection of breast cancer. Gros's French publications of the 1950s and 1960s—such as La radiographie du sein helped spread his methods throughout Europe and influenced radiologists worldwide, including Robert Egan in the United States.

Charles Gros was also a great humanist and created the concept of Senology, the idea of multidisciplinary treatment of breast disease and the philosophy of treating a woman with a diseased breast as a whole, not a diseased part of her body.



Charles Gros, 1954, "Radiographie du Sein" in Dalsace (editor), Gynecologie, Radiologique at Radographie du Sein. From the author's medical library.

1964: Robert Egan

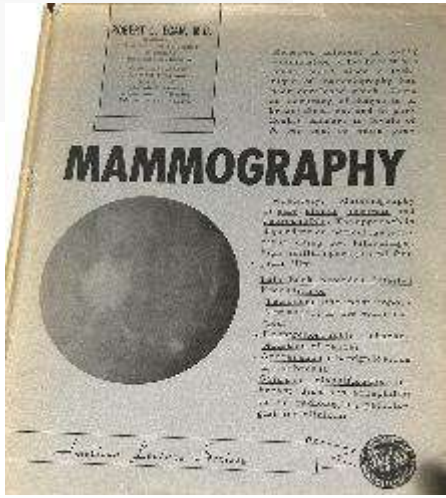
Considered the father of mammography. Used low dose radiation and fine-grain film to show that mammography could detect non-palpable tumors.

Robert L. Egan (1914–2001) revolutionized mammography by transforming it from a crude experimental method into a reliable, standardized diagnostic procedure. At the University of Texas M.D. Anderson Hospital in the 1950s, he developed a consistent technique using low kilovoltage x-rays, high milliamperage, fine-grain industrial film and firm breast compression, producing clear images with exceptional soft-tissue contrast and minimal radiation. These refinements—published in his seminal 1964 textbook Mammography—allowed radiologists to visualize small, nonpalpable lesions and microcalcifications for the first time, establishing mammography as a true clinical discipline rather than a research curiosity.

Egan also conducted large-scale clinical studies showing that mammography could detect breast cancers long before they became clinically apparent, leading to earlier diagnosis and improved survival outcomes. He famously found 54 cases of occult breast cancer in his MD Anderson study.

Through his teaching courses, atlases and advocacy, he trained hundreds of radiologists and helped standardize breast imaging worldwide. His “Egan technique” became the prototype for modern screen-film mammography and directly influenced the design of dedicated mammographic equipment. For these achievements, Robert Egan is recognized as the father of modern mammography, the pivotal figure who made breast x-ray imaging an essential tool in cancer diagnosis and prevention.

References: Lukong (2017).



Robert L. Egan, 1964, Mammography, C. C. Thomas, From the author’s medical library.

1966: Philip Strax

Ran a 60,000 women clinical trial on mammography and showed it made a difference in finding cancer. This paper was highly influential in motivating the use of mammograms.

Dr. Philip Strax (1909–1999) was a radiologist whose work in the early 1960s transformed breast cancer care by proving that early detection saves lives. At a time when most breast cancers were diagnosed only after they became palpable or symptomatic, Strax recognized the potential of X-ray imaging to find tumors too small to feel. In 1963, he partnered with the Health Insurance Plan of Greater New York to design one of the first large-scale, randomized controlled trials in preventive oncology—the HIP Breast Cancer Screening Project. This study enrolled 60,000 women aged 40–64 and compared outcomes between those who received annual mammography and clinical breast exams to those who did not.

The results, published in 1966 in *JAMA*, were groundbreaking. Strax and his colleagues showed that mammography could detect breast cancers when they were smaller, less invasive and more curable. More importantly, the trial revealed a significant reduction in breast cancer mortality among women who were screened—a finding that provided the first solid evidence that screening could prevent deaths from cancer. This challenged widespread skepticism within the medical community.

Following the publication of these results, Dr. Strax became a leading advocate for routine mammography screening and devoted much of his later career to expanding public health programs that made the technology widely accessible.

References: ASCO Foundation 2025.

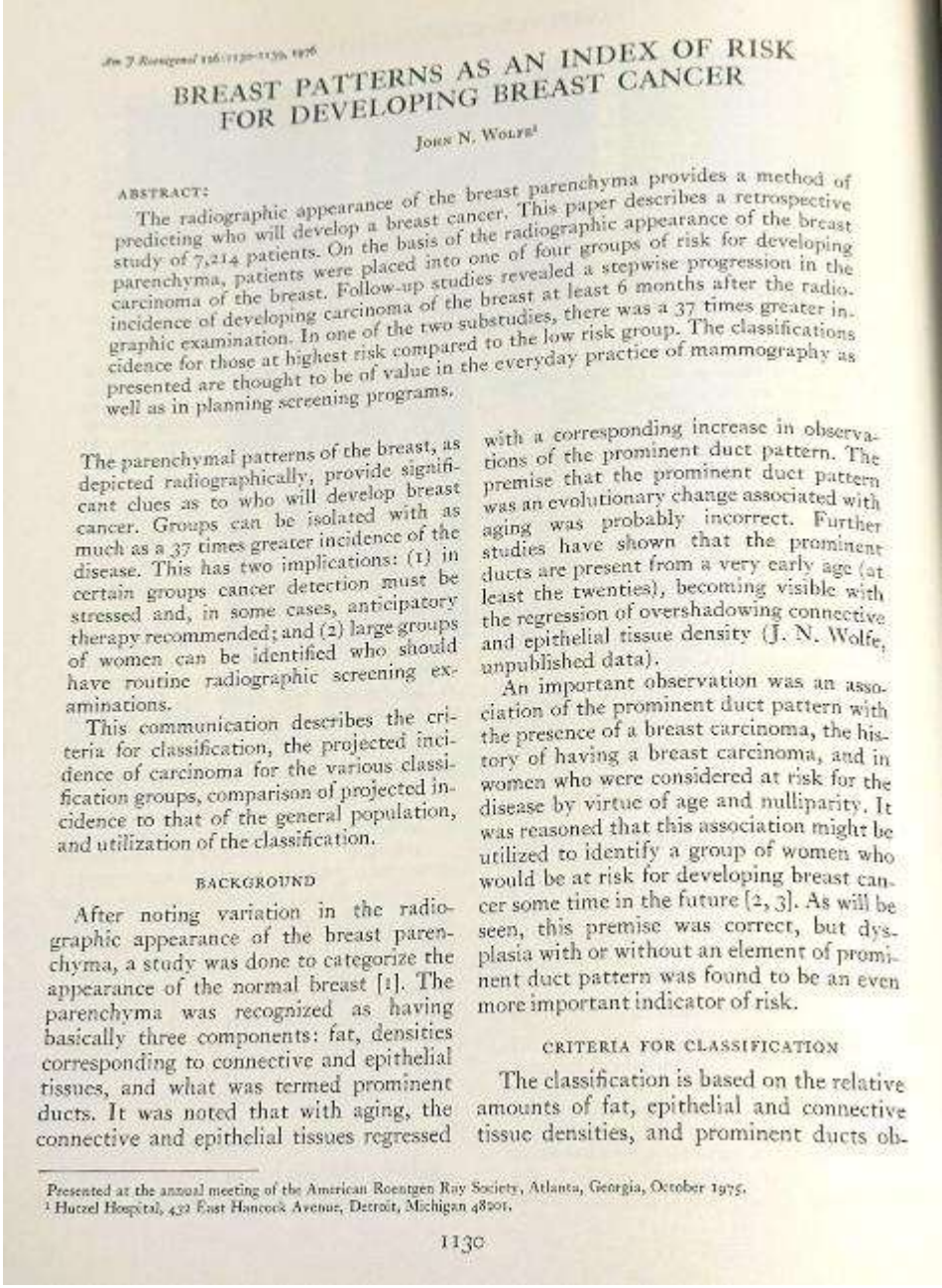
Key Research Paper: Shapiro S, Strax P, Venet L., 1966, Evaluation of periodic breast cancer screening with mammography. Methodology and early observations. *JAMA*. Feb 28;195(9):731-8.

1976: John N. Wolfe

Showed how a four-category grading system for mammograms could successfully predict the incidence of breast cancer.

John N. Wolfe's 1976 paper, "Breast Patterns as an Index of Risk for Developing Breast Cancer" (published in the American Journal of Roentgenology, June 1976), was a landmark study that introduced the concept of mammographic parenchymal patterns as potential predictors of breast cancer risk. Wolfe analyzed thousands of screening mammograms and classified breast tissue into four distinct radiologic patterns based on the relative proportions of fat, connective tissue and glandular elements—ranging from predominantly fatty (Pattern N1) to markedly dense, nodular and dysplastic (Pattern DY). He found that women with denser, fibroglandular breast patterns had a significantly higher incidence of breast cancer compared with those whose breasts were primarily fatty. This correlation suggested that mammography could be used not only for early detection but also for risk stratification, identifying women at higher risk who might benefit from closer surveillance.

The implications of Wolfe's study were profound and enduring. It reframed mammography from a purely diagnostic tool into a predictive biomarker of breast cancer susceptibility, catalyzing decades of research into breast density, hormonal influences and imaging-based risk models. While later studies refined and sometimes questioned the precise magnitude of risk Wolfe proposed, his classification laid the foundation for the now widely accepted concept that mammographic density is an independent risk factor for breast cancer. His work influenced both screening protocols and preventive strategies, contributing to the integration of radiologic features into modern risk-assessment models such as the Tyrer–Cuzick and Gail models. In essence, Wolfe's 1976 paper pioneered the scientific and clinical recognition that the visual texture of breast tissue—captured through mammography—could hold critical insights into a woman's future cancer risk.



BREAST PATTERNS AS AN INDEX OF RISK FOR DEVELOPING BREAST CANCER

JOHN N. WOLFE[1]

ABSTRACT:

The radiographic appearance of the breast parenchyma provides a method of predicting who will develop a breast cancer. This paper describes a retrospective study of 7,214 patients. On the basis of the radiographic appearance of the breast parenchyma, patients were placed into one of four groups of risk for developing carcinoma of the breast. Follow-up studies revealed a stepwise progression in the incidence of developing carcinoma of the breast at least 6 months after the radiographic examination. In one of the two substudies, there was a 37 times greater incidence for those at highest risk compared to the low risk group. The classifications presented are thought to be of value in the everyday practice of mammography as well as in planning screening programs.

The parenchymal patterns of the breast, as depicted radiographically, provide significant clues as to who will develop breast cancer. Groups can be isolated with as much as a 37 times greater incidence of the disease. This has two implications: (1) in certain groups cancer detection must be stressed and, in some cases, anticipatory therapy recommended; and (2) large groups of women can be identified who should have routine radiographic screening examinations.

This communication describes the criteria for classification, the projected incidence of carcinoma for the various classification groups, comparison of projected incidence to that of the general population, and utilization of the classification.

BACKGROUND

After noting variation in the radiographic appearance of the breast parenchyma, a study was done to categorize the appearance of the normal breast [1]. The parenchyma was recognized as having basically three components: fat, densities corresponding to connective and epithelial tissues, and what was termed prominent ducts. It was noted that with aging, the connective and epithelial tissues regressed with a corresponding increase in observations of the prominent duct pattern. The premise that the prominent duct pattern was an evolutionary change associated with aging was probably incorrect. Further studies have shown that the prominent ducts are present from a very early age (at least the twenties), becoming visible with the regression of overshadowing connective and epithelial tissue density (J. N. Wolfe, unpublished data).

An important observation was an association of the prominent duct pattern with the presence of a breast carcinoma, the history of having a breast carcinoma, and in women who were considered at risk for the disease by virtue of age and nulliparity. It was reasoned that this association might be utilized to identify a group of women who would be at risk for developing breast cancer some time in the future [2, 3]. As will be seen, this premise was correct, but dysplasia with or without an element of prominent duct pattern was found to be an even more important indicator of risk.

CRITERIA FOR CLASSIFICATION

The classification is based on the relative amounts of fat, epithelial and connective tissue densities, and prominent ducts ob-

Presented at the annual meeting of the American Roentgen Ray Society, Atlanta, Georgia, October 1975.
[1] Hutzel Hospital, 432 East Hancock Avenue, Detroit, Michigan 48201.

1130

John N. Wolfe, 1976, "Breast patterns as an index of risk for developing breast cancer," in *The American Journal of Roentgenology*, June, 126(6):1130-7.

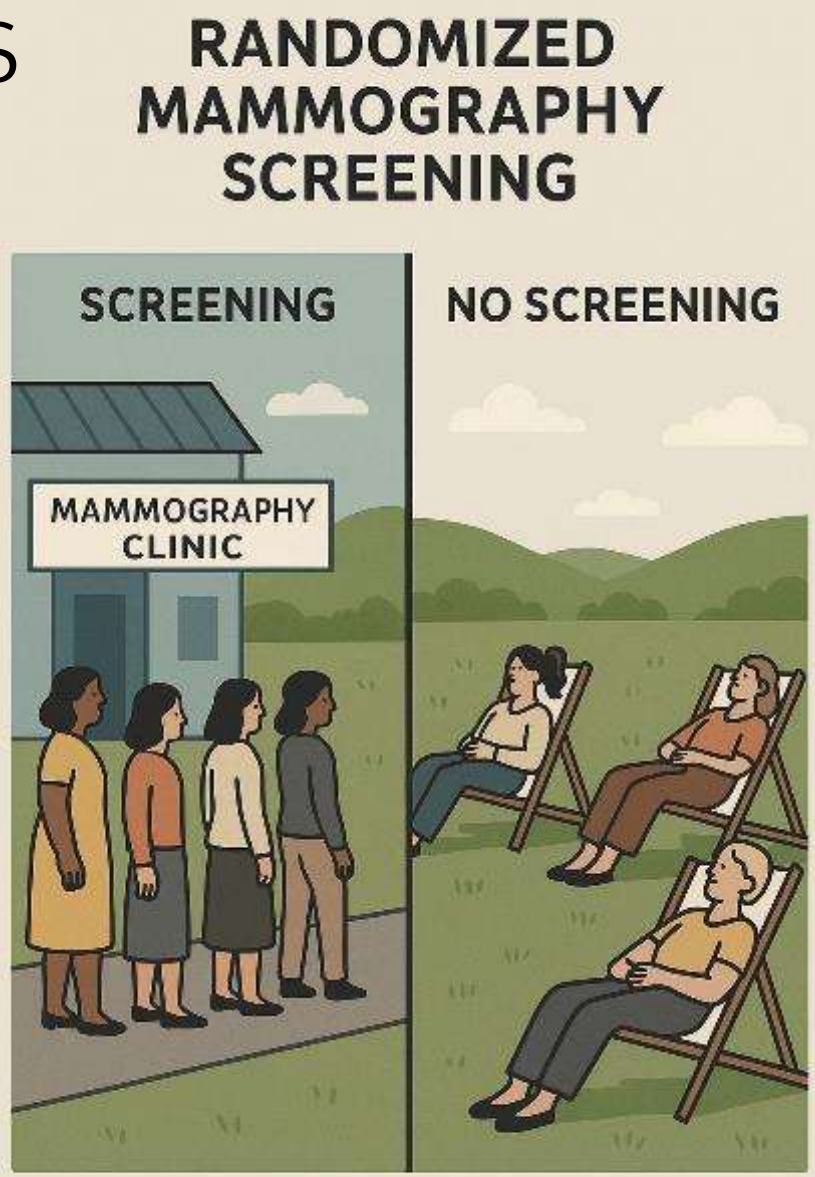
2011: Lazlo Tabar and Colleagues

Show that mammography improved women's survival in a large population study. This was the most definitive population health level mammography study ever done.

The study presents long-term follow-up (up to ~29 years) of the randomized population-based trial conducted in two Swedish counties (aged 40-74 years) where geographic clusters of women were randomly invited to mammographic screening (single-view, every 24-33 months) or usual care (no screening invitation). The authors used negative-binomial regression to compare breast cancer–specific mortality between the invited (screening) group and the non-invited group, based on both local end point committee data and a consensus (external) committee. They found a highly significant reduction in breast cancer mortality among women invited to screening (relative risk ~0.69; 95% CI 0.56-0.84) according to local data and ~0.73 (95% CI 0.59-0.89) according to consensus data. They also derived absolute measures: at ~29 years follow-up, the number of women needed to undergo screening for 7 years to prevent one breast cancer death was 414 (local data) and 519 (consensus data). Importantly, the authors emphasized that full impact of screening requires long follow-up, because many of the prevented deaths would otherwise have occurred beyond the first 10 years.

The Tabár et al. paper strongly supports the value of organized mammographic screening in reducing breast-cancer mortality at the population level, with durable benefit over decades. It underpins the rationale for routine screening programs: by identifying breast cancers earlier (smaller size, fewer node metastases) the trial suggests improved prognostic distribution and thus fewer deaths from breast cancer. In clinical practice the findings contributed to the widespread adoption of mammography for women in defined age groups, the structuring of screening intervals and the message that sustained, regular participation in screening is critical to realize mortality reductions.

References: Sanli (2022).

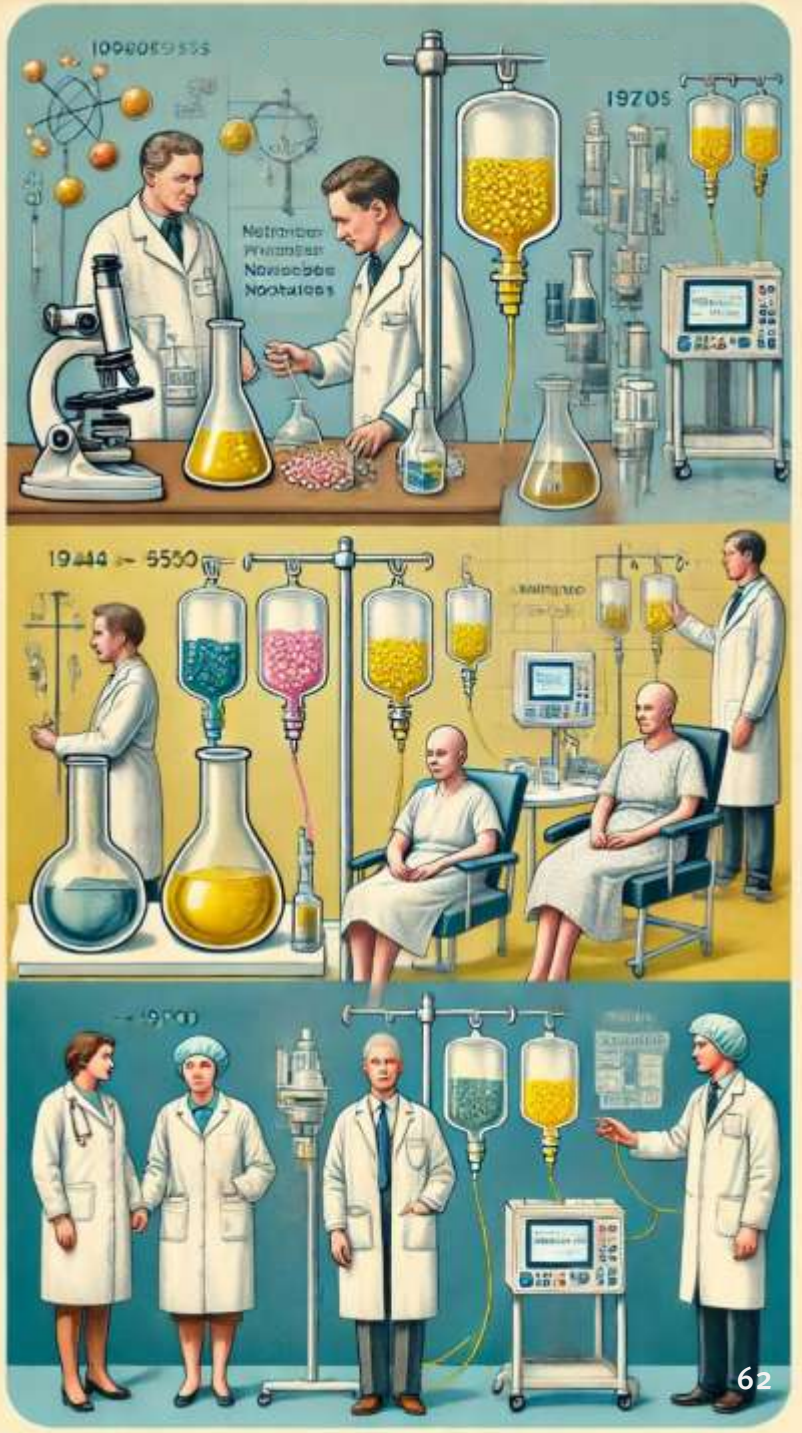


Tabár L, Vitak B, Chen TH, Yen AM, Cohen A, Tot T, Chiu SY, Chen SL, Fann JC, Rosell J, Fohlin H, Smith RA, Duffy SW. "Swedish two-county trial: impact of mammographic screening on breast cancer mortality during 3 decades." *Radiology*. Sep;260(3):658-63.

Section 4.C: Chemotherapy

Chemotherapy for breast cancer emerged in the mid-20th century as a transformative extension of wartime research following the explosion of nitrogen mustard at Bari in 1943. The first wave began in the late 1940s with nitrogen mustards, whose cell-killing properties inspired the idea that cancer might be selectively targeted by toxic agents. The 1950s and 1960s saw the systematic testing of antimetabolites like methotrexate and 5-fluorouracil, which interfered with DNA synthesis in rapidly dividing cells. By the 1970s, the anthracycline antibiotics—most notably adriamycin — ushered in a new era of potency. Pioneers ike Gianni Bonadonna demonstrated that combinations of these drugs could significantly prolong survival in early-stage breast cancer, establishing combination chemotherapy as a global standard.

In the ensuing decades, chemotherapy became the cornerstone of systemic breast cancer therapy—first as adjuvant treatment to prevent recurrence, later as neoadjuvant therapy to shrink tumors pre-surgery and eventually in metastatic disease management. Landmark U.S. trials confirmed that systemic therapy could rival or surpass radical surgery in improving survival, cementing a shift from purely local to systemic thinking about cancer. The 1980s and 1990s introduced taxanes (paclitaxel and docetaxel), which improved outcomes even further. In the 21st century, chemotherapy's role has evolved alongside targeted and hormonal therapies—it remains essential, often integrated with agents like trastuzumab, CDK4/6 inhibitors and immunotherapies.



Milestones in Development of Chemotherapy

1910 Ehrlich and Hata – Describe the concept of a chemotherapy for the first time – a "magic bullet" for disease

1946 Alfred Gilman – Reveals for the first time a secret WWII project to apply nitrogen mustards for cancer

1951 Jane Cooke Wright – Methotrexate can also shrink tumors – motivating work on chemo

1953 Harry Shay – First published cases of use of chemotherapy in breast cancer

1956 Roy Hertz – First published study with a complete cure of a solid tumor with chemotherapy

1969 Farmitalia Team– Invented adriamycin, an anthracycline chemotherapy

1976 Hoogstratten et al. – 39% monotherapy response rate with adriamycin in advanced breast cancer

1976 Bonadonna – shows benefit of adjuvant chemotherapy in BC in major trial

1991 Holmes et al. shows 56% ORR of taxol in metastatic BC among adriamycin failures

2003 Larry Norton et al. shows major improvement in mortality in stacking chemo into more frequent windows

1951: Jane Cooke Wright

Shows that methotrexate, an antimetabolite agent, could shrink solid tumors. This was influential in motivating more work on chemotherapy.

Dr. Jane Cooke Wright (1919–2013) was a trailblazing physician, surgeon and cancer researcher whose work helped to transformed chemotherapy from a fringe experimental idea into a cornerstone of modern cancer treatment. A graduate of New York Medical College and daughter of pioneering Black surgeon Louis T. Wright, she became one of the highest-ranking African American women in medicine of her time. In the early 1950s, Wright and her team at the Harlem Hospital Cancer Research Foundation tested the drug methotrexate, showing that it could shrink tumors in patients with breast cancer, skin cancer and leukemia. Her studies were among the first to demonstrate that chemical agents could target cancer cells while sparing normal tissue—a discovery that helped shift oncology toward systematic, evidence-based chemotherapy.

Beyond her laboratory achievements, Dr. Wright made lasting institutional and scientific contributions. She developed techniques for using patient tumor biopsies to test the effects of drugs *in vitro*, a forerunner of personalized medicine. She became the head of cancer chemotherapy research at New York Medical College, helped to found the American Society of Clinical Oncology (ASCO) and served as its only woman and African American co-founder at the time. Over her career, she published more than 100 scientific papers, advised federal health agencies and championed the inclusion of women and minorities in clinical research.

References: ASCO Foundation 2025.

Key Research Paper: Wright JC, Prigot A, Wright B, Weintraub S, Wright LT., 1951, "An evaluation of folic acid antagonists in adults with neoplastic diseases: a study of 93 patients with incurable neoplasms," *Journal of the National Medical Association*, 43:211-40.

1953: Harry Shay et al.

First known example of use of chemotherapy successfully used to treat breast cancer.

We have backtracked through the literature and can say that Harry Shay and colleagues 1953 paper, published in *JAMA* under the title “Treatment of Leukemia with Triethylenethiophosphoramide (Thio-TEPA)”, shows the first case where breast cancer was successfully treated with chemotherapy. While the study focused on leukemia, two breast cancer patients were included in the study and both responded.

Conducted at Temple University, Shay and colleagues administered Thio-TEPA—an analog of nitrogen mustard with triethylene and thiophosphoramide groups—to patients with various forms of leukemia and breast cancer. Their objective was to test whether this new compound, known for its DNA-alkylating properties, could suppress malignant white-cell proliferation. The study reported that Thio-TEPA produced temporary remissions and measurable reductions in leukocyte counts, along with improvement in symptoms such as splenomegaly and anemia, though complete and durable remissions were rare. Toxicities, including bone-marrow suppression and mucosal irritation, were noted but were generally reversible with dose adjustment.

At a time when most cancer treatment still relied on surgery and radiation, Shay’s investigation provided crucial early human data demonstrating that synthetic alkylating agents could exert selective cytotoxic effects against malignant hematologic cells. This study’s careful documentation of both therapeutic response and toxicity illustrated the delicate balance between efficacy and tolerability—a principle that would guide all subsequent chemotherapy development.

References: Bateman (1955).

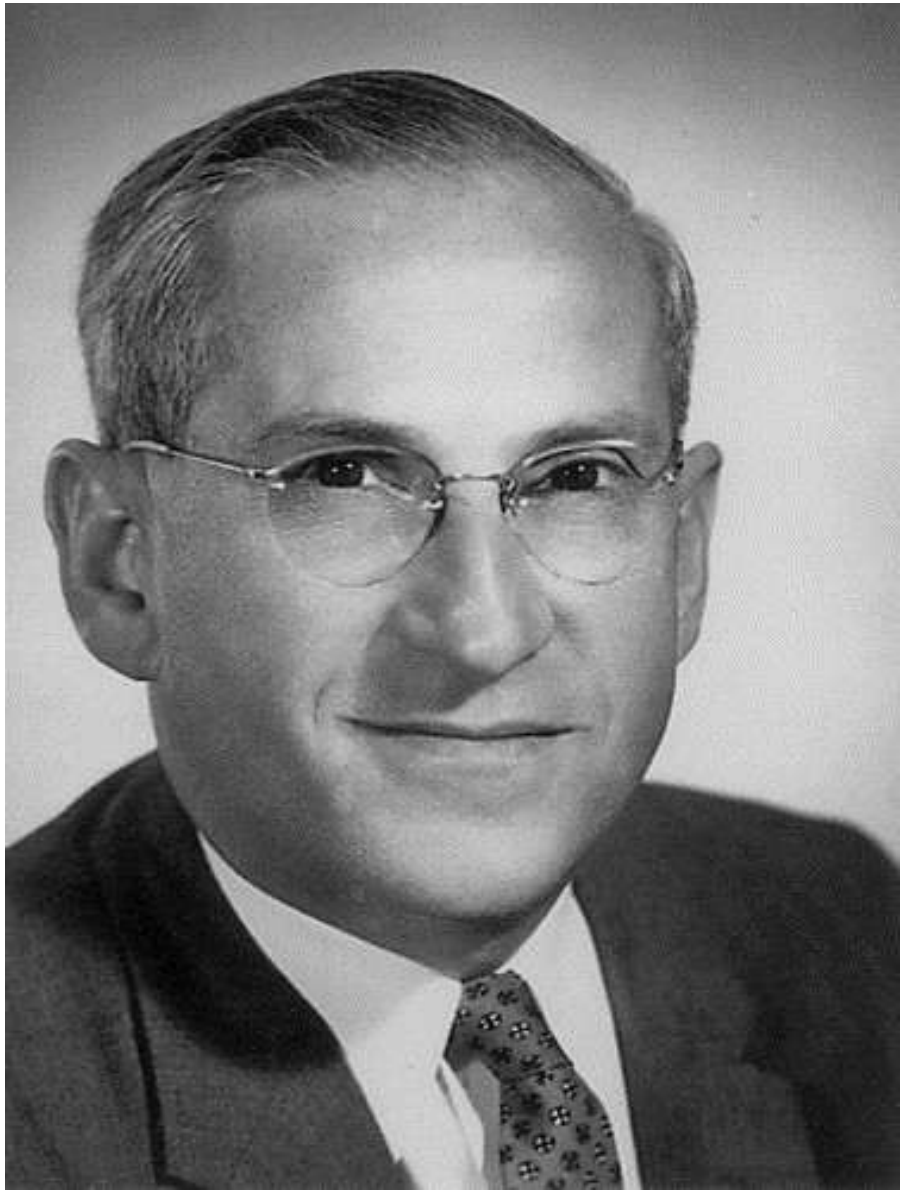
Harry Shay et al., 1953, "Treatment of leukemia with triethylene thiophosphoramide (Thio-Tepa)," *Archives of Internal Medicine*, 1953, Volume 92, pp. 628-645. From the author’s medical library. Photograph of Harry Shay is courtesy of the National Library of Medicine.
.

1956: Roy Hertz

NCI researchers Roy Hertz and Min Chiu Li were the first to completely cure a human solid tumor with chemotherapy. This highlighted what would soon become possible with chemo in breast cancer.

Yarris and Hunter wrote in 2003: "Dr. Roy Hertz has left a lasting impact in the field of medicine and cancer chemotherapy. Dr. Hertz is one of two scientists credited with the first medical cure of a solid cancer as chronicled in this 1956 paper. [I]n 1956, Hertz and M.C. Li showed that methotrexate was an effective treatment for choriocarcinoma and it could cure this malignant and metastatic cancer. Prior to moving to the NCI, Dr. Li recognized the possible link between β-hCG secretion and antifolates. In light of Dr. Hertz demonstrating that the female genitourinary tract had a high folic acid requirement, Li and Hertz hypothesized that chorionic gonadotropin producing tumors might respond to methotrexate. Later, under the direction of Dr. Hertz, Li administered methotrexate as an emergency palliative treatment to a critically ill 24-year-old woman with widely metastatic choriocarcinoma. A fall in the urinary gonadotrophin level was observed along with a dramatic clinical and radiographic improvement of the metastatic disease. The patient returned home from the hospital 4 months later fully recovered from her disease. This was the first cure of a solid tumor using chemotherapy. Subsequently, in 1956 Li and Hertz reported similar results in two other patients. Drs. Hertz and Li demonstrated that methotrexate given for 4 to 5 days every 2 weeks could clear distant metastases and was quickly hailed as the beginning of a new era in chemotherapy. In 1957 Hertz and co-workers published a study of 27 patients with choriocarcinoma and related trophoblastic tumors who were treated with a methotrexate regimen. A complete remission was produced in five patients. By 1962 the cure rate of the previously fatal choriocarcinoma had significantly improved to about 80%."

References: Olson (2002, p. 97), Yarris and Hunter (2003), Zubrod (1979)



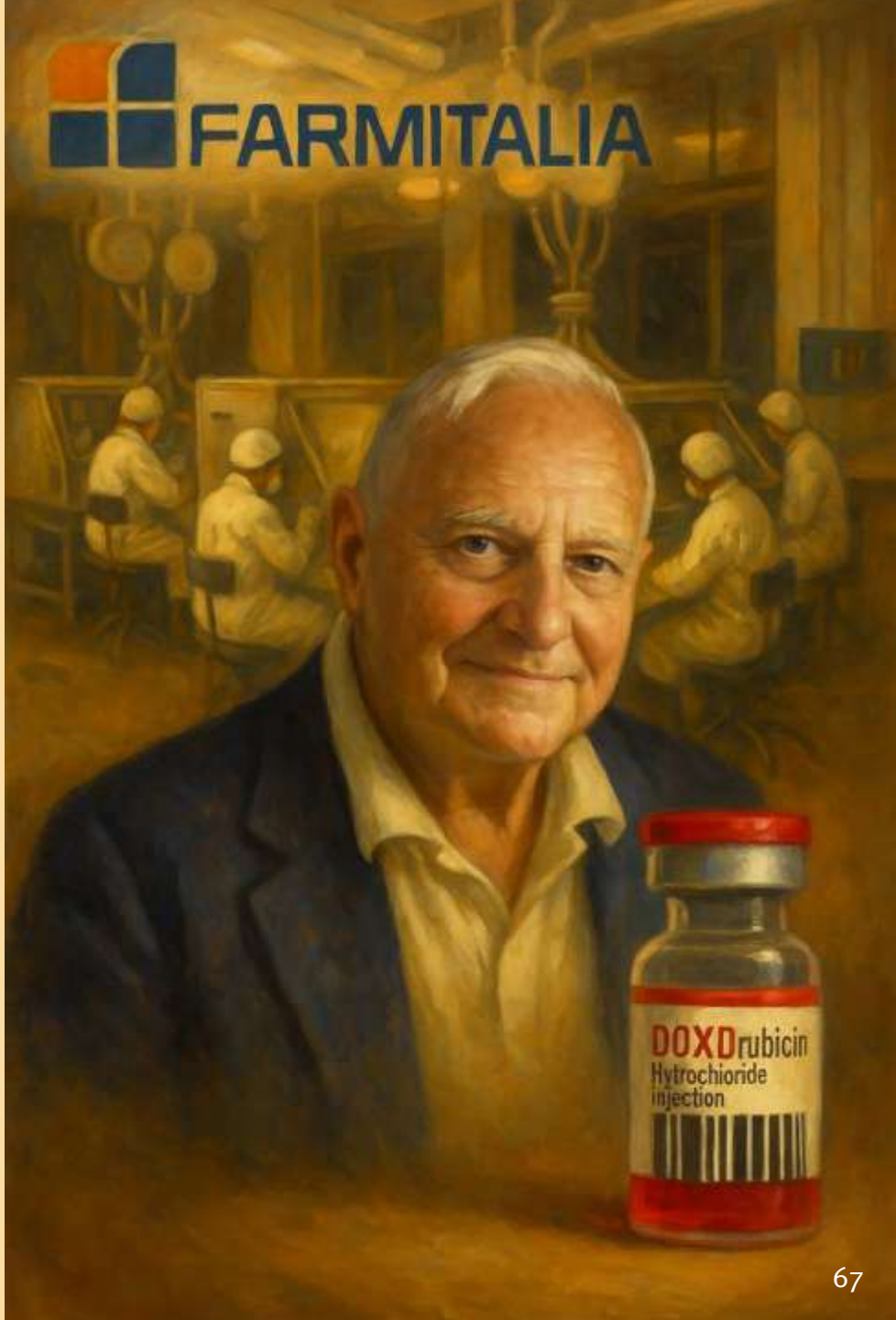
Roy Hertz and Min Chiu Li, 1956, "Effect of methotrexate therapy upon choriocarcinoma and chorioadenoma," *Proceedings of the Society for Experimental Biology and Medicine*, November, 93(2):361-6. From the author's medical library.

1969: Federico Arcamone and Farmitalia Team

Arcamone was lead of a team at Farmitalia that invented Adriamycin (doxorubicin), an anthracycline chemotherapeutic that would go on to transform breast cancer survival.

Farmitalia's Milan research labs—led scientifically by chemist Federico Arcamone with colleagues Aurelio (Gianni) Di Marco, Giovanni Cassinelli and Franco Gaetani—took anthracyclines from soil microbe to oncology mainstay. After the team's early isolation and characterization of daunorubicin ("daunomycin") from *Streptomyces peucetius* in the early 1960s, they created a mutant strain, *S. peucetius var. caesius*, that yielded 14-hydroxydaunomycin, soon named adriamycin/doxorubicin. Arcamone's 1969 paper formally reported the new antibiotic and its properties, establishing the structural relationship to daunorubicin and inaugurating clinical exploration. Reviews and later mechanistic work codified that doxorubicin intercalates DNA and poisons topoisomerase II, distinguishing it from alkylating agents and explaining its broad antitumor activity.

Clinically, Farmitalia's handoff of early vials in 1969 to Gianni Bonadonna in Milan (and parallel programs in New York) sparked pivotal trials that helped make anthracyclines core components of breast-cancer and other solid-tumor regimens in the 1970s–1980s (e.g., AC/FAC), even as cardiotoxicity prompted dose limits and later liposomal strategies. Historical reviews credit the Farmitalia group with transforming a microbial metabolite into one of the most widely used anticancer drugs and modern biosynthetic and metabolic-engineering studies still trace their lineage to the Farmitalia strain and methods. In short, the Adriamycin/Doxorubicin story—discovery, structure, production strain and early clinical translation—was a signature accomplishment of Arcamone and the Farmitalia team with lasting impact on oncology.



The Remarkable Impact of Adriamycin (Doxorubicin)

Clinical results from Adriamycin were immediate and tangible. Oncopedia does a nice job of summarizing the origin story of this drug and notes that its development required the concerted efforts of many players. Key research papers were:

1. Bonadonna G., Monfardini S., De Lena M., Fossati-Bellani F. (1969). Clinical Evaluation of Adriamycin, a New Antitumour Antibiotic. *British Medical Journal*, 3, 503-506. Advanced cancer patients were rapidly enrolled in a Phase 1 study in Milan. Rapid remissions were observed in leukemias, lymphomas and solid tumors.
2. Hoogstraten et al., "Combination chemotherapy and adriamycin in patients with advanced breast cancer. A Southwest Oncology Group study," *Cancer* 1976. — This trial compared single-agent Adriamycin vs. combination chemotherapy in advanced breast cancer: found ~39% response rate for Adriamycin alone. (in author's medical library).

This drug began to be used heavily in breast cancer treatment in the 1970s with tangible results – and, unfortunately, some serious side effects including cardio toxicity and hair loss.

Side effects or not, this drug has probably moved the breast cancer survival curve more than any other drug.

Key milestones were the 1974 FDA approval in breast cancer and the label expansion to include neoadjuvant use in node-positive breast cancer the in early 1980s. The introduction of Adriamycin with a broad label in breast cancer coincided with the availability of tamoxifen for ER+ breast carcinoma. Narod et al. (2015) generated the following chart associating the broad use of anthracyclines with the largest drop in 10-year breast cancer fatality rates.

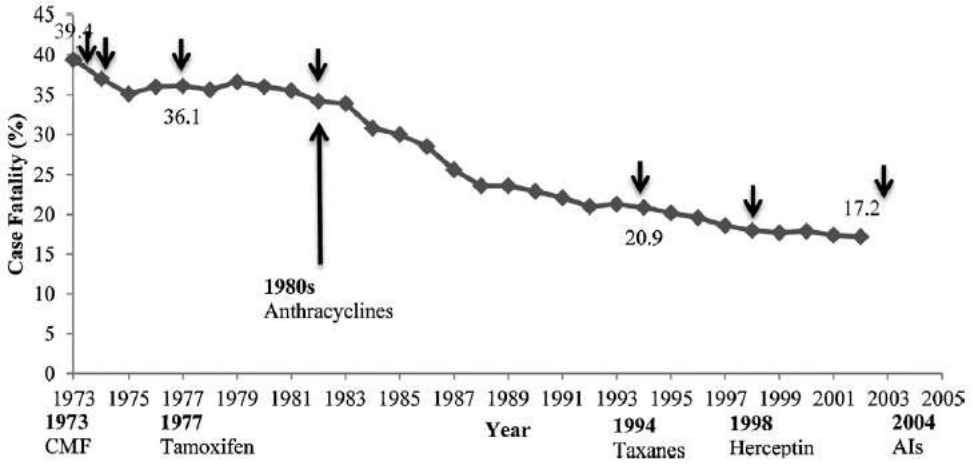


Fig. 17. 10-Year breast cancer case fatality and historical timeline of breast cancer chemotherapy.

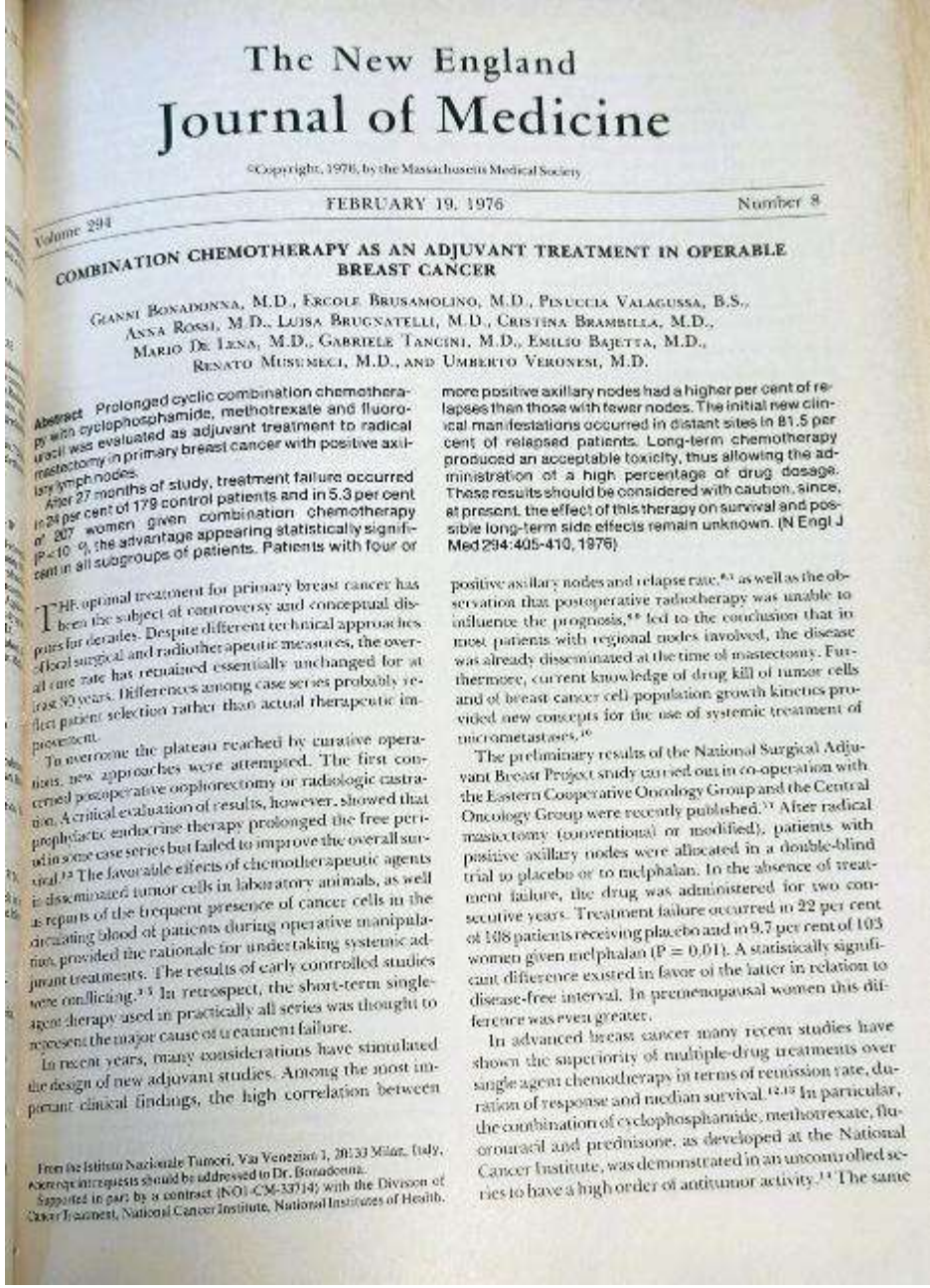
1976: Gianni Bonadonna et al.

First paper in a mainstream journal to show that adjuvant chemotherapy reduced recurrence risk in breast cancer.

In the study, Bonadonna and colleagues evaluated, in women with operable breast cancer and positive axillary lymph nodes, the effect of adding a prolonged cyclic combination chemotherapy regimen of cyclophosphamide, methotrexate and fluorouracil (CMF) following radical mastectomy. After a median follow-up period of about 27 months, they found that only 5.3% of the 207 women assigned to the CMF regimen had had a relapse, compared with 24% of 179 patients in the control (no adjuvant chemotherapy) group — the difference was highly statistically significant ($P < 10^{-6}$). They also noted that the advantage appeared across all subgroups (e.g., different numbers of involved nodes) and that the majority of new clinical manifestations of relapse were distant (81.5%) rather than local. The toxicity of the prolonged chemotherapy was deemed acceptable, allowing a high percentage of scheduled dose delivery. However, the authors pointed out that at that early time-point survival data and long-term side-effects remained unknown; the primary outcome assessed was recurrence rather than long-term overall survival.

The 1976 Bonadonna trial is widely regarded as a landmark in the development of adjuvant systemic therapy for breast cancer. It provided convincing early evidence that after surgery for operable breast cancer, the use of multi-drug "combination" chemotherapy could reduce the risk of relapse — a paradigm shift at the time when surgery (often radical mastectomy) was the primary modality and systemic micrometastases were less appreciated.

References: Ades (2017), DeVita and Rosenberg (2012), Ekmektzoglou (2009), Olson (2002, p. 251).



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COMBINATION CHEMOTHERAPY AS AN ADJUVANT TREATMENT IN OPERABLE BREAST CANCER

GIANNI BONADONNA, M.D., ERCOLE BRUSAMOLINO, M.D., PINUCCIA VALAGUSSA, B.S., ANNA ROSSI, M.D., LUISA BRUGNATELLI, M.D., CRISTINA BRAMBILLA, M.D., MARIO DE LENA, M.D., GABRIELE TANCINI, M.D., EMILIO BAJETTA, M.D., RENATO MUSELLI, M.D., AND UMBERTO VERONESI, M.D.

Abstract Prolonged cyclic combination chemotherapy with cyclophosphamide, methotrexate and fluorouracil was evaluated as adjuvant treatment to radical mastectomy in primary breast cancer with positive axillary lymph nodes.

After 27 months of study, treatment failure occurred in 24 per cent of 179 control patients and in 5.3 per cent of 207 women given combination chemotherapy ($P < 10^{-6}$), the advantage appearing statistically significant in all subgroups of patients. Patients with four or more positive axillary nodes had a higher per cent of relapses than those with fewer nodes. The initial new clinical manifestations occurred in distant sites in 81.5 per cent of relapsed patients. Long-term chemotherapy produced an acceptable toxicity, thus allowing the administration of a high percentage of drug dosage. These results should be considered with caution, since, at present, the effect of this therapy on survival and possible long-term side effects remain unknown. (N Engl J Med 294:405-410, 1976)

THE optimal treatment for primary breast cancer has been the subject of controversy and conceptual disputes for decades. Despite different technical approaches in local surgical and radiotherapeutic measures, the overall cure rate has remained essentially unchanged for at least 50 years. Differences among case series probably reflect patient selection rather than actual therapeutic improvement.

To overcome the plateau reached by curative operations, new approaches were attempted. The first concerned postoperative oophorectomy or radiologic castration. A critical evaluation of results, however, showed that prophylactic endocrine therapy prolonged the free period in some case series but failed to improve the overall survival.[1,2] The favorable effects of chemotherapeutic agents in disseminated tumor cells in laboratory animals, as well as reports of the frequent presence of cancer cells in the circulating blood of patients during operative manipulations, provided the rationale for undertaking systemic adjuvant treatments. The results of early controlled studies were conflicting.[3-5] In retrospect, the short-term single-agent therapy used in practically all series was thought to represent the major cause of treatment failure.

In recent years, many considerations have stimulated the design of new adjuvant studies. Among the most important clinical findings, the high correlation between positive axillary nodes and relapse rate,[6,7] as well as the observation that postoperative radiotherapy was unable to influence the prognosis,[8] led to the conclusion that in most patients with regional nodes involved, the disease was already disseminated at the time of mastectomy. Furthermore, current knowledge of drug kill of tumor cells and of breast cancer cell population growth kinetics provided new concepts for the use of systemic treatment of micrometastases.[9]

The preliminary results of the National Surgical Adjuvant Breast Project study carried out in co-operation with the Eastern Cooperative Oncology Group and the Central Oncology Group were recently published.[10] After radical mastectomy (conventional or modified), patients with positive axillary nodes were allocated in a double-blind trial to placebo or to melphalan. In the absence of treatment failure, the drug was administered for two consecutive years. Treatment failure occurred in 22 per cent of 148 patients receiving placebo and in 9.7 per cent of 103 women given melphalan ($P = 0.01$). A statistically significant difference existed in favor of the latter in relation to disease-free interval. In premenopausal women this difference was even greater.

In advanced breast cancer many recent studies have shown the superiority of multiple-drug treatments over single agent chemotherapy in terms of remission rate, duration of response and median survival.[11-13] In particular, the combination of cyclophosphamide, methotrexate, fluorouracil and prednisone, as developed at the National Cancer Institute, was demonstrated in an uncontrolled series to have a high order of antitumor activity.[14] The same

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Supported in part by a contract (NO1-CM-33714) with the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health.

G. Bonadonna, 1976, Combination chemotherapy as an adjuvant treatment in operable breast cancer. *N Engl J Med.* Feb 19;294(8):405-10. From the author's medical library.

1991: Frankie Ann Holmes et al.

Dramatically improved efficacy of chemo in advanced breast cancer with taxol (paclitaxel). Approved by the FDA in 1994.

n Holmes FA et al (1991) researchers reported one of the first large multicenter Phase II trials evaluating paclitaxel (Taxol) in patients with metastatic breast cancer who had received extensive prior chemotherapy.

The study included 45 evaluable women, most of whom had already been treated with anthracyclines (Adriamycin/doxorubicin) or other standard regimens. Paclitaxel was administered as a 3-hour intravenous infusion every 21 days. The trial demonstrated a remarkable overall response rate of 56%, including several complete responses, in a heavily pretreated population. The major toxicities were neutropenia and peripheral neuropathy, but these were generally manageable and cardiotoxicity—a major limitation of Adriamycin—was notably absent.

This study was pivotal because it provided the first clear evidence that paclitaxel was highly active against breast cancer, even in patients resistant to conventional agents such as Adriamycin. The results suggested that paclitaxel worked through a distinct cytotoxic mechanism—stabilizing microtubules rather than damaging DNA—allowing for non–cross-resistant activity and synergy with anthracyclines in later combination regimens. The paper's implications were immediate: it positioned Taxol as a promising new therapeutic class, justified large Phase III trials and opened the path toward its FDA approval for metastatic breast cancer in 1994. In comparison with Adriamycin, paclitaxel offered a different toxicity spectrum and meaningful activity in refractory disease, fundamentally expanding treatment options for advanced breast cancer.

Holmes FA, Walters RS, Theriault RL, Forman AD, Newton LK, Raber MN, Buzdar AU, Frye DK, Hortobagyi GN. 1991, "Phase II trial of taxol, an active drug in the treatment of metastatic breast cancer," *J Natl Cancer Inst*. Dec 18;83(24):1797-805.

2003: Larry Norton

Showed that lumping chemotherapy into a two-week window was associated with better efficacy and similar side effects as the then conventional three-week window. Argued for Norton's "dose dense" approach.

Larry Norton and colleagues' landmark 2003 study, published in Journal of Clinical Oncology, reported the results of Intergroup Trial C9741/CALGB 9741—a pivotal randomized trial that tested the concept of "dose-dense" adjuvant chemotherapy in women with node-positive breast cancer.

The investigators compared the conventional three-weekly schedule of doxorubicin, cyclophosphamide and paclitaxel to a regimen in which the same drugs were delivered every two weeks with growth factor (G-CSF) support, effectively compressing treatment time without changing cumulative dose.

The trial also evaluated sequential versus concurrent administration of these agents. The dose-dense regimen was based on Norton's mathematical "growth-fraction" model, predicting that shortening the interval between cycles would prevent tumor regrowth and improve cure rates.

The study demonstrated that dose-dense chemotherapy significantly improved disease-free survival and overall survival compared with standard scheduling, without increasing severe toxicity. At three years, the relative reduction in risk of recurrence was roughly 26% and mortality was reduced by about one-third. Sequential administration showed similar efficacy to concurrent combination therapy, indicating flexibility in regimen design.

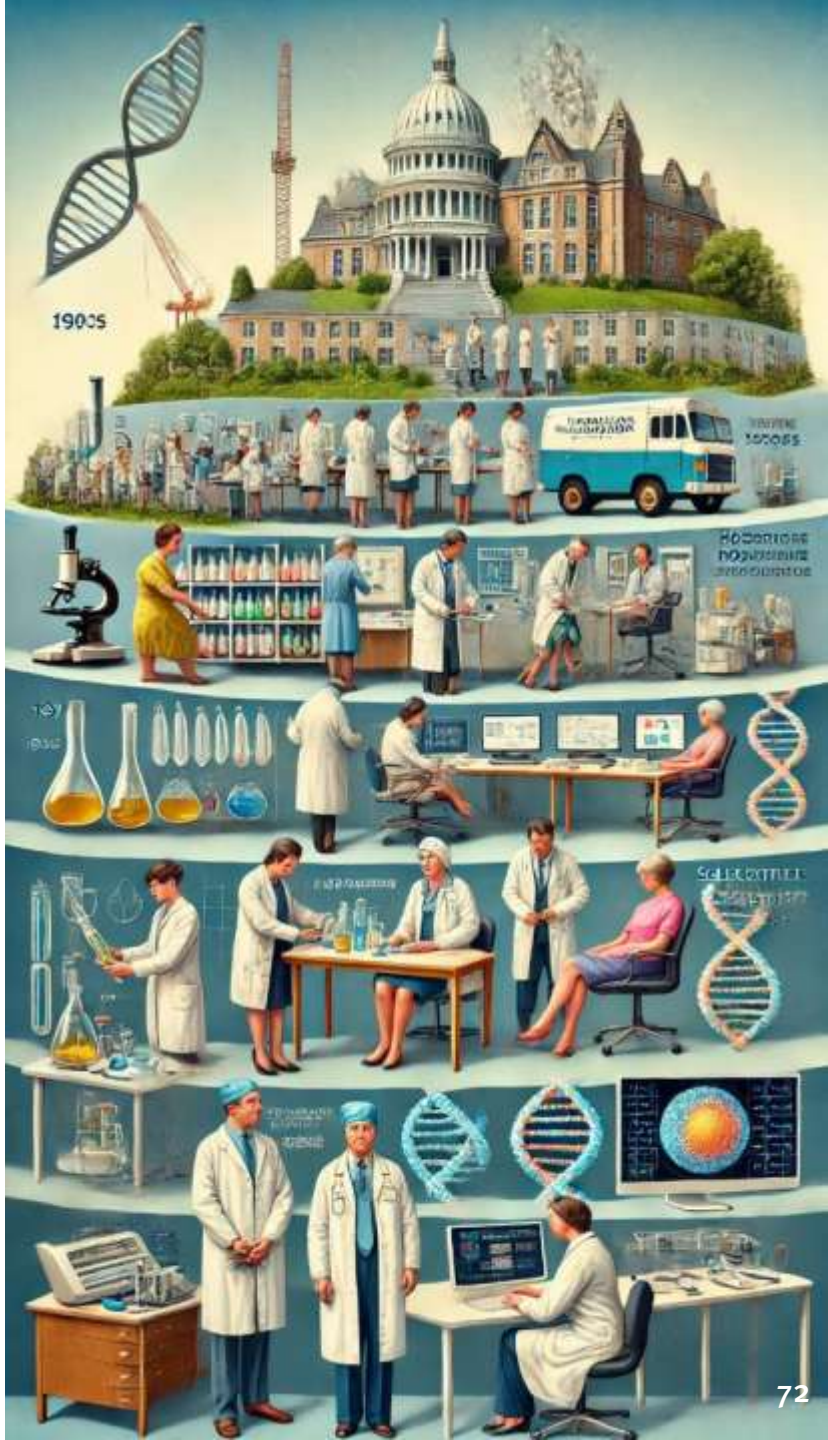
Citron ML, Norton L., et.al., 2003 "Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741," *J Clin Oncol*. Apr 15;21(8):1431-9.

Section 4.D: Hormonal Therapy

The history of hormonal therapy for breast cancer began with a bold surgical insight at the close of the 19th century. In 1896, the Scottish surgeon George Beatson observed that removing the ovaries could induce remission in some women with advanced breast cancer, suggesting that the disease depended on ovarian hormones.

His observation inaugurated the hormonal theory of breast cancer—that estrogens and later other hormones could drive tumor growth. Through the early 20th century, researchers such as Haddow expanded this concept by demonstrating that estrogens could promote mammary tumor formation in animals. Today, more than 1.5 million American women are on hormonal therapy to prevent the recurrence of the roughly 75% of breast cancers that are ER+.

The modern era began with the introduction of selective estrogen receptor modulators (SERMs), especially tamoxifen, synthesized in the 1960s and repurposed in the 1970s as an anti-estrogen by the ICI team. Approved in 1977, Tamoxifen became the first targeted systemic therapy to dramatically reduce recurrence and mortality in ER+ breast cancer. This was followed by aromatase inhibitors (anastrozole, letrozole) to suppress ovarian function. Increasingly, the focus has turned to drugs to overcome estrogen receptor (ESR1) mutations. SERDs are an area of high focus today as these can overcome ESR1 mutation resistance.



Milestones in Hormonal Therapy for Breast Cancer

1896 Beatson – Unexpectedly finds that ovary removal can cure some breast cancers

1941 Charles Huggins – Finds that prostate cancer linked to androgens. Later linked BC and hormones

1944 Haddow – Uses synthetic estrogens to treat breast cancers

1966 ICI Team – Synthesizes tamoxifen, the first SERM

1973 Elwood Jensen – Finds the estrogen receptor (ESR1) for the first time

1973 Nolvadex Trial Organization – Finds that tamoxifen can save many lives

1977 Angela Brodie– Publishes on a novel hormonal approach – the aromatase inhibitor

1998 Bernard Fisher– Showed striking evidence that SERMs could prevent breast cancer recurrence

2005 ATAC Trialist Group – Neoadjuvant use of tamoxifen associated with major survival advantage

2013 Toy et al. – First to show that mutations in ESR1 receptor responsible for therapeutic resistance

2015 Duke Team – Publish a paper showing that elacestrant is a SERD

2023 Ian Kunkler – Hormonal therapy plus lumpectomy enough. Don't need radiation

1966: Mike Harper, Dora Richardson and Arthur Walpole

First discussion in print of tamoxifen (then known as ICI 46,474), the first antiestrogenic breast cancer drug.

from V Craig Jordan's review of the Tamoxifen story in Steroids (2014): "During the early years of the 1960's, Arthur Walpole, Mike Harper and Dora Richardson were the key members of the Fertility Control program at ICI Pharmaceuticals Division, Alderley Park, near Macclesfield, Cheshire. Walpole was the senior scientist and head of the program, Harper was the experimental reproductive endocrinologist and Richardson the synthetic organic chemist. The team was tasked with advancing the goal of discovering a safe and effective "post coital" contraceptive and the work on reproduction would be continued by Labbsetwar into the 1970's despite the fact that the fertility program was going nowhere. The principal achievements of the team was the discovery that the geometric isomers of a substituted triphenylethylene were estrogenic or antiestrogenic: the cis isomer ICI 47,699 was an estrogen and the trans isomer ICI 46,474 was an antiestrogen with antifertility properties in the rat by preventing implantation that was found to be an estrogen dependent process. Most importantly, for the future development of ICI 46,474, as a long term anticancer agent, the antiestrogen did not increase desmosterol levels in rats."

From these ignominious beginnings, AstraZeneca's Tamoxifen revolutionized breast cancer treatment by becoming the first widely successful targeted endocrine therapy. Introduced in the 1970s, it acts as a selective estrogen receptor modulator (SERM)—blocking estrogen's proliferative effects on breast tissue while preserving beneficial estrogen activity in other organs. Its use dramatically improved survival in estrogen receptor–positive (ER^+) breast cancer, both as adjuvant therapy after surgery and in metastatic disease. We estimate that over 1 million lives were saved by this drug.

References: DeVita and Rosenberg (2012), Jordan (2014), Lukong (2017), Olson (2002, p. 184).

Walpole Richardson Harper

Contrasting Endocrine Activities of *cis* and *trans* Isomers in a Series of Substituted Triphenylethylenes

ALTHOUGH triphenylethylene[1,2] and many substituted triphenylethylenes[3] are known to be oestrogenic, more complex endocrine activity has been encountered in some of its basic derivatives. A notable example is clomiphene, 1-(*p*-diethylaminoethoxyphenyl)-1,2-diphenyl-2-chloroethylene (citrate)[4], which has the unexpected property of stimulating ovulation in women with ovulatory failure of certain types[5,6].

A series of analogous 1-(*p*-dialkylaminoalkoxyphenyl)-1,2-diphenyl-2-alkylethylenes has been made here[7] and in many instances the respective isomers isolated in which the unsubstituted phenyl groups are *cis* and *trans* relative to the ethylenic double bond[8]. We have found remarkable and subtle differences in biological properties between the isomeric forms of these compounds, exemplified by *cis*- and *trans*-1-(*p*-dimethylaminoethoxyphenyl)-1,2-diphenyl-2-ethylethylene (I.C.I. compounds No. 47,699 and 46,474 respectively).

Mike Harper and Arthur Walpole, 1966, Contrasting endocrine activities of cis and trans isomers in a series of substituted triphenylethylenes. *Nature*. 1966 Oct 1;212(5057):87. From the author's medical library.

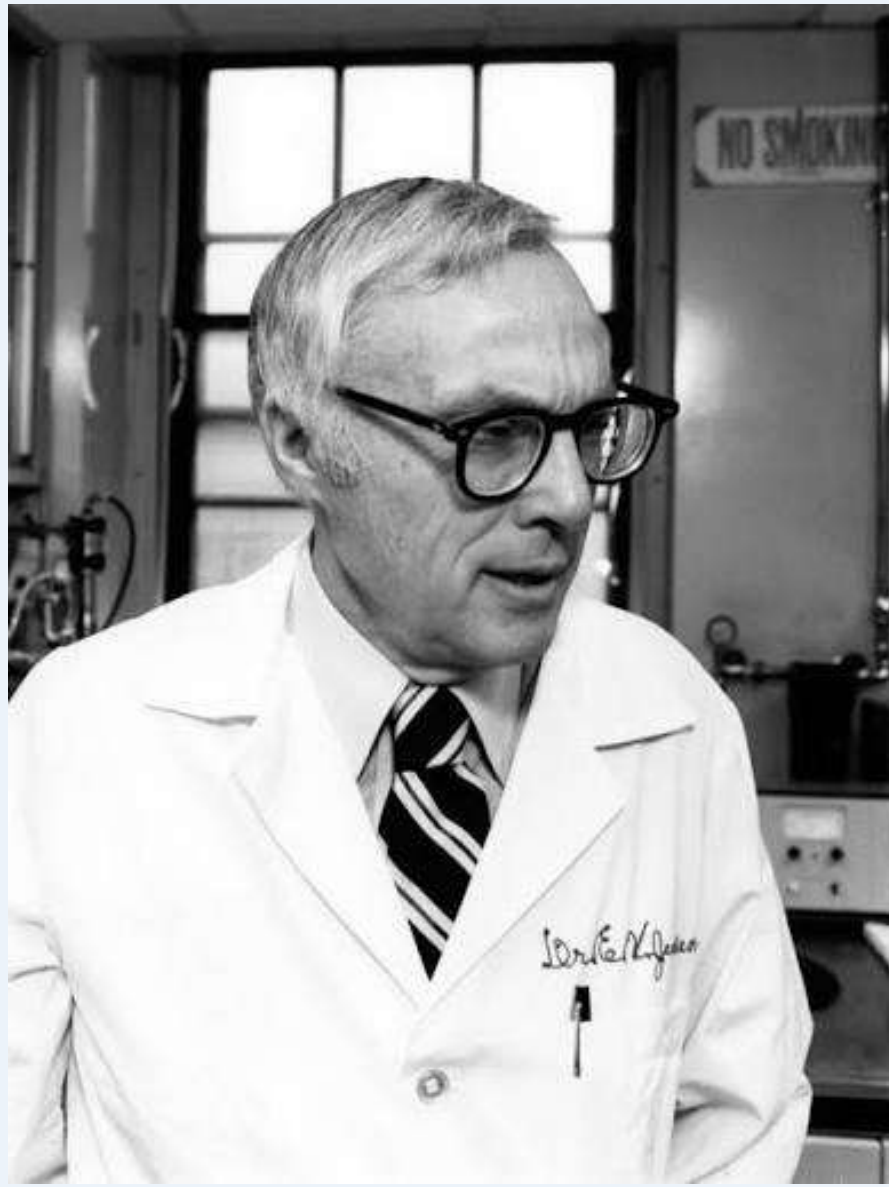
1973: Elwood Jensen

Discovered the mammalian estrogen receptor. His work led to treatments that extended and saved the lives of many women.

Elwood V. Jensen's 1973 paper, "The Role of Estrogen Receptors in the Estrogen Action," published in *Science*, crystallized two decades of pioneering research that transformed the understanding of hormone-dependent breast cancer. In this paper, Jensen described the molecular mechanism by which estrogen exerts its biological effects through specific, high-affinity intracellular receptors rather than nonspecific tissue stimulation. Using radiolabeled estradiol, he demonstrated that these estrogen receptors (ERs) were ligand-dependent transcription factors that bind DNA and activate gene expression, initiating cell proliferation in estrogen-responsive tissues such as the breast and uterus. Jensen's work provided the first direct biochemical evidence that cancer growth in some breast tumors was driven by the hormone–receptor complex, establishing a molecular target for therapeutic intervention and changing the direction of breast cancer biology from empirical endocrinology to receptor-based molecular medicine.

The implications of Jensen's research were profound. His discovery of the estrogen receptor laid the foundation for the modern era of targeted hormonal therapy in breast cancer, guiding the clinical use of anti-estrogen drugs like tamoxifen, which he and his collaborators helped validate as an ER antagonist. By correlating ER presence with therapeutic responsiveness, Jensen introduced the concept of receptor testing as a predictive biomarker—still a central principle in oncology today. His work also advanced the field of molecular endocrinology, leading to later insights into nuclear hormone receptors, gene regulation and the role of selective estrogen receptor modulators (SERMs). Over his career, Jensen's research bridged the laboratory and clinic, demonstrating that molecular profiling of tumors could directly inform treatment—an insight that remains foundational in precision oncology.

References: Ades (2017), Ekmektzoglou (2009).



Elwood Jensen, 1970, "Estrogen-receptor interaction," *Science*, Oct 12, pp. 126-134 (with De Sombre). From the author's medical library.

1977: Angela Hartley Brodie

First to publish on a selective and workable aromatase inhibitor for the treatment of breast cancer.

Angela Hartley Brodie (1934–2017) was a British-born biochemist whose groundbreaking research at the University of Maryland transformed breast cancer treatment through her invention of the first selective aromatase inhibitor, pioneering a new era of targeted hormonal therapy that has saved countless lives.

Her 1977 *Endocrinology* paper showed for the first time that blocking the enzyme aromatase—responsible for converting androgens to estrogens—could selectively suppress estrogen production and thereby inhibit the growth of estrogen-dependent tumors. Brodie and colleagues synthesized and tested 4-hydroxy-4-androstene-3,17-dione (4-OHA), a steroidal analogue designed to bind irreversibly to the aromatase enzyme. In laboratory and animal studies, they showed that this compound markedly reduced estrogen formation without broadly suppressing other steroid pathways, a key advance over earlier nonspecific inhibitors like aminoglutethimide.

This paper introduced the concept of the selective aromatase inhibitor, creating a new therapeutic strategy for hormone-responsive breast cancer. By demonstrating that estrogen deprivation could be achieved enzymatically—rather than by surgical oophorectomy or adrenalectomy—it laid the biochemical and pharmacologic foundation for an entire class of anticancer drugs.

The work ultimately led to the development of second- and third-generation inhibitors such as formestane, anastrozole and letrozole, transforming the treatment of postmenopausal breast cancer and earning Brodie recognition as the pioneer of this modern endocrine therapy.

References: Lukong (2017).

Brodie, Angela et al. 1977, " The effect of an aromatase inhibitor, 4-hydroxy-4-androstene-3,17-dione, on estrogen-dependent processes in reproduction and breast cancer," *Endocrinology*. Jun;100(6):1684-95. Image from the University of Maryland School of Medicine.

1983: Nolvadex Adjuvant Trial Organization

First high-quality evidence that a SERM (tamoxifen) saves human lives.

The 1983 paper published in *The Lancet* under the title "Controlled Trial of Tamoxifen as an Adjuvant Agent in the Management of Early Breast Cancer: Interim Analysis at Four Years," was a pivotal milestone in establishing tamoxifen as a standard adjuvant therapy for hormone-responsive breast cancer. This multicenter randomized trial evaluated whether adding tamoxifen to surgery (and, in some cases, radiation) could improve disease-free and overall survival in women with early-stage breast cancer. After four years of follow-up, the investigators reported a significant reduction in cancer recurrence rates among women treated with tamoxifen compared to controls, particularly in those whose tumors were estrogen receptor positive (ER+). The study also observed emerging trends toward improved overall survival and fewer contralateral (opposite breast) cancers, suggesting that tamoxifen had both therapeutic and preventive effects.

The implications of this paper were transformative. It provided the first large-scale clinical confirmation that long-term anti-estrogen therapy could meaningfully alter the natural course of early breast cancer, turning tamoxifen from an experimental agent into a cornerstone of adjuvant treatment. The trial's findings validated Elwood Jensen's receptor-based paradigm, proving that selective estrogen receptor modulation could suppress micrometastatic disease and prolong remission. Subsequent follow-ups and meta-analyses would show that five years of tamoxifen reduced breast-cancer mortality by roughly one-third, influencing global treatment protocols.

References: Jordan (2014), Lukong (2017).

The Lancet · Saturday 5 February 1983

CONTROLLED TRIAL OF TAMOXIFEN AS ADJUVANT AGENT IN MANAGEMENT OF EARLY BREAST CANCER

Interim Analysis at Four Years by Nolvadex Adjuvant Trial Organisation*

Summary Tamoxifen ('Nolvadex'), an anti-oestrogen, has been evaluated as an adjunct to the local treatment of early breast cancer in a prospective randomised clinical trial. 1285 women (with pathological stage II premenopausal and pathological stage I and II postmenopausal disease) were treated by total mastectomy with either axillary node clearance or axillary node sampling and then randomised to receive either tamoxifen 10 mg twice daily for two years or no further treatment. Treatment failure (recurrent disease or death) at 21 months was reduced in patients receiving tamoxifen (14·2%) compared with controls (20·5%) (p=0·01). This is equivalent to a prolongation of the disease-free interval from 21 months to 30 months at the mean follow-up time of 21 months. Subgroup analyses by menopausal, axillary lymph node, and oestrogen receptor status did not reveal a significantly different treatment effect in any of these subgroups. There has been no significant effect on mortality at this point in the study. This endocrine adjuvant therapy was well tolerated and treatment was discontinued in only 14 (2·2%) patients as a direct result of side-effects. Thus, tamoxifen significantly delays recurrence in early breast cancer. The magnitude of the effect is comparable with that associated with adjuvant cytotoxic chemotherapy at a similar follow-up time, but with minimal toxicity and excellent compliance.

Introduction

BREAST cancer is believed to have spread systemically[1] in most cases by the time the primary tumour presents. On this basis, local therapy with surgery or radiotherapy alone and without adjuvant therapy would have limited value in controlling the disease. The early adjuvant studies[2-5] of ovarian ablation demonstrated delay in the appearance of recurrent disease but had a limited effect on survival. Improved 10-year-survival data from a study in which prolonged administration of prednisone was added to ovarian ablation[6] suggest that blockade of both adrenal and ovarian oestrogen production is beneficial. However, this approach does not prevent peripheral aromatisation of steroids and the tumour is still exposed to some oestrogenic stimulation.

The introduction of non-steroidal anti-oestrogens, which are thought to act by blocking the stimulatory effects of oestradiol at the tumour, has provided an effective way in which the tumour might be deprived of all oestrogenic stimuli. One such agent, tamoxifen ('Nolvadex'), has been extensively used as a treatment for advanced disease and has been shown to be safe, effective, relatively free of side-effects, and orally active.[7] At a time when adjuvant cytotoxic chemotherapy is being extensively recommended in breast cancer, this interim report on a large prospective controlled trial of tamoxifen as adjuvant therapy in premenopausal and postmenopausal women permits comparison with the early results of the more toxic and less acceptable chemotherapeutic approaches.

Patients and Methods

Patients

1285 patients aged 75 years or less were entered into the trial from thirty-seven hospital centres in the British Isles and two centres in New Zealand. Surgery comprised a total mastectomy with either axillary node clearance or axillary node sampling. The patients were either premenopausal with one or more histologically proven ipsilateral axillary lymph nodes or postmenopausal with or without nodal involvement. Participating surgeons agreed to enter all of their patients with a particular nodal or menopausal status and elected to use the same operation throughout the study. Standard regional postoperative radiotherapy was scheduled in patients with involved nodes whose axillae had been sampled but not cleared.

Trial Design

Patients were randomised to receive either 10 mg tamoxifen twice daily for 2 years or no further treatment. Treatment was to be started within 8 weeks of mastectomy and the two groups were followed up identically. Recruitment began on Nov. 1, 1977, and closed on Feb. 6, 1981. Randomisation between tamoxifen and no treatment arms was done centrally and balanced within each centre. A trial coordinator checked the log of all patients operated on at each centre to assess any pre-randomisation selection bias. The central trial office allocated the treatment on demand (by telephone) from the trial centres.

76 of the 642 patients randomised to tamoxifen and 75 of the 643 randomised to no further treatment were found, on receipt of the written entry data, to be ineligible and were withdrawn from the study. The most common reasons for ineligibility were inoperable or metastatic disease (22 tamoxifen, 21 controls) or the randomisation

*Members of the steering committee were: Prof. M. BAUM (chairman), Dr D. M. BRINKLEY, Dr J. A. DOSSETT, Dr K. MCPHERSON, Dr J. S. PATTERSON, Dr R. D. RUBENS, Mr F. G. SMIDDY, Dr B. A. STOLL, Mr A. WILSON, Miss J. C. LEA, Mr D. RICHARDS and Mr S. H. ELLIS

8319 © The Lancet Ltd, 1983

Tamoxifen Steering Committee, 1983, "Controlled trial of tamoxifen as adjuvant agent in management of early breast cancer. Interim analysis at four years by Nolvadex Adjuvant Trial Organisation, *Lancet* , Volume 321, Issue 8319, p257-261

1998: Bernard Fisher

One of the most heavily cited papers in the history of women's health research. Showed large effect of estrogen receptor blocker in cancer prevention in older women but did not see a mortality benefit.

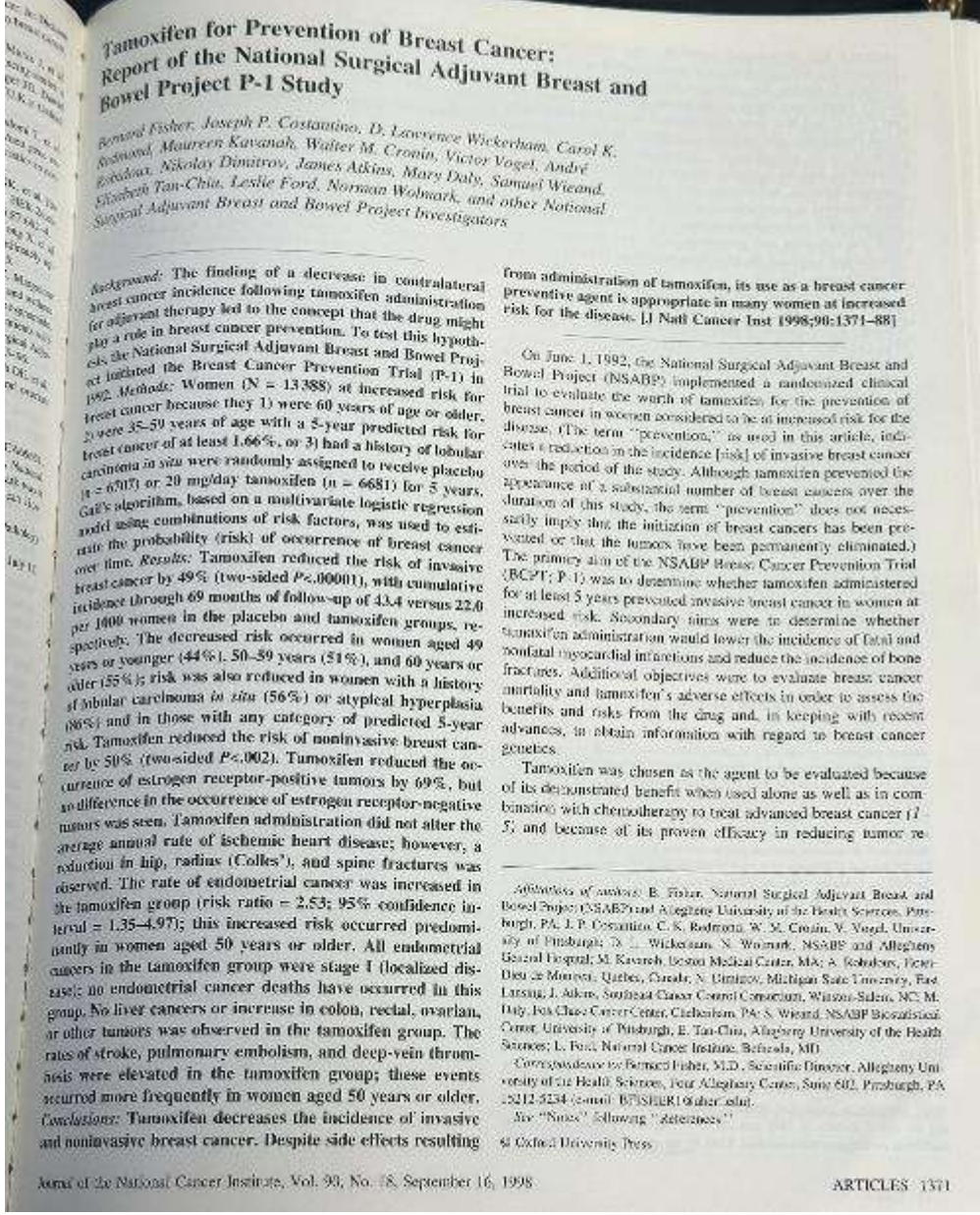
Bernie Fisher's 1998 paper on tamoxifen as a method of preventing breast cancer was a seminal work that launched the modern era of chemoprevention in oncology. Building on earlier NSABP trials showing tamoxifen's efficacy as an adjuvant therapy for hormone receptor–positive breast cancer, Fisher hypothesized that this selective estrogen receptor modulator (SERM) could also prevent breast cancer from developing in high-risk women.

Fisher proposed using a pharmacologic agent to interrupt carcinogenesis at a preclinical stage, extending the preventive model long used in cardiovascular medicine to cancer.

The results of the NSABP P-1 trial, published in JAMA in 1998, confirmed Fisher's foresight. Tamoxifen reduced the incidence of invasive breast cancer by approximately 49% in high-risk women and was particularly effective against estrogen receptor–positive tumors. These findings established tamoxifen as the first proven chemopreventive agent for any solid tumor and validated the concept of targeted hormonal prevention.

Later studies, including the IBIS-I and Royal Marsden trials, corroborated the benefit while refining safety profiles and duration of therapy. Tamoxifen's success also spurred the development of second-generation SERMs such as raloxifene and aromatase inhibitors like anastrozole (IBIS-II, 2013) for postmenopausal prevention. Fisher's 1988 paper thus marked a paradigm shift—from cancer as an inevitable disease to one that could be prevented through molecular intervention.

References: Lukong (2017), Sanli (2022).



Tamoxifen for Prevention of Breast Cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study

Bernard Fisher, Joseph P. Costantino, D. Lawrence Wickerham, Carol K. Redmond, Maureen Kavanah, Walter M. Cronin, Victor Vogel, André Robidoux, Nikolay Dimitrov, James Atkins, Mary Daly, Samuel Wieand, Elizabeth Tan-Chiu, Leslie Ford, Norman Wolmark, and other National Surgical Adjuvant Breast and Bowel Project Investigators

Background: The finding of a decrease in contralateral breast cancer incidence following tamoxifen administration for adjuvant therapy led to the concept that the drug might play a role in breast cancer prevention. To test this hypothesis, the National Surgical Adjuvant Breast and Bowel Project initiated the Breast Cancer Prevention Trial (P-1) in 1992. *Methods:* Women (N = 13388) at increased risk for breast cancer because they 1) were 60 years of age or older, 2) were 35–59 years of age with a 5-year predicted risk for breast cancer of at least 1.66%, or 3) had a history of lobular carcinoma *in situ* were randomly assigned to receive placebo (n = 6707) or 20 mg/day tamoxifen (n = 6681) for 5 years. Gail's algorithm, based on a multivariate logistic regression model using combinations of risk factors, was used to estimate the probability (risk) of occurrence of breast cancer over time. *Results:* Tamoxifen reduced the risk of invasive breast cancer by 49% (two-sided $P<.00001$), with cumulative incidence through 69 months of follow-up of 43.4 versus 22.0 per 1000 women in the placebo and tamoxifen groups, respectively. The decreased risk occurred in women aged 49 years or younger (44%), 50–59 years (51%), and 60 years or older (55%); risk was also reduced in women with a history of lobular carcinoma *in situ* (56%) or atypical hyperplasia (86%) and in those with any category of predicted 5-year risk. Tamoxifen reduced the risk of noninvasive breast cancer by 50% (two-sided $P<.002$). Tamoxifen reduced the occurrence of estrogen receptor-positive tumors by 69%, but no difference in the occurrence of estrogen receptor-negative tumors was seen. Tamoxifen administration did not alter the average annual rate of ischemic heart disease; however, a reduction in hip, radius (Colles'), and spine fractures was observed. The rate of endometrial cancer was increased in the tamoxifen group (risk ratio = 2.53; 95% confidence interval = 1.35–4.97); this increased risk occurred predominantly in women aged 50 years or older. All endometrial cancers in the tamoxifen group were stage I (localized disease); no endometrial cancer deaths have occurred in this group. No liver cancers or increase in colon, rectal, ovarian, or other tumors was observed in the tamoxifen group. The rates of stroke, pulmonary embolism, and deep-vein thrombosis were elevated in the tamoxifen group; these events occurred more frequently in women aged 50 years or older. *Conclusions:* Tamoxifen decreases the incidence of invasive and noninvasive breast cancer. Despite side effects resulting from administration of tamoxifen, its use as a breast cancer preventive agent is appropriate in many women at increased risk for the disease. [J Natl Cancer Inst 1998;90:1371–88]

On June 1, 1992, the National Surgical Adjuvant Breast and Bowel Project (NSABP) implemented a randomized clinical trial to evaluate the worth of tamoxifen for the prevention of breast cancer in women considered to be at increased risk for the disease. (The term "prevention," as used in this article, indicates a reduction in the incidence [risk] of invasive breast cancer over the period of the study. Although tamoxifen prevented the appearance of a substantial number of breast cancers over the duration of this study, the term "prevention" does not necessarily imply that the initiation of breast cancers has been prevented or that the tumors have been permanently eliminated.) The primary aim of the NSABP Breast Cancer Prevention Trial (BCPT; P-1) was to determine whether tamoxifen administered for at least 5 years prevented invasive breast cancer in women at increased risk. Secondary aims were to determine whether tamoxifen administration would lower the incidence of fatal and nonfatal myocardial infarctions and reduce the incidence of bone fractures. Additional objectives were to evaluate breast cancer mortality and tamoxifen's adverse effects in order to assess the benefits and risks from the drug and, in keeping with recent advances, to obtain information with regard to breast cancer genetics.

Tamoxifen was chosen as the agent to be evaluated because of its demonstrated benefit when used alone as well as in combination with chemotherapy to treat advanced breast cancer [1–5] and because of its proven efficacy in reducing tumor re

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See "Notes" following "References."

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Bernard Fisher et al., 1988, "Tamoxifen for Prevention of Breast Cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study," *Journal of the National Cancer Institute*, Sep, 90(18), pp. 1371-88. From the author's medical book collection.

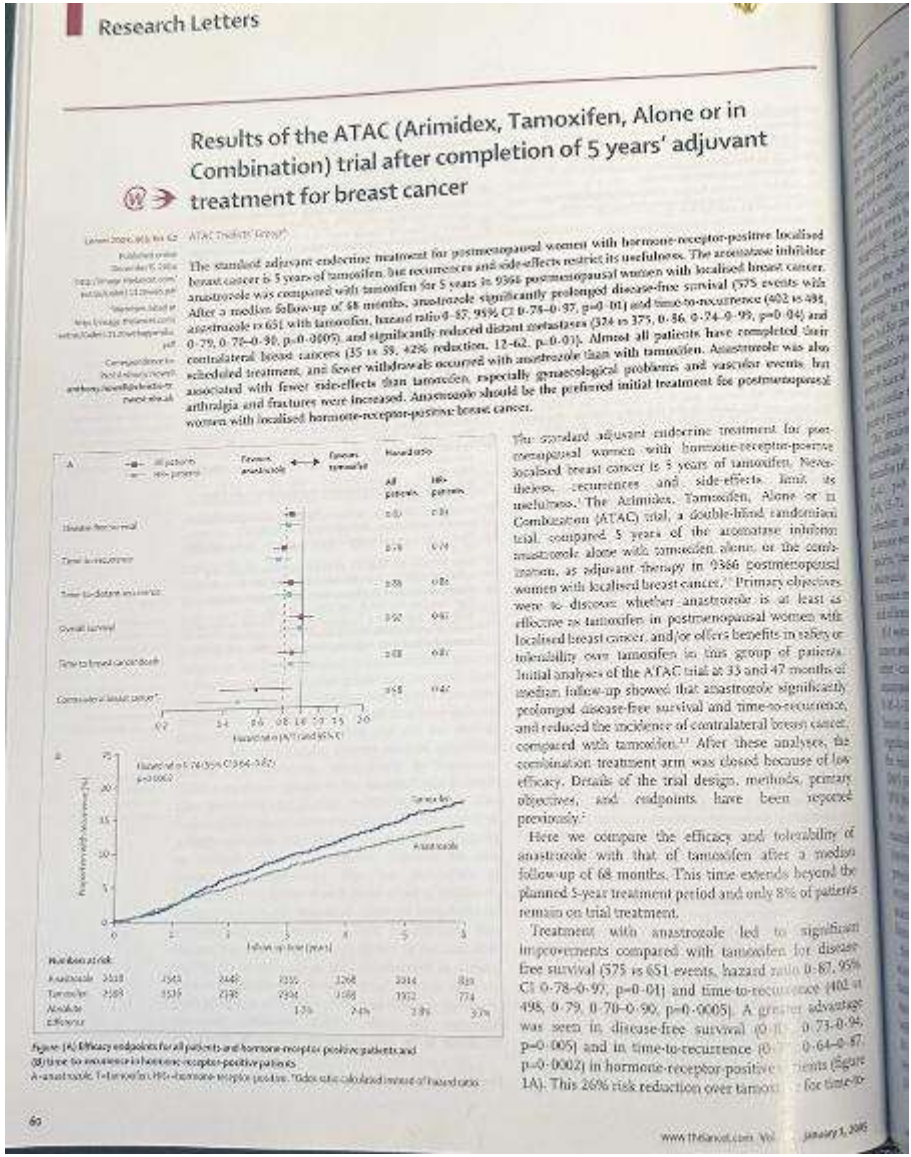
2005: ATAC Trialists Group

This consortium trial showed that adjuvant use of tamoxifen and chemotherapy generates a major survival advantage to women over 15 years after experiencing early breast cancer.

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) 2005 meta-analysis, published in *Lancet* in 2005 was one of the most comprehensive and influential syntheses in oncology history.

Drawing data from over 145,000 women enrolled in 194 randomized trials, the study pooled individual patient data to evaluate the long-term effects of adjuvant systemic therapy—both chemotherapy and hormonal therapy—on recurrence and mortality. The EBCTCG found that both polychemotherapy and tamoxifen substantially reduced 15-year breast cancer mortality, with benefits persisting long after treatment cessation. Specifically, anthracycline-based chemotherapy regimens reduced the annual breast cancer death rate by about 30–40% in women under 50 and 20–30% in women aged 50–69, while five years of tamoxifen reduced 15-year breast cancer mortality by roughly one-third in estrogen receptor–positive disease, regardless of age or nodal status. Importantly, the analysis showed that the absolute survival benefit increases with time, emphasizing the long-term durability of adjuvant therapy effects.

By quantifying survival gains across decades, the study cemented adjuvant systemic therapy as the cornerstone of early breast cancer management and provided the statistical foundation for risk-adapted adjuvant treatment strategies. It also highlighted the crucial importance of tumor biology—especially hormone receptor status—in guiding therapy selection. In the years that followed, these insights catalyzed research into targeted agents (e.g., HER2-directed therapies) and genomic assays for recurrence risk prediction, helping to shift breast cancer treatment from a one-size-fits-all model to the era of personalized oncology.


Research Letters

Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer

ATAC Trialists' Group*

The standard adjuvant endocrine treatment for postmenopausal women with hormone-receptor-positive localised breast cancer is 5 years of tamoxifen, but recurrences and side-effects restrict its usefulness. The aromatase inhibitor anastrozole was compared with tamoxifen for 5 years in 9366 postmenopausal women with localised breast cancer. After a median follow-up of 68 months, anastrozole significantly prolonged disease-free survival (575 events with anastrozole vs 651 with tamoxifen, hazard ratio 0·87, 95% CI 0·78–0·97, p=0·01) and time-to-recurrence (402 vs 498, 0·79, 0·70–0·90, p=0·0005), and significantly reduced distant metastases (324 vs 375, 0·86, 0·74–0·99, p=0·04) and contralateral breast cancers (35 vs 58, 42% reduction, 12–62, p=0·03). Almost all patients have completed their scheduled treatment, and fewer withdrawals occurred with anastrozole than with tamoxifen. Anastrozole was also associated with fewer side-effects than tamoxifen, especially gynaecological problems and vascular events, but arthralgia and fractures were increased. Anastrozole should be the preferred initial treatment for postmenopausal women with localised hormone-receptor-positive breast cancer.

ATAC Trialists Group, "Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer," Lancet, Jan 1, Volume 365, Issue 9453P60-62. From the author's medical book library.

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Articles

Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials

Summary

Introduction

EBTCG, 2005, ""Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials," Lancet, May, 365(9472):1687-717. From the author's medical library.

2013: Weiyi Toy et. al.

Provided the first evidence linking ESR1 mutations directly to acquired endocrine resistance in patients.

In 2013, Weiyi Toy and colleagues at Memorial Sloan Kettering Cancer Center published a landmark paper in *Nature Genetics* titled “ESR1 ligand-binding domain mutations in hormone-resistant breast cancer.” Toy, a postdoctoral researcher in the laboratory of Dr. Sarat Chandarlapaty, led a team that analyzed metastatic ER-positive breast cancers from patients whose disease had progressed after aromatase inhibitor therapy. Using next-generation sequencing, they discovered recurrent mutations in the ligand-binding domain of the estrogen receptor gene (ESR1), notably Y537S, Y537N and D538G, which rendered the receptor constitutively active even in the absence of estrogen. This was the first definitive demonstration that ESR1 mutations were not only present in human tumors but directly linked to acquired resistance to endocrine therapy—a crucial shift in understanding why some breast cancers relapse despite hormonal blockade.

The implications of Toy’s discovery were profound. The paper catalyzed a wave of clinical and translational research into endocrine resistance mechanisms and ushered in a new era of precision oncology for ER-positive breast cancer. Within two years, multiple groups (Robinson et al., Jeselsohn et al.) confirmed these mutations across independent cohorts, showing they occur almost exclusively in metastatic, post-aromatase-inhibitor settings. Subsequent studies established ESR1 mutations as predictive biomarkers for poor response to standard endocrine agents and targets for next-generation selective estrogen receptor degraders (SERDs) such as elacestrant, approved by the FDA in 2023. The Toy et al. discovery thus bridged molecular biology and clinical practice—transforming a conceptual insight into a new diagnostic and therapeutic paradigm in breast cancer.

ESR1 ligand-binding domain mutations in hormone-resistant breast cancer

Weiyi Toy[1], Yang Shen[2], Helen Won[1], Bradley Green[3], Rita A Sakr[4], Marie Will[5], Zhiqiang Li[1], Kinisha Gala[1], Sean Fanning[3], Tari A King[4], Clifford Hudis[5,6], David Chen[7], Tetiana Taran[7], Gabriel Hortobagyi[8], Geoffrey Greene[3], Michael Berger[1,9], José Baselga[1,5] & Sarat Chandarlapaty[1,5,6]

Seventy percent of breast cancers express estrogen receptor (ER), and most of these are sensitive to ER inhibition. However, many such tumors for unknown reasons become refractory to inhibition of estrogen action in the metastatic setting. We conducted a comprehensive genetic analysis of two independent cohorts of metastatic ER-positive breast tumors and identified mutations in *ESR1* affecting the ligand-binding domain (LBD) in 14 of 80 cases. These included highly recurrent mutations encoding p.Tyr537Ser, p.Tyr537Asn and p.Asp538Gly alterations. Molecular dynamics simulations suggest that the structures of the Tyr537Ser and Asp538Gly mutants involve hydrogen bonding of the mutant amino acids with Asp351, thus favoring the agonist conformation of the receptor. Consistent with this model, mutant receptors drive ER-dependent transcription and proliferation in the absence of hormone and reduce the efficacy of ER antagonists. These data implicate LBD-mutant forms of ER in mediating clinical resistance to hormonal therapy and suggest that more potent ER antagonists may be of substantial therapeutic benefit.

ER is a member of the nuclear receptor family and regulates the transformed phenotype of the majority of breast cancers. Pharmacological inhibitors of estrogen-driven signaling are effective in many of these cases[1]. Therapeutics in this class include drugs that suppress estrogen production (aromatase inhibitors and gonadotropin-releasing hormone agonists) and direct inhibitors of ER (selective ER modulators (SERMs) or selective ER degraders (SERDs))[2]. Although most patients with ER-positive breast cancer derive a benefit from these drugs, resistance often emerges after prolonged exposure[1,3–5]. The mechanisms underlying this phenomenon are unclear, and a better understanding of acquired resistance to hormone antagonists is essential for the development of more durable and effective therapeutics.

RESULTS

***ESR1* mutations in metastatic breast cancer**

To identify possible genetic mechanisms underlying acquired resistance to hormonal therapy, we sought to characterize tumors from individuals with metastatic ER-positive breast cancer treated for at least 3 months with hormonal therapy and whose tumors had grown or spread to new sites while on therapy. As part of a metastatic breast tumor procurement protocol (National Clinical Trials Registry 00897702), we identified 38 of 71 samples that met these criteria and had sufficient tumor DNA for analysis. We used a targeted approach to genomic characterization, surveying for mutations and copy number alterations in 230 genes commonly mutated in cancer through massively parallel sequencing (MSKCC sequencing panel)[6]. Two cases were excluded from the analysis because they did not pass quality control testing for being from a single source. In the MSKCC cohort, we had normal DNA from white blood cells for comparison in 22 cases. Analysis of these 22 matched samples identified an average of 4.3 mutations per tumor with a mean coverage depth of ~500× (normal sample, 441×; metastatic sample, 696×) (**Supplementary Table 1**). Six genes were mutated in more than 10% of the matched cases. We compared the prevalence of mutations in these genes in our set of relapsed tumors with their prevalence in The Cancer Genome Atlas (TCGA) invasive primary (untreated) breast cancer and luminal A and luminal B primary breast cancer cases and found that the prevalence of mutations in *TP53*, *PIK3CA* and *GATA3* was comparable in all sets (**Fig. 1a**)[7]. By contrast, *ESR1*, *RPTOR* and *ERBB3* mutations were detected at much higher rates in our samples than in those reported by TGCA. The fact that these mutations are enriched among tumors from patients who had relapsed while on hormonal therapy suggests that they may have a role in the development of acquired resistance. Gene copy number was also analyzed in these samples, and the genes that were frequently amplified are shown in **Figure 1b**. Amplification of *ERBB2* (refs. 8–10), *CCND1* (ref. 11) or *FGFR1* (ref. 12) was common and has previously been associated with hormone resistance, but these amplifications were not commonly observed to be acquired in those cases where we had information on the primary tumor.

[1]Human Oncology and Pathogenesis Program, Memorial Sloan-Kettering Cancer Center (MSKCC), New York, New York, USA. [2]Toyota Technological Institute at Chicago, Chicago, Illinois, USA. [3]Ben May Department of Cancer Research, University of Chicago, Chicago, Illinois, USA. [4]Breast Service, Department of Surgery, MSKCC, New York, New York, USA. [5]Weill Cornell Medical College, New York, New York, USA. [6]Breast Cancer Medicine Service, Solid Tumor Division, Department of Medicine, MSKCC, New York, New York, USA. [7]Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA. [8]Department of Breast Medical Oncology, MD Anderson Cancer Center, Houston, Texas, USA. [9]Department of Pathology, MSKCC, New York, New York, USA. Correspondence should be addressed to S.C. (chandars@mskcc.org).

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2015: Duke Group Show Elacestrant is a SERD

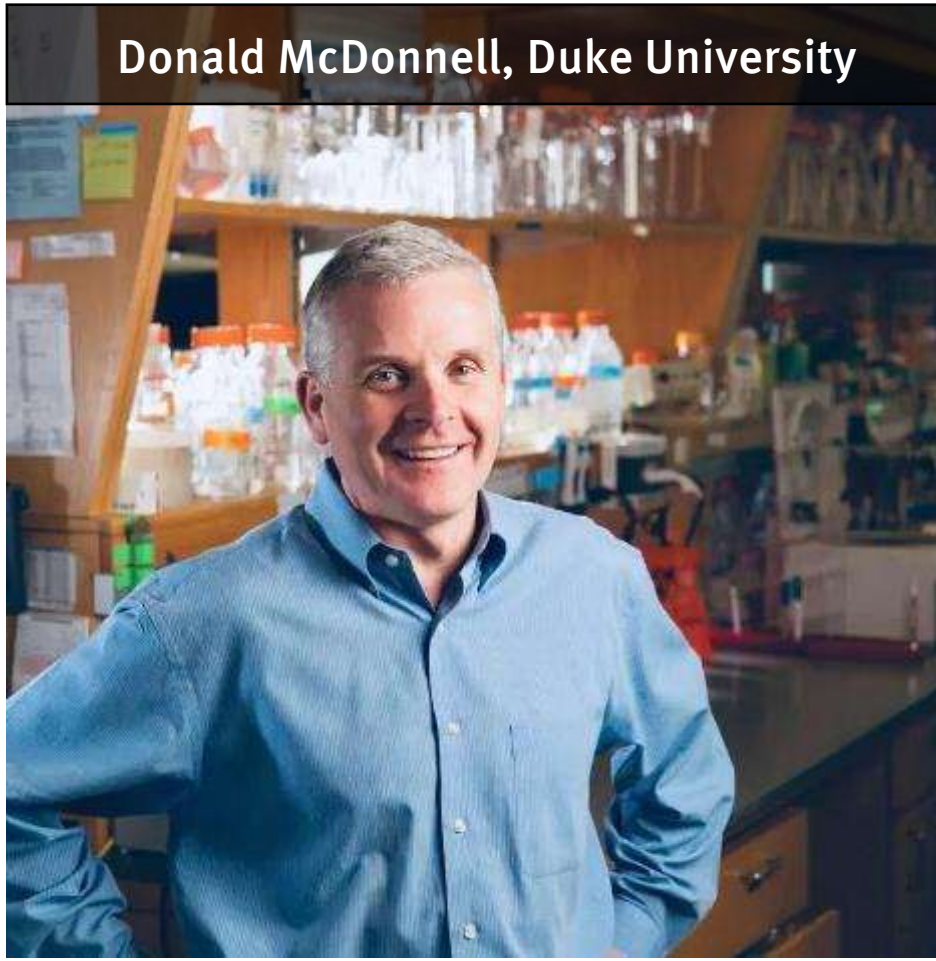
Two grad students in McDonnell's Lab at Duke University found that a Radius Therapeutics hot flashes drug could knock down ESR1 (a SERD)

Interview with McDonnell in 2023:

Q: There's a lot of buzz right now around elacestrant following successful Phase 3 trials and the NDA (New Drug Application) filing with the FDA for marketing approval. I understand that this drug (originally called RAD1901) was designed to treat hot flashes brought on by menopause but failed. Instead, members of your lab discovered a new utility — that it could work to treat ER+ breast cancer.

A: Yes. That's right. We love drugs that don't work the way they're supposed to and/or demonstrate peculiar pharmacology. You can learn a lot by defining the mechanism of action of such drugs. Suzanne Wardell, PhD (an assistant professor working in my lab) and Erik Nelson, PhD (now at the University of Illinois and a former post-doctoral trainee), elucidated the drug's mechanism of action with their eureka moment coming just two weeks after starting work on the project in 2012.

They found in their studies of human breast cell lines that RAD1901 was effective at blocking estrogen from binding to the receptor, thus stopping cell growth — a SERM property. Quite unexpectedly they also found that the drug had SERD properties and downregulated the expression of the receptor in breast cancer cells. They further demonstrated that the drug effectively inhibited the growth of ER-positive tumors in mouse models of breast cancer.



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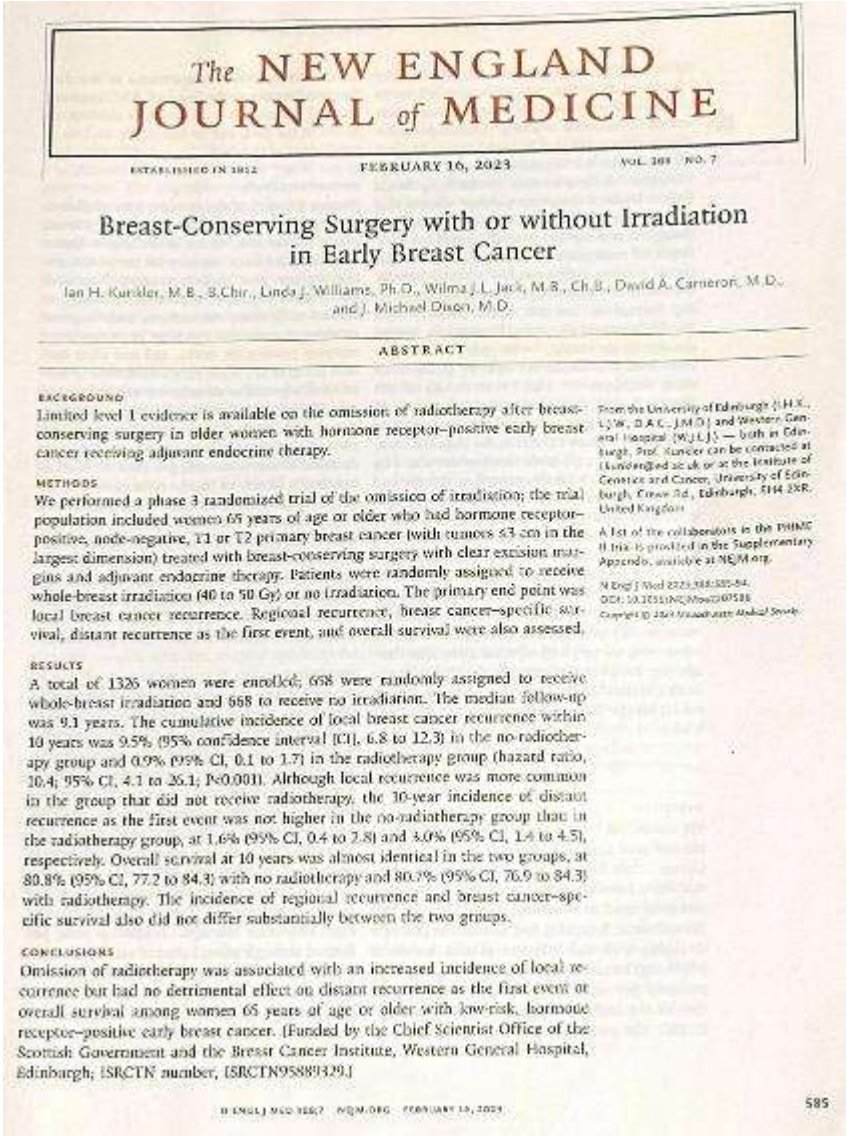
2023: Ian Kunkler

Showed the benefit of tailored therapy for older women with early HR+ breast cancer, arguing that radiation can be omitted.

The study was a phase III randomized trial (known as the PRIME II trial; ISRCTN95889329) that evaluated whether omitting whole-breast irradiation after breast-conserving surgery (BCS) would compromise outcomes in a specific low-risk group of older women. Participants were women aged ≥ 65 years, with hormone receptor–positive, node-negative, T1 or T2 (≤3 cm) invasive breast cancer, who had clear surgical margins and were receiving adjuvant endocrine therapy. They were randomly assigned to receive either whole-breast irradiation (40-50 Gy) or no further radiotherapy. The primary endpoint was ipsilateral breast-tumour recurrence; secondary endpoints included regional recurrence, distant recurrence as first event, breast cancer–specific survival and overall survival. After a median follow-up of 9.1 years, the 10-year cumulative incidence of local (in-breast) recurrence was 9.5% in the no-irradiation group versus 0.9% in the radiotherapy group (hazard ratio ~10.4; 95% CI 4.1-26.1; P < 0.001).

The findings of the Kunkler et al. paper have major implications for practice. Firstly, they provide high-quality evidence that for older women (≥ 65 years) with early, hormone receptor–positive, node-negative, low-risk breast cancer treated with BCS and endocrine therapy, omission of adjuvant whole-breast irradiation is a viable option, albeit with a higher rate of local recurrence but without compromising distant disease control or survival. This supports a more individualized, de-escalated approach to adjuvant radiotherapy in selected patients — potentially sparing older women the cost, inconvenience and side-effects of radiation. Secondly, the study underscores the importance of risk stratification (age, tumour biology, nodal status) when planning radiotherapy, rather than applying a one-size-fits-all strategy.



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Breast-Conserving Surgery with or without Irradiation in Early Breast Cancer

Ian H. Kunkler, M.B., B.Chir., Linda J. Williams, Ph.D., Wilma J.L. Jack, M.B., Ch.B., David A. Cameron, M.D., and J. Michael Dixon, M.D.

ABSTRACT

BACKGROUND
Limited level 1 evidence is available on the omission of radiotherapy after breast-conserving surgery in older women with hormone receptor–positive early breast cancer receiving adjuvant endocrine therapy.

METHODS
We performed a phase 3 randomized trial of the omission of irradiation; the trial population included women 65 years of age or older who had hormone receptor–positive, node-negative, T1 or T2 primary breast cancer (with tumors ≤3 cm in the largest dimension) treated with breast-conserving surgery with clear excision margins and adjuvant endocrine therapy. Patients were randomly assigned to receive whole-breast irradiation (40 to 50 Gy) or no irradiation. The primary end point was local breast cancer recurrence. Regional recurrence, breast cancer–specific survival, distant recurrence as the first event, and overall survival were also assessed.

RESULTS
A total of 1326 women were enrolled; 658 were randomly assigned to receive whole-breast irradiation and 668 to receive no irradiation. The median follow-up was 9.1 years. The cumulative incidence of local breast cancer recurrence within 10 years was 9.5% (95% confidence interval [CI], 6.8 to 12.3) in the no-radiotherapy group and 0.9% (95% CI, 0.1 to 1.7) in the radiotherapy group (hazard ratio, 10.4; 95% CI, 4.1 to 26.1; P<0.001). Although local recurrence was more common in the group that did not receive radiotherapy, the 10-year incidence of distant recurrence as the first event was not higher in the no-radiotherapy group than in the radiotherapy group, at 1.6% (95% CI, 0.4 to 2.8) and 3.0% (95% CI, 1.4 to 4.5), respectively. Overall survival at 10 years was almost identical in the two groups, at 80.8% (95% CI, 77.2 to 84.3) with no radiotherapy and 80.7% (95% CI, 76.9 to 84.3) with radiotherapy. The incidence of regional recurrence and breast cancer–specific survival also did not differ substantially between the two groups.

CONCLUSIONS
Omission of radiotherapy was associated with an increased incidence of local recurrence but had no detrimental effect on distant recurrence as the first event or overall survival among women 65 years of age or older with low-risk, hormone receptor–positive early breast cancer. (Funded by the Chief Scientist Office of the Scottish Government and the Breast Cancer Institute, Western General Hospital, Edinburgh; ISRCTN number, ISRCTN95889329.)

From the University of Edinburgh (I.H.K., L.J.W., D.A.C., J.M.D.) and Western General Hospital (W.J.L.J.) — both in Edinburgh, Prof. Kunkler can be contacted at I.kunkler@ed.ac.uk or at the Institute of Genetics and Cancer, University of Edinburgh, Crewe Rd., Edinburgh, EH4 2XR, United Kingdom.

A list of the collaborators in the PRIME II trial is provided in the Supplementary Appendix, available at NEJM.org.

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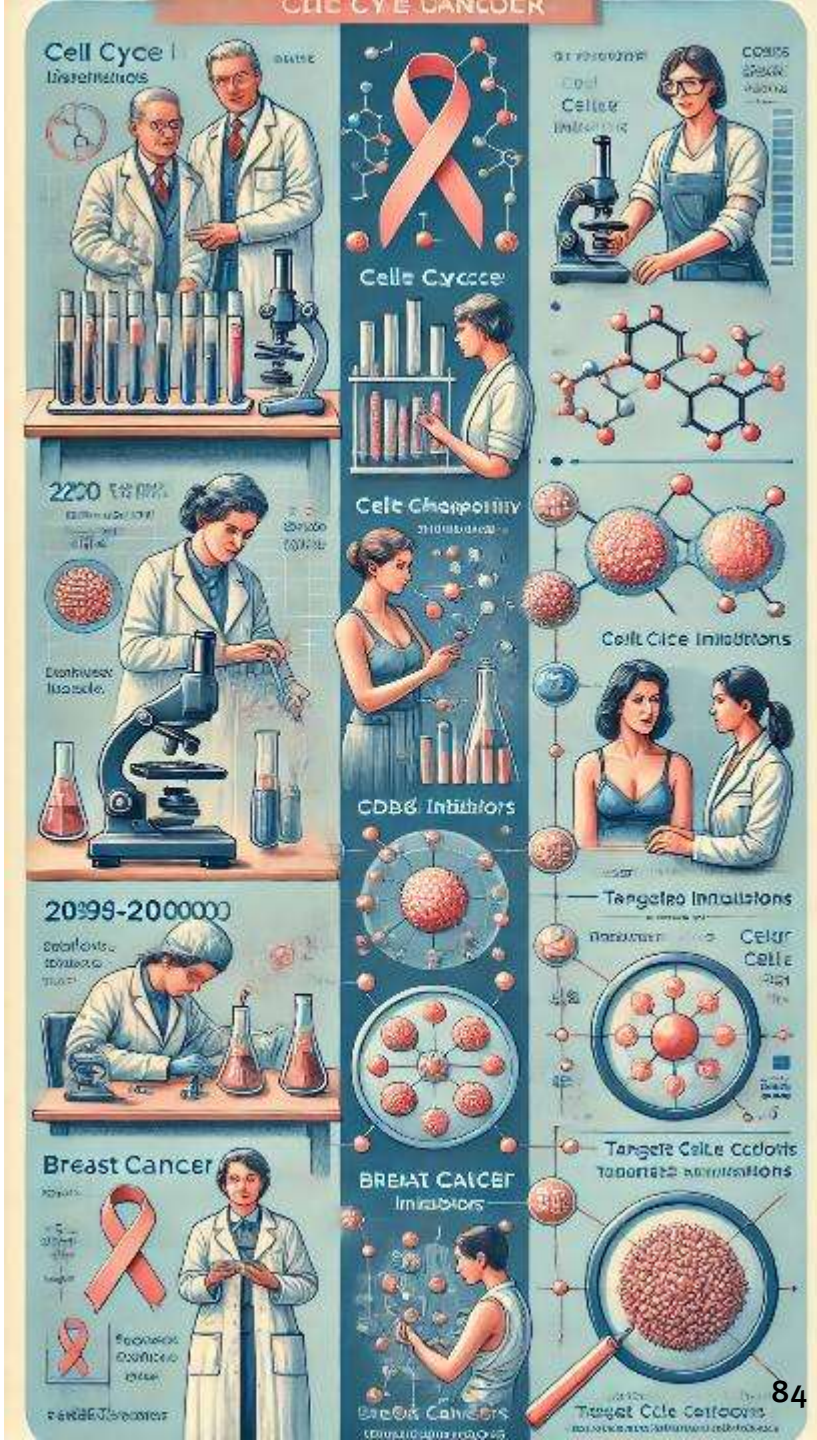
Kunkler IH, Williams LJ, Jack WJL, Cameron DA, Dixon JM., 2023, Breast-Conserving Surgery with or without Irradiation in Early Breast Cancer. *N Engl J Med.* Feb 16;388(7):585-594, First edition. From the author's medical library.

Section 4.E: Cell Cycle Inhibitors

The concept of targeting the cell cycle in cancer therapy traces back to the mid-20th century, when early chemotherapeutic agents such as antimetabolites and mitotic poisons were found to act by halting specific phases of cellular division. However, true molecular understanding of the cell cycle emerged only in the late 20th century through fundamental discoveries in yeast and mammalian systems. In the 1970s and 1980s, pioneering work by Leland Hartwell, Paul Nurse and Tim Hunt—later honored with the 2001 Nobel Prize—identified key regulators such as cyclins and cyclin-dependent kinases (CDKs) as the molecular engines driving cell division. This insight shifted cancer biology from descriptive pathology to precise molecular control: cancer was increasingly seen as a disease of deregulated cell cycle checkpoints.

After decades of refinement, the CDK4/6 inhibitors—palbociclib (Ibrance), ribociclib (Kisqali) and abemaciclib (Verzenio)—ushered in a new era of targeted therapy for ER-positive, HER2-negative breast cancer. By selectively halting progression from the G1 to S phase in tumor cells while sparing normal tissues, these agents offered a rational and well-tolerated means to control disease Their success validated the concept that disrupting the cancer cell's internal clock could be as powerful as blocking external growth signals. Work continues in this area with intense interest today, for example on CDK2 inhibition as a promising route to breast cancer treatment.

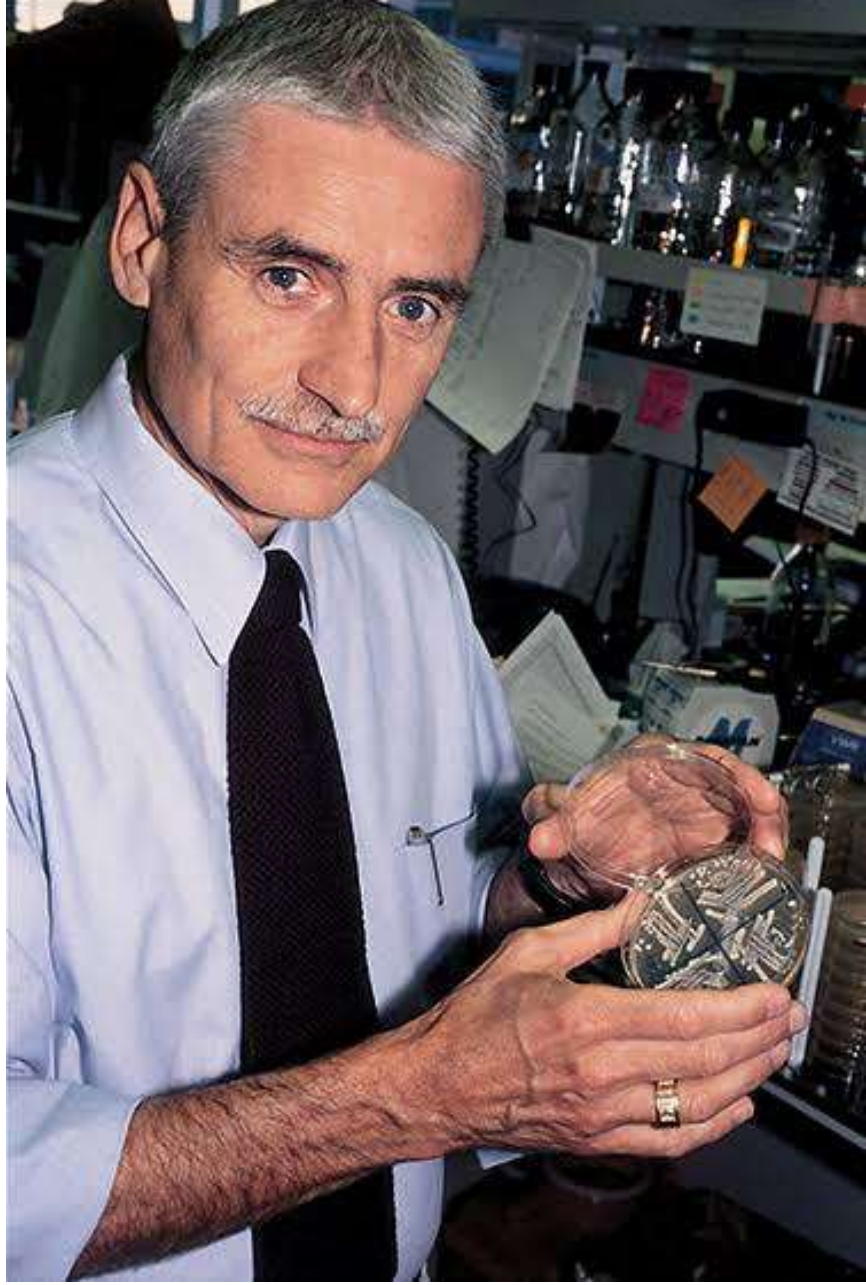


1970: Lee Hartwell

Work on gene mutants controlling the cell cycle in yeast led to CDK inhibitors (and a Nobel Prize).

Lee Hartwell's 1970 paper, "Genetic Control of the Cell Division Cycle in Yeast I," published in the Journal of Molecular Biology, marked a turning point in molecular biology and cancer research. In this landmark study, Hartwell used the budding yeast *Saccharomyces cerevisiae* as a model system to identify temperature-sensitive mutants that became arrested at specific points in the cell cycle. These mutants, which he called cdc (cell division cycle) mutants, revealed that the process of cell division was governed by discrete, genetically controlled checkpoints rather than a continuous biochemical flow. Hartwell's systematic approach established yeast as a powerful genetic model for understanding eukaryotic cell-cycle control and introduced key concepts such as the "start" checkpoint, where cells commit to DNA replication and division. This work provided the genetic framework that later allowed molecular biologists to identify specific regulatory proteins, cyclins and kinases that orchestrate cell-cycle progression.

Over the next two decades, Hartwell's discoveries—expanded upon by Paul Nurse and Tim Hunt—laid the foundation for the molecular understanding of cell-cycle regulation, particularly the mechanisms ensuring accurate DNA replication and chromosomal segregation. His concept of cell-cycle checkpoints proved essential in explaining how cells maintain genomic integrity and how their failure contributes to cancer. Together with Nurse and Hunt, Hartwell shared the 2001 Nobel Prize in Physiology or Medicine "for their discoveries of key regulators of the cell cycle." Hartwell's pioneering genetic dissection of the cell cycle thus transformed our understanding of cellular proliferation, aging and tumor biology—foundations upon which modern cancer therapeutics, such as CDK inhibitors, are built.



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1987: Paul Nurse

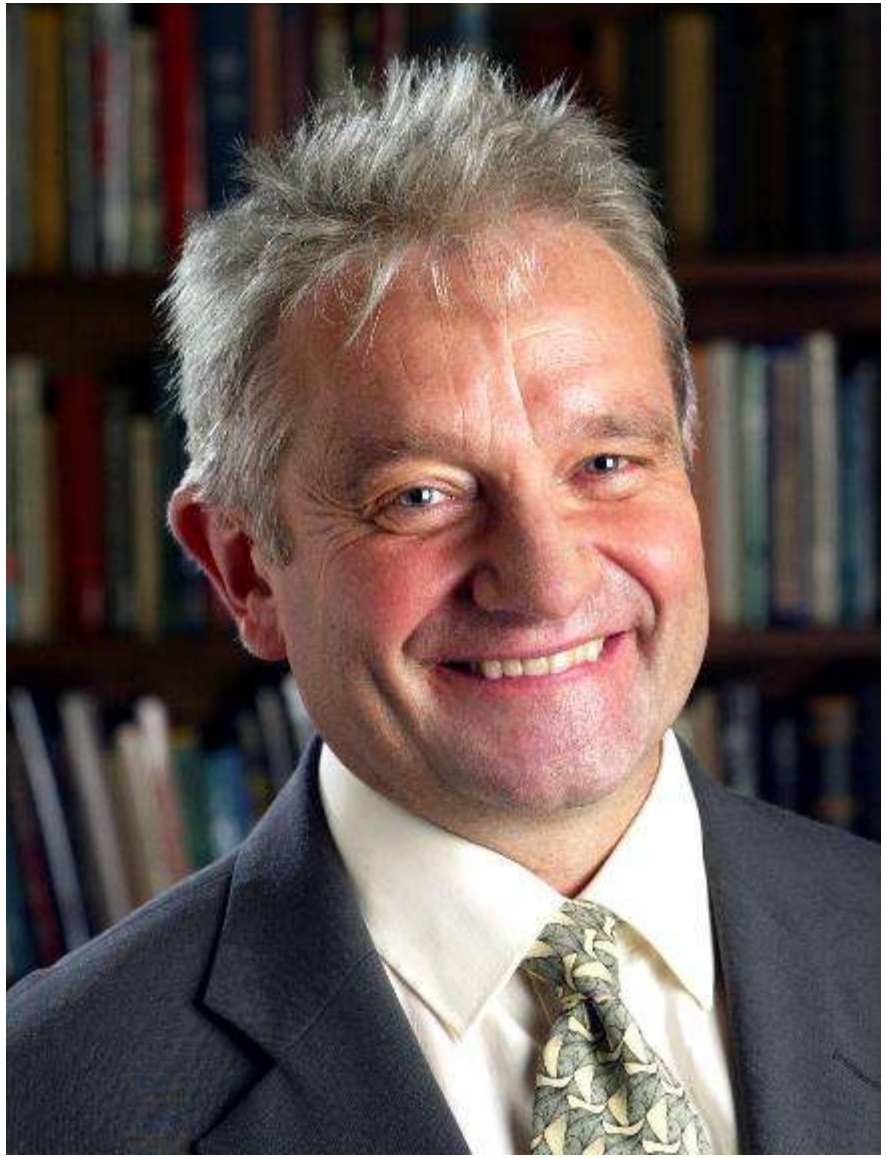
Nurse's work provided the conceptual foundation for viewing cancer as a disease of uncontrolled cell-cycle progression rather than merely of uncontrolled growth. This led to eventual development of CDK inhibitors for breast cancer.

Nobel Prize Press Release (2001): "In the middle of the 1970s, Paul Nurse discovered the gene cdc2 in S. pombe. He showed that this gene had a key function in the control of cell division (transition from G2 to mitosis, M).

Later he found that cdc2 had a more general function. It was identical to the gene ("start") that Hartwell earlier had identified in baker's yeast, controlling the transition from G1 to S. This gene (cdc2) was thus found to regulate different phases of the cell cycle.

In 1987 Paul Nurse isolated the corresponding gene in humans and it was later given the name CDK1 (cyclin dependent kinase 1). The gene encodes a protein that is a member of a family called cyclin dependent kinases, CDK. Nurse showed that activation of CDK is dependent on reversible phosphorylation, i.e. that phosphate groups are linked to or removed from proteins. On the basis of these findings, half a dozen different CDK molecules have been found in humans."

Insights from Nurse and others revealed that cell cycle dysregulation—through overactive CDKs, loss of tumor suppressors like RB1, or amplified cyclins such as cyclin D1—is a hallmark of cancer, including many breast tumors. Nurse's work provided the conceptual foundation for viewing cancer as a disease of uncontrolled cell-cycle progression rather than merely of uncontrolled growth.



Paul Nurse et al. "Complementation used to clone a human homologue of the fission yeast cell cycle control gene cdc2," *Nature*, June 1987, Volume 387. From the author's medical book collection.

2016: Richard Finn and Dennis Slamon

First definitive data for a CDK4/6 inhibitor in breast cancer. Palbociclib resulted in substantially longer progression-free survival than the comparator.

This paper examined the combination of the CDK4/6 inhibitor Palbociclib with the aromatase inhibitor Letrozole as first-line therapy in post-menopausal women with hormone-receptor–positive (ER$^+$), HER2-negative advanced breast cancer. In a phase 3, randomized, double-blinded trial involving 666 patients who had not yet received systemic therapy for their advanced disease, patients were assigned in a 2:1 ratio to palbociclib + letrozole or placebo + letrozole. The primary endpoint was progression-free survival (PFS). The results showed a median PFS of 24.8 months (95% CI: 22.1 to not estimable) in the palbociclib-letrozole arm versus 14.5 months (95% CI: 12.9 to 17.1) in the placebo-letrozole arm, corresponding to a hazard ratio (HR) of 0.58 (95% CI: 0.46 to 0.72; P < 0.001). The most common high-grade adverse event was neutropenia, occurring in 66.4% of palbociclib-treated patients versus 1.4% in controls; other significant toxicities included leukopenia and fatigue.

The implications of this study were substantial for the management of advanced breast cancer. By demonstrating that adding a targeted CDK4/6 inhibitor to standard endocrine therapy significantly extended PFS, the paper helped establish palbociclib + letrozole as a new standard of care for first-line treatment of ER$^+$/HER2-negative advanced disease. It underscored the importance of combining endocrine strategies with cell-cycle–targeted therapies to overcome or delay endocrine resistance. Clinically, this meant patients could experience longer disease control before resorting to chemotherapy, often with a manageable safety profile. On a broader scale, the trial represented a paradigm shift: it reinforced the notion that even in hormone-driven cancers, targeting the downstream proliferation machinery (CDK4/6) can enhance outcomes—opening avenues for other CDK inhibitors and further biomarker-driven treatment strategies in breast oncology.


The NEW ENGLAND JOURNAL of MEDICINE

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Palbociclib and Letrozole in Advanced Breast Cancer

Richard S. Finn, M.D., Miguel Martin, M.D., Hope S. Rugo, M.D., Stephen Jones, M.D., Seock-Ah Im, M.D., Ph.D., Karen Gelmon, M.D., Nadia Harbeck, M.D., Ph.D., Oleg N. Lipatov, M.D., Janice M. Walshe, M.D., Stacy Moulder, M.D., Eric Gauthier, Pharm.D., Ph.D., Dongrui R. Lu, M.Sc., Sophia Randolph, M.D., Ph.D., Véronique Diéras, M.D., and Dennis J. Slamon, M.D., Ph.D.

ABSTRACT

BACKGROUND

A phase 2 study showed that progression-free survival was longer with palbociclib plus letrozole than with letrozole alone in the initial treatment of postmenopausal women with estrogen-receptor (ER)–positive, human epidermal growth factor receptor 2 (HER2)–negative advanced breast cancer. We performed a phase 3 study that was designed to confirm and expand the efficacy and safety data for palbociclib plus letrozole for this indication.

METHODS

In this double-blind study, we randomly assigned, in a 2:1 ratio, 666 postmenopausal women with ER-positive, HER2-negative breast cancer, who had not had prior treatment for advanced disease, to receive palbociclib plus letrozole or placebo plus letrozole. The primary end point was progression-free survival, as assessed by the investigators; secondary end points were overall survival, objective response, clinical benefit response, patient-reported outcomes, pharmacokinetic effects, and safety.

RESULTS

The median progression-free survival was 24.8 months (95% confidence interval [CI], 22.1 to not estimable) in the palbociclib–letrozole group, as compared with 14.5 months (95% CI, 12.9 to 17.1) in the placebo–letrozole group (hazard ratio for disease progression or death, 0.58; 95% CI, 0.46 to 0.72; P<0.001). The most common grade 3 or 4 adverse events were neutropenia (occurring in 66.4% of the patients in the palbociclib–letrozole group vs. 1.4% in the placebo–letrozole group), leukopenia (24.8% vs. 0%), anemia (5.4% vs. 1.8%), and fatigue (1.8% vs. 0.5%). Febrile neutropenia was reported in 1.8% of patients in the palbociclib–letrozole group and in none of the patients in the placebo–letrozole group. Permanent discontinuation of any study treatment as a result of adverse events occurred in 43 patients (9.7%) in the palbociclib–letrozole group and in 13 patients (5.9%) in the placebo–letrozole group.

CONCLUSIONS

Among patients with previously untreated ER-positive, HER2-negative advanced breast cancer, palbociclib combined with letrozole resulted in significantly longer progression-free survival than that with letrozole alone, although the rates of myelotoxic effects were higher with palbociclib–letrozole. (Funded by Pfizer; PALOMA-2 ClinicalTrials.gov number, NCT01740427.)

From the Department of Medicine, Division of Hematology and Oncology, David Geffen School of Medicine at the University of California, Los Angeles, Santa Monica (R.S.F., D.J.S.), the Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, San Francisco (H.S.R.), and Pfizer, La Jolla (E.G., D.R.L., S.R.) — all in California; Hospital Gregorio Maranon, Universidad Complutense, Madrid (M.M.); U.S. Oncology Research, The Woodlands, TX (S.J.); Cancer Research Institute, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, South Korea (S.-A.I.); British Columbia Cancer Agency, Vancouver, Canada (K.G.); Brustzentrum der Universität München (LMU), Munich, Germany (N.H.); State Budget Medical Institution Republican Clinical Oncology, Ufa, Russia (O.N.L.); All-Ireland Cooperative Oncology Research Group, Dublin (J.M.W.); M.D. Anderson Cancer Center, University of Texas, Houston (S.M.); and Institut Curie, Paris (V.D.). Address reprint requests to Dr. Finn at the Department of Medicine, Division of Hematology and Oncology, David Geffen School of Medicine at UCLA, 2825 Santa Monica Blvd., Suite 200, Santa Monica, CA 90404, or at rfinn@mednet.ucla.edu.

N Engl J Med 2016;375:1925-36.
DOI: 10.1056/NEJMoa1607303
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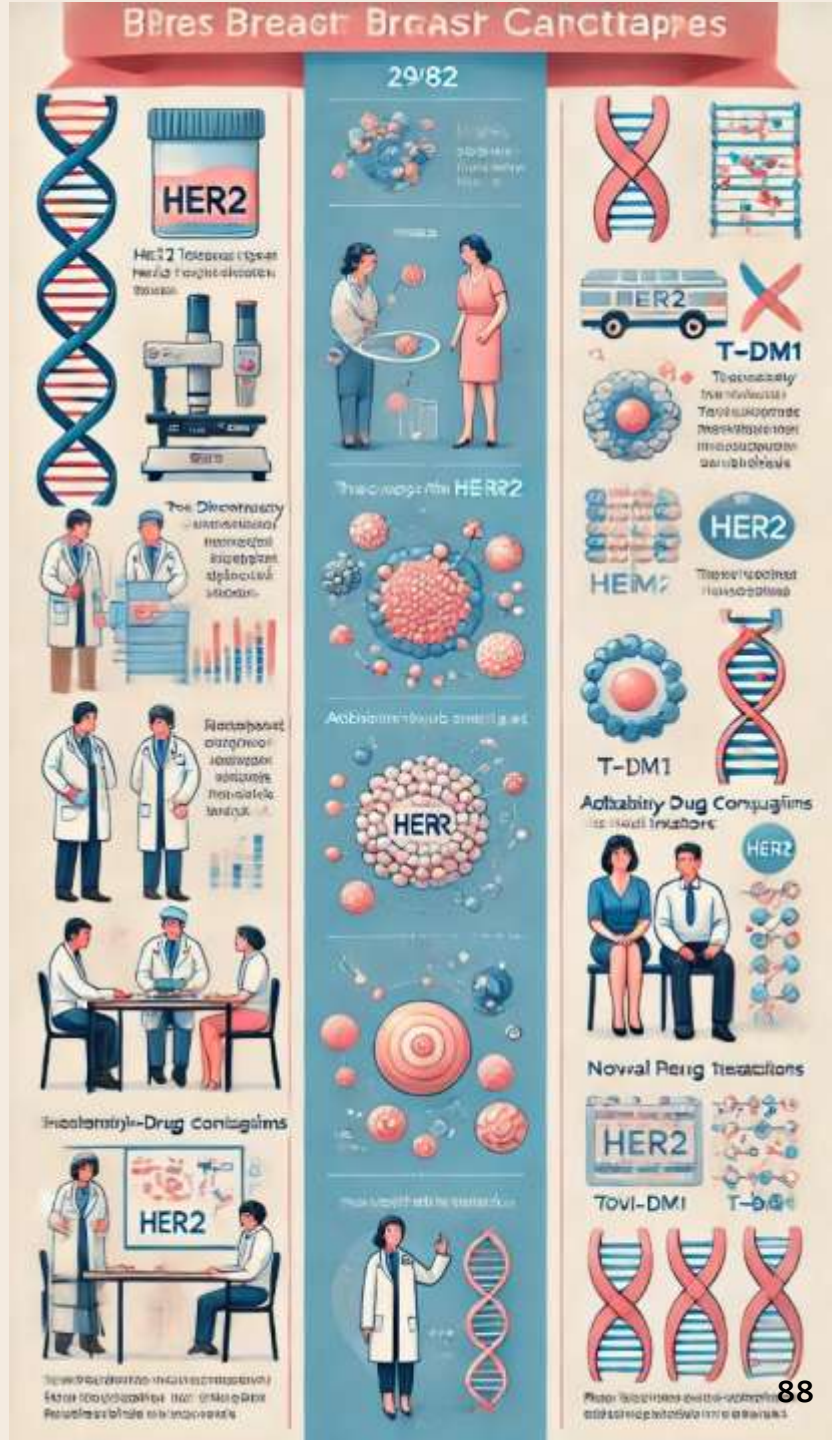
Finn RS, Martin M, Rugo HS, Jones S, Im SA, Gelmon K, Harbeck N, Lipatov ON, Walshe JM, Moulder S, Gauthier E, Lu DR, Randolph S, Diéras V, Slamon DJ., "Palbociclib and Letrozole in Advanced Breast Cancer," New England Journal of Medicine," Nov 17;375(20):1925-1936.

Section 4.F: HER2 Therapies

In the early 1980s, researchers Dennis Slamon, Axel Ullrich and colleagues discovered that amplification of the HER2/neu oncogene occurred in roughly 20–25% of breast cancers and was associated with aggressive tumor growth and poor prognosis. HER2 encodes a tyrosine kinase receptor that, when overexpressed, drives unchecked cell proliferation. HER2 soon became a therapeutic target. By the late 1980s, Genentech had developed a monoclonal antibody that could block HER2 signaling—an experimental agent that would become trastuzumab (Herceptin). After years of skepticism and clinical refinement, landmark trials led by Slamon in the 1990s demonstrated that trastuzumab, when combined with chemotherapy, dramatically improved survival in HER2-positive breast cancer, marking a paradigm shift from empiricism to precision therapy.

The success of trastuzumab ignited a revolution in targeted HER2 inhibition. The 2000s saw the approval of lapatinib, a dual HER2/EGFR tyrosine kinase inhibitor and pertuzumab, which binds a different domain of the HER2 receptor to enhance blockade when combined with trastuzumab. Later, antibody–drug conjugates such as trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (Enhertu) extended this strategy by delivering potent cytotoxins directly to HER2-expressing cells, achieving efficacy even in metastatic and low-HER2 settings. These therapies transformed HER2-positive breast cancer from one of the deadliest subtypes into one with among the best long-term outcomes.



1987: Dennis Slamon

Identified the HER2 subtype of breast cancer through DNA analysis with a group of colleagues. This eventually led to the development of Herceptin, the first successful pharmaceutical precision therapeutic.

Dennis Slamon, the Chief of the Oncology-Hematology Division at UCLA, was born the son of a West Virginia coal miner. He has gone on to be one of the most important contributors to breast oncology in history.

With a number of key colleagues including Axel Ullrich of Genentech, he authored a landmark 1987 *Science* paper titled “Human Breast Cancer: Correlation of Relapse and Survival with Amplification of the HER-2/neu Oncogene.” This study was among the first to demonstrate a genetic marker with clear prognostic significance in breast cancer. By analyzing DNA from 189 primary human breast tumors, the investigators found that approximately 25–30% exhibited amplification of the HER2/neu (ERBB2) oncogene, located on chromosome 17q21. Critically, this genetic amplification correlated strongly with shorter relapse-free and overall survival, independent of tumor size or lymph-node status.

The authors concluded that HER2 amplification identified a biologically aggressive subtype of breast cancer, one that might behave differently and respond poorly to conventional therapies. This was a groundbreaking assertion in 1987: the idea that molecular alterations, not just histologic features, could define tumor behavior and prognosis. The implications of this discovery were transformative. The identification of HER2 as both a prognostic and predictive biomarker laid the foundation for a new era of molecularly targeted therapy in oncology. Over the next decade, Slamon and others would translate this basic insight into clinical practice through the development of trastuzumab (Herceptin).

References: Ekmektzoglou (2009), Lukong (2017), Sanli (2022).

Dennis Slamon et al., 1987, Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene, *Science*, Jan 9, 1987

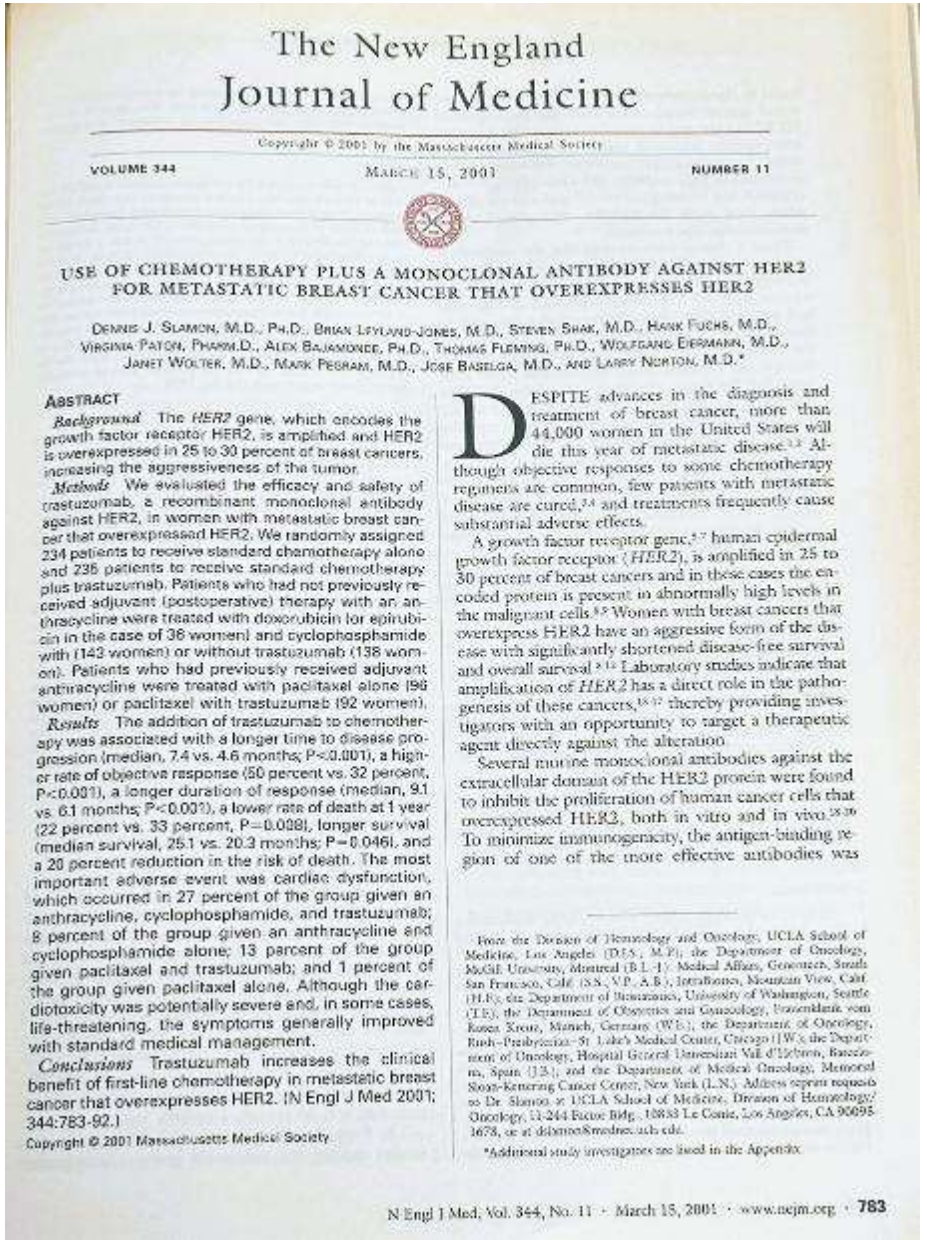
2001: Dennis Slamon

This pathbreaking paper showed the profound benefit of Herceptin in treating breast cancer for HER2+ patients.

Dennis J. Slamon transformed the treatment of breast cancer through the discovery and clinical validation of HER2 (human epidermal growth factor receptor 2) as a therapeutic target. Slamon and his team at UCLA in the 1980s identified that amplification of the HER2/neu gene occurred in approximately 20–30% of breast cancers and was associated with aggressive tumor behavior and poor prognosis. This insight led to the development of trastuzumab (Herceptin), a monoclonal antibody designed to block HER2 signaling. Despite skepticism and funding challenges, Slamon's persistence culminated in a new biologically targeted therapy that marked a paradigm shift—from nonspecific cytotoxic chemotherapy to precision oncology based on molecular profiling. Other key contributors included Virginia Paton, Jose Baselga and Larry Norton.

In his 2001 *New England Journal of Medicine* paper, Slamon and colleagues reported the results of a randomized clinical trial showing that adding trastuzumab to standard chemotherapy significantly improved overall survival and time to disease progression in women with metastatic HER2-positive breast cancer. The study demonstrated that Herceptin reduced the risk of death by about one-third and produced durable responses even in advanced disease. These findings validated HER2 as a critical oncogenic driver and established trastuzumab as the first successful targeted therapy for solid tumors. Slamon's work not only revolutionized the management of HER2-positive breast cancer but also opened the door for subsequent generations of targeted and antibody-based treatments, profoundly influencing the trajectory of modern cancer therapy.

References: ASCO Foundation (2025), Ekmektzoglou (2009), Lukong (2017), Sanli (2022).



The New England Journal of Medicine

VOLUME 344 · MARCH 15, 2001 · NUMBER 11

USE OF CHEMOTHERAPY PLUS A MONOCLONAL ANTIBODY AGAINST HER2 FOR METASTATIC BREAST CANCER THAT OVEREXPRESSES HER2

Dennis J. Slamon, M.D., Ph.D., Brian Leyland-Jones, M.D., Steven Shak, M.D., Hank Fuchs, M.D., Virginia Paton, Pharm.D., Alex Bajamonde, Ph.D., Thomas Fleming, Ph.D., Wolfgang Eiermann, M.D., Janet Wolter, M.D., Mark Pegram, M.D., Jose Baselga, M.D., and Larry Norton, M.D.*

ABSTRACT

Background The *HER2* gene, which encodes the growth factor receptor HER2, is amplified and HER2 is overexpressed in 25 to 30 percent of breast cancers, increasing the aggressiveness of the tumor.

Methods We evaluated the efficacy and safety of trastuzumab, a recombinant monoclonal antibody against HER2, in women with metastatic breast cancer that overexpressed HER2. We randomly assigned 234 patients to receive standard chemotherapy alone and 235 patients to receive standard chemotherapy plus trastuzumab. Patients who had not previously received adjuvant (postoperative) therapy with an anthracycline were treated with doxorubicin (or epirubicin in the case of 36 women) and cyclophosphamide with (143 women) or without trastuzumab (138 women). Patients who had previously received adjuvant anthracycline were treated with paclitaxel alone (96 women) or paclitaxel with trastuzumab (92 women).

Results The addition of trastuzumab to chemotherapy was associated with a longer time to disease progression (median, 7.4 vs. 4.6 months; P<0.001), a higher rate of objective response (50 percent vs. 32 percent, P<0.001), a longer duration of response (median, 9.1 vs. 6.1 months; P<0.001), a lower rate of death at 1 year (22 percent vs. 33 percent, P=0.008), longer survival (median survival, 25.1 vs. 20.3 months; P=0.046), and a 20 percent reduction in the risk of death. The most important adverse event was cardiac dysfunction, which occurred in 27 percent of the group given an anthracycline, cyclophosphamide, and trastuzumab; 8 percent of the group given an anthracycline and cyclophosphamide alone; 13 percent of the group given paclitaxel and trastuzumab; and 1 percent of the group given paclitaxel alone. Although the cardiotoxicity was potentially severe and, in some cases, life-threatening, the symptoms generally improved with standard medical management.

Conclusions Trastuzumab increases the clinical benefit of first-line chemotherapy in metastatic breast cancer that overexpresses HER2. (N Engl J Med 2001; 344:783-92.)

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DESPITE advances in the diagnosis and treatment of breast cancer, more than 44,000 women in the United States will die this year of metastatic disease.[1,2] Although objective responses to some chemotherapy regimens are common, few patients with metastatic disease are cured,[3,4] and treatments frequently cause substantial adverse effects.

A growth factor receptor gene,[5,6] human epidermal growth factor receptor (*HER2*), is amplified in 25 to 30 percent of breast cancers and in these cases the encoded protein is present in abnormally high levels in the malignant cells.[5,6] Women with breast cancers that overexpress HER2 have an aggressive form of the disease with significantly shortened disease-free survival and overall survival.[7-14] Laboratory studies indicate that amplification of *HER2* has a direct role in the pathogenesis of these cancers,[15-17] thereby providing investigators with an opportunity to target a therapeutic agent directly against the alteration.

Several murine monoclonal antibodies against the extracellular domain of the HER2 protein were found to inhibit the proliferation of human cancer cells that overexpressed HER2, both in vitro and in vivo.[18-20] To minimize immunogenicity, the antigen-binding region of one of the more effective antibodies was

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*Additional study investigators are listed in the Appendix.

Dennis Slamon et al., 2001, "Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2," *New England Journal of Medicine*, March 15, Volume 384. From the author's medical library.

2005: Romond and Colleagues

Adjuvant trastuzumab reduces recurrence/mortality in early HER2-positive disease, setting a new practice-defining standard. This paper has received over 7000 citations.

This pivotal clinical trial—jointly analyzing data from two large studies (NSABP B-31 and NCCTG N9831)—evaluated whether adding trastuzumab (Herceptin) to standard adjuvant chemotherapy could improve outcomes for women with early-stage, HER2-positive breast cancer. Patients received doxorubicin and cyclophosphamide followed by paclitaxel, with or without concurrent and subsequent trastuzumab. The results were dramatic: after a median follow-up of just two years, the addition of trastuzumab led to a 52% reduction in disease recurrence and a 33% reduction in mortality, with significantly improved disease-free and overall survival. Although cardiac toxicity occurred more frequently in the trastuzumab group, it was generally manageable with careful monitoring.

The contribution of Romond et al. (2005) was practice-changing. This study definitively established trastuzumab as the first targeted biologic therapy proven to improve survival in early-stage breast cancer, confirming that inhibition of the HER2 pathway could prevent recurrence and death in a subset of patients defined by tumor biology rather than anatomy. It validated the translational bridge from the 1987 discovery of HER2 amplification to a curative, molecularly guided therapy. Following its publication, trastuzumab became standard of care for adjuvant treatment in HER2-positive disease worldwide, ushering in the era of precision oncology in breast cancer. The trial also set a model for integrating targeted agents with cytotoxic chemotherapy and highlighted the necessity of biomarker testing for treatment selection—concepts that now underpin modern cancer therapeutics.

References: Sanli (2022).

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trastuzumab plus Adjuvant Chemotherapy for Operable HER2-Positive Breast Cancer

Edward H. Romond, M.D., Edith A. Perez, M.D., John Bryant, Ph.D., Vera J. Suman, Ph.D., Charles E. Geyer, Jr., M.D., Nancy E. Davidson, M.D., Elizabeth Tan-Chiu, M.D., Silvana Martino, D.O., Soonmyung Paik, M.D., Peter A. Kaufman, M.D., Sandra M. Swain, M.D., Thomas M. Pisansky, M.D., Louis Fehrenbacher, M.D., Leila A. Kutteh, M.D., Victor G. Vogel, M.D., Daniel W. Visscher, M.D., Greg Yothers, Ph.D., Robert B. Jenkins, M.D., Ph.D., Ann M. Brown, Sc.D., Shaker R. Dakhil, M.D., Eleftherios P. Mamounas, M.D., M.P.H., Wilma L. Lingle, Ph.D., Pamela M. Klein, M.D., James N. Ingle, M.D., and Norman Wolmark, M.D.

ABSTRACT

BACKGROUND

We present the combined results of two trials that compared adjuvant chemotherapy with or without concurrent trastuzumab in women with surgically removed HER2-positive breast cancer.

METHODS

The National Surgical Adjuvant Breast and Bowel Project trial B-31 compared doxorubicin and cyclophosphamide followed by paclitaxel every 3 weeks (group 1) with the same regimen plus 52 weeks of trastuzumab beginning with the first dose of paclitaxel (group 2). The North Central Cancer Treatment Group trial N9831 compared three regimens: doxorubicin and cyclophosphamide followed by weekly paclitaxel (group A), the same regimen followed by 52 weeks of trastuzumab after paclitaxel (group B), and the same regimen plus 52 weeks of trastuzumab initiated concomitantly with paclitaxel (group C). The studies were amended to include a joint analysis comparing groups 1 and A (the control group) with groups 2 and C (the trastuzumab group). Group B was excluded because trastuzumab was not given concurrently with paclitaxel.

RESULTS

By March 15, 2005, 394 events (recurrent, second primary cancer, or death before recurrence) had been reported, triggering the first scheduled interim analysis. Of these, 133 were in the trastuzumab group and 261 in the control group (hazard ratio, 0.48; P<0.0001). This result crossed the early stopping boundary. The absolute difference in disease-free survival between the trastuzumab group and the control group was 12 percent at three years. Trastuzumab therapy was associated with a 33 percent reduction in the risk of death (P=0.015). The three-year cumulative incidence of class III or IV congestive heart failure or death from cardiac causes in the trastuzumab group was 4.1 percent in trial B-31 and 2.9 percent in trial N9831.

Romond EH, Perez EA, Bryant J, Suman VJ, Geyer CE Jr, Davidson NE, Tan-Chiu E, Martino S, Paik S, Kaufman PA, Swain SM, Pisansky TM, Fehrenbacher L, Kutteh LA, Vogel VG, Visscher DW, Yothers G, Jenkins RB, Brown AM, Dakhil SR, Mamounas EP, Lingle WL, Klein PM, Ingle JN, Wolmark N. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med. 2005 Oct 20;353(16):1673-84.

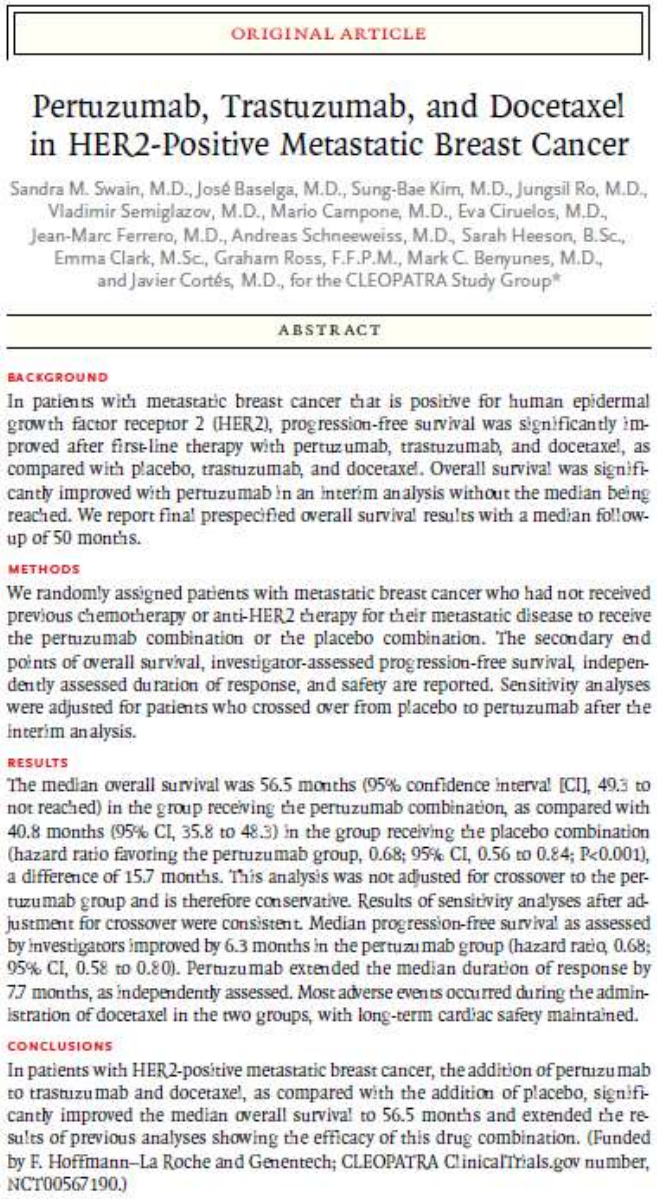
2015: CLEOPATRA Study Group

Perjeta + Herceptin + chemo compared to Herceptin + chemo alone changed standard of care in HER2+ breast. The effect of adding Perjeta was quite meaningful for patients.

Perjeta (pertuzumab) is a monoclonal antibody designed to block a different part of the HER2 receptor than trastuzumab, preventing the receptor from pairing—or "dimerizing"—with other HER family receptors. This complementary mechanism enhances HER2 blockade and amplifies tumor inhibition. The pivotal study published in the New England Journal of Medicine in 2015, known as the CLEOPATRA trial, evaluated the addition of pertuzumab to standard trastuzumab and docetaxel in women with previously untreated metastatic HER2-positive breast cancer.

The study showed a remarkable improvement in median overall survival, extending it from about 41 months with trastuzumab and chemotherapy alone to more than 56 months with the triple-drug combination. Progression-free survival and duration of response were also significantly longer, with no major increase in cardiac toxicity.

This trial transformed the treatment landscape for HER2-positive breast cancer. Before CLEOPATRA, trastuzumab plus chemotherapy was the universal first-line regimen; after it, dual antibody blockade with pertuzumab and trastuzumab became the new global standard. The success of Perjeta in the metastatic setting spurred a series of trials testing this combination in early-stage and neoadjuvant disease, ultimately expanding its use across the spectrum of HER2-positive breast cancer. The findings established that deeper, more complete HER2 inhibition could translate into meaningful survival gains—a milestone that redefined expectations for targeted therapy in breast oncology.



ORIGINAL ARTICLE

Pertuzumab, Trastuzumab, and Docetaxel in HER2-Positive Metastatic Breast Cancer

Sandra M. Swain, M.D., José Baselga, M.D., Sung-Bae Kim, M.D., Jungsil Ro, M.D., Vladimir Semiglazov, M.D., Mario Campone, M.D., Eva Ciruelos, M.D., Jean-Marc Ferrero, M.D., Andreas Schneeweiss, M.D., Sarah Heeson, B.Sc., Emma Clark, M.Sc., Graham Ross, F.F.P.M., Mark C. Benyunes, M.D., and Javier Cortés, M.D., for the CLEOPATRA Study Group*

ABSTRACT

BACKGROUND

In patients with metastatic breast cancer that is positive for human epidermal growth factor receptor 2 (HER2), progression-free survival was significantly improved after first-line therapy with pertuzumab, trastuzumab, and docetaxel, as compared with placebo, trastuzumab, and docetaxel. Overall survival was significantly improved with pertuzumab in an interim analysis without the median being reached. We report final prespecified overall survival results with a median follow-up of 50 months.

METHODS

We randomly assigned patients with metastatic breast cancer who had not received previous chemotherapy or anti-HER2 therapy for their metastatic disease to receive the pertuzumab combination or the placebo combination. The secondary end points of overall survival, investigator-assessed progression-free survival, independently assessed duration of response, and safety are reported. Sensitivity analyses were adjusted for patients who crossed over from placebo to pertuzumab after the interim analysis.

RESULTS

The median overall survival was 56.5 months (95% confidence interval [CI], 49.3 to not reached) in the group receiving the pertuzumab combination, as compared with 40.8 months (95% CI, 35.8 to 48.3) in the group receiving the placebo combination (hazard ratio favoring the pertuzumab group, 0.68; 95% CI, 0.56 to 0.84; P<0.001), a difference of 15.7 months. This analysis was not adjusted for crossover to the pertuzumab group and is therefore conservative. Results of sensitivity analyses after adjustment for crossover were consistent. Median progression-free survival as assessed by investigators improved by 6.3 months in the pertuzumab group (hazard ratio, 0.68; 95% CI, 0.58 to 0.80). Pertuzumab extended the median duration of response by 7.7 months, as independently assessed. Most adverse events occurred during the administration of docetaxel in the two groups, with long-term cardiac safety maintained.

CONCLUSIONS

In patients with HER2-positive metastatic breast cancer, the addition of pertuzumab to trastuzumab and docetaxel, as compared with the addition of placebo, significantly improved the median overall survival to 56.5 months and extended the results of previous analyses showing the efficacy of this drug combination. (Funded by F. Hoffmann–La Roche and Genentech; CLEOPATRA ClinicalTrials.gov number, NCT00567190.)

Swain SM, Baselga J, Kim SB, Ro J, Semiglazov V, Campone M, Ciruelos E, Ferrero JM, Schneeweiss A, Heeson S, Clark E, Ross G, Benyunes MC, Cortés J; CLEOPATRA Study Group, 2015, "Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer," *N Engl J Med*. Feb 19;372(8):724-34.

2016: Daiichi Sankyo ADC Team

A team of five members of Daiichi-Sankyo's Oncology R&D team published a paper on ENHERTU®, a HER2 targeting ADC for the first time.

Recognizing the limitations of earlier ADCs, Daiichi Sankyo built its proprietary "DXd" platform to combine precise antibody targeting with potent cytotoxic payloads. The five-member team shown at right played key leadership and operational roles in building out the platform in a deliberate way starting around 2010.

This team developed ENHERTU which couples a humanized anti-HER2 antibody to a topoisomerase I inhibitor via a stable, cleavable linker that enables highly selective drug delivery to HER2-expressing cancer cells while limiting systemic toxicity.

This engineering breakthrough allowed Daiichi Sankyo's researchers to overcome the common pitfalls of linker instability and suboptimal drug–antibody ratios that had constrained prior ADC generations. The team's key paper on ENHERTU (see lower right) was published in 2016.

Daiichi Sankyo's ENHERTU has become one of the most successful oncology drugs of the decade, redefining the treatment of HER2-positive and HER2-low breast cancer. In multiple global trials, the drug has consistently demonstrated major survival and response advantages over standard therapies, including large reductions in recurrence risk, high rates of complete pathological response in early-stage disease, and meaningful activity in patients with brain metastases. These clinical breakthroughs have expanded ENHERTU's reach from advanced to earlier disease settings and across a broader spectrum of HER2 expression. Commercially, ENHERTU has rapidly grown into a multibillion-dollar franchise, serving as a cornerstone of Daiichi Sankyo's oncology strategy and establishing the company as a world leader in antibody-drug conjugate innovation.


Toshinori Agatsuma


Yuki Abe


Yusuke Ogitani


Hiroyuke Naito


Takashi Nakada

Ogitani Y, Aida T, Hagihara K, Yamaguchi J, Ishii C, Harada N, Soma M, Okamoto H, Oitate M, Arakawa S, Hirai T, Atsumi R, Nakada T, Hayakawa I, Abe Y, Agatsuma T., 2016, DS-8201a, A Novel HER2-Targeting ADC with a Novel DNA Topoisomerase I Inhibitor, Demonstrates a Promising Antitumor Efficacy with Differentiation from T-DM1. *Clin Cancer Res.* Oct 15;22(20):5097-5108.

2022: DESTINY-Breast04 Investigators

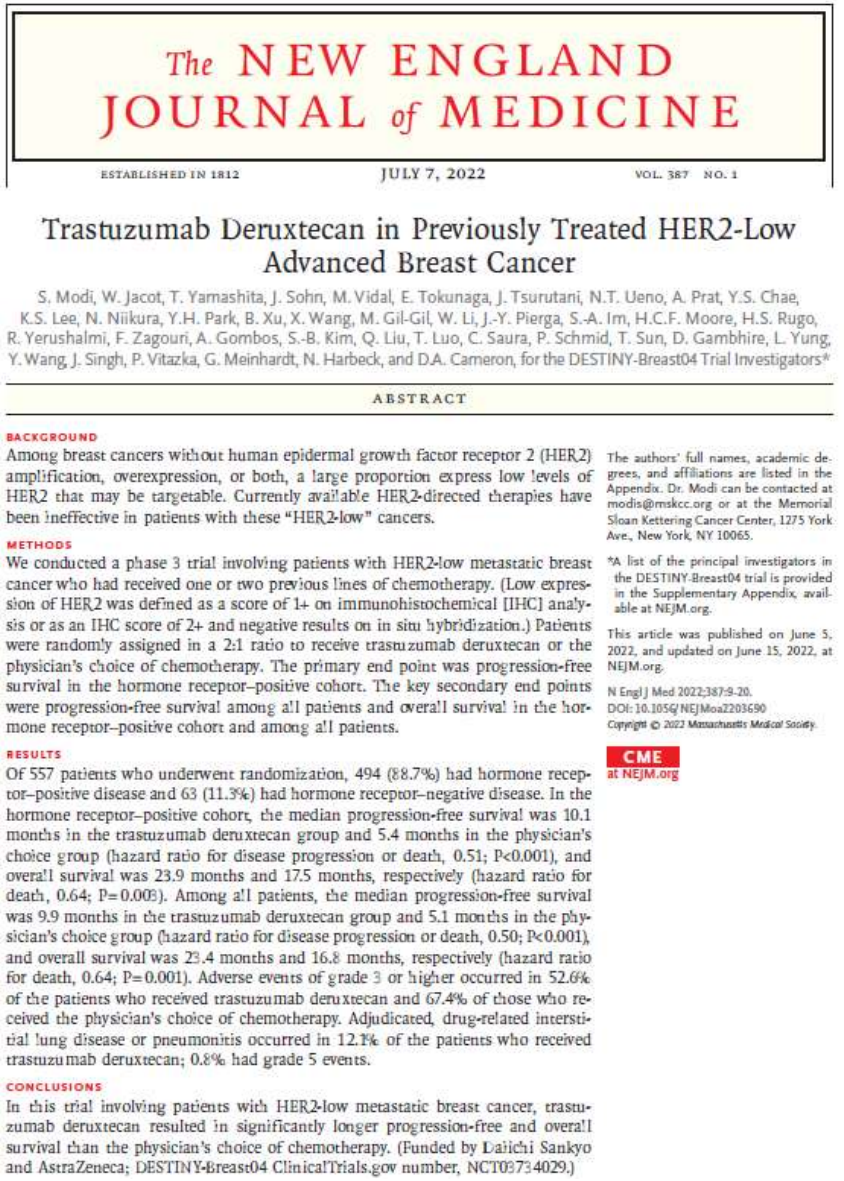
Showed that a HER2 targeted ADC (Enhertu®) could provide a major survival benefit even for breast cancer patients who had low levels of HER2 expression.

The 2022 *New England Journal of Medicine* article by Shanu Modi and colleagues, titled "Trastuzumab deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer" reported the results of the phase 3 trial known as DESTINY Breast 04 using the antibody-drug conjugate ENHERTU®. The study enrolled patients with unresectable or metastatic breast cancer whose tumours had "HER2-low" expression — defined as immunohistochemical (IHC) 1+ or IHC 2+ with negative in situ hybridization for HER2.

Patients had received one or two prior lines of chemotherapy in the advanced setting. The median progression-free survival (PFS) in the trastuzumab deruxtecan arm was 9.9 months, compared to 5.1 months in the physician's-choice chemotherapy arm (hazard ratio [HR] for progression or death ~0.50). Overall survival was also improved: 23.4 months in the experimental arm vs 16.8 months in the control (HR ~0.64). The overall response rate (tumour shrinkage) was markedly higher with trastuzumab deruxtecan (≈52.3%) vs ~16.3% in the control arm.

This trial was highly significant because it re-defines the therapeutic landscape for the large subgroup of breast-cancer patients whose tumours express low levels of HER2 (so-called "HER2-low") — a group previously considered essentially HER2-negative and ineligible for HER2-targeted therapies.

Gratifyingly, the large audience hearing the results of this paper provided a standing ovation to the authors – reflecting the value that this innovation will bring to patients for years to come.



The NEW ENGLAND JOURNAL of MEDICINE

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Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer

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ABSTRACT

BACKGROUND

Among breast cancers without human epidermal growth factor receptor 2 (HER2) amplification, overexpression, or both, a large proportion express low levels of HER2 that may be targetable. Currently available HER2-directed therapies have been ineffective in patients with these "HER2-low" cancers.

METHODS

We conducted a phase 3 trial involving patients with HER2-low metastatic breast cancer who had received one or two previous lines of chemotherapy. (Low expression of HER2 was defined as a score of 1+ on immunohistochemical [IHC] analysis or as an IHC score of 2+ and negative results on in situ hybridization.) Patients were randomly assigned in a 2:1 ratio to receive trastuzumab deruxtecan or the physician's choice of chemotherapy. The primary end point was progression-free survival in the hormone receptor–positive cohort. The key secondary end points were progression-free survival among all patients and overall survival in the hormone receptor–positive cohort and among all patients.

RESULTS

Of 557 patients who underwent randomization, 494 (88.7%) had hormone receptor–positive disease and 63 (11.3%) had hormone receptor–negative disease. In the hormone receptor–positive cohort, the median progression-free survival was 10.1 months in the trastuzumab deruxtecan group and 5.4 months in the physician's choice group (hazard ratio for disease progression or death, 0.51; P<0.001), and overall survival was 23.9 months and 17.5 months, respectively (hazard ratio for death, 0.64; P=0.008). Among all patients, the median progression-free survival was 9.9 months in the trastuzumab deruxtecan group and 5.1 months in the physician's choice group (hazard ratio for disease progression or death, 0.50; P<0.001), and overall survival was 23.4 months and 16.8 months, respectively (hazard ratio for death, 0.64; P=0.001). Adverse events of grade 3 or higher occurred in 52.6% of the patients who received trastuzumab deruxtecan and 67.4% of those who received the physician's choice of chemotherapy. Adjudicated, drug-related interstitial lung disease or pneumonitis occurred in 12.1% of the patients who received trastuzumab deruxtecan; 0.8% had grade 5 events.

CONCLUSIONS

In this trial involving patients with HER2-low metastatic breast cancer, trastuzumab deruxtecan resulted in significantly longer progression-free and overall survival than the physician's choice of chemotherapy. (Funded by Daiichi Sankyo and AstraZeneca; DESTINY-Breast04 ClinicalTrials.gov number, NCT03734029.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Modi can be contacted at modis@mskcc.org or at the Memorial Sloan Kettering Cancer Center, 1275 York Ave., New York, NY 10065.

*A list of the principal investigators in the DESTINY-Breast04 trial is provided in the Supplementary Appendix, available at NEJM.org.

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Modi Shanu et al., "Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer," NEJM, June 5, 2022, Volume 387, No. 1, pp. 9-20. From the author's medical library.

Section 4.G: Immunotherapy

The roots of immunotherapy stretch back to the 1890s, when William Coley injected bacterial toxins into cancer patients, believing infections might trigger the immune system to attack tumors. Though primitive, his “Coley’s toxins” foreshadowed a concept that would take more than a century to mature: that the immune system could be harnessed to fight cancer. The real breakthrough came in the early 2000s with the discovery of immune checkpoints—molecular brakes such as CTLA-4 and PD-1/PD-L1 that tumors exploit to evade immune destruction. Pioneering work by James Allison (CTLA-4) and Tasuku Honjo (PD-1), recognized by the 2018 Nobel Prize in Physiology or Medicine, led to the development of monoclonal antibodies that could “release the brakes” and reactivate antitumor immunity.

The first checkpoint inhibitors—ipilimumab (anti-CTLA-4), nivolumab and pembrolizumab (anti-PD-1)—redefined the treatment of melanoma, lung cancer and other malignancies in the 2010s. Breast cancer, long considered immunologically “cold,” initially responded poorly to such approaches, but the discovery that triple-negative breast cancer (TNBC) often expresses PD-L1 opened the door to meaningful benefit.

Clinical trials such as IMpassion130 (atezolizumab plus nab-paclitaxel) and KEYNOTE-355 (pembrolizumab combinations) demonstrated improved progression-free and overall survival in PD-L1-positive TNBC, leading to the first FDA approvals of checkpoint inhibitors for breast cancer in 2019–2020.

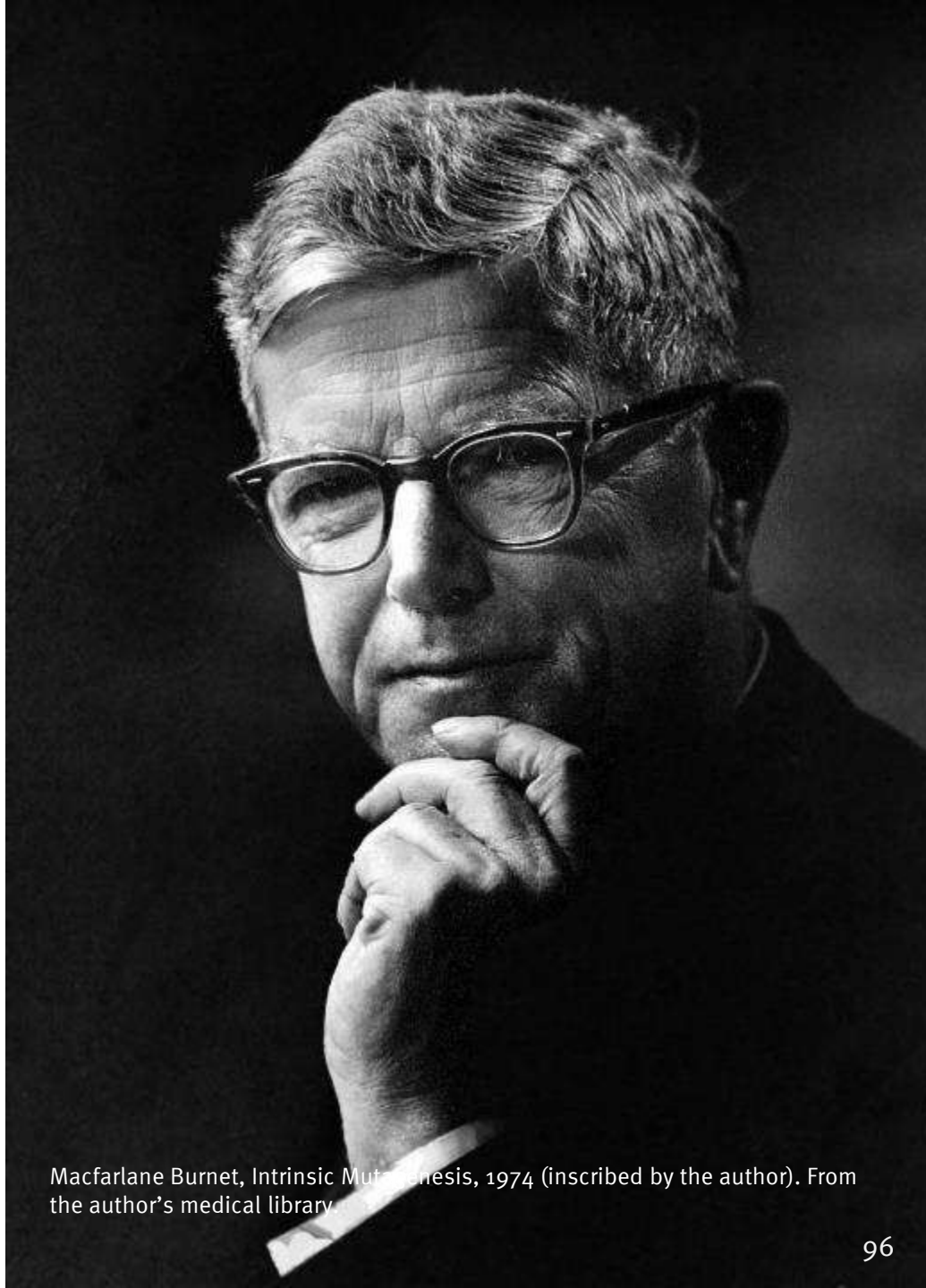
1974: Macfarlane Burnet

Remarkably clear thinking on cancer as a failure of immune response – well before the checkpoint inhibitor revolution.

Frank Macfarlane Burnet's 1974 book *Intrinsic Mutagenesis: A Genetic Approach to Ageing, Cancer and Evolution* synthesized his late-career reflections on the biological origins of cancer and its relationship to immune surveillance and aging. Building on his earlier immunological theories, Burnet proposed that cancer arises as a natural consequence of the body's intrinsic mutational processes—spontaneous genetic errors that accumulate during cellular replication over a lifetime.

He viewed these mutations as inevitable by-products of evolution and cellular renewal, not primarily caused by external carcinogens, though such agents could accelerate the process. Within this framework, cancer was interpreted as a disease of somatic evolution within the body, in which mutant clones escape normal regulatory control. Burnet linked this to the aging process, arguing that as organisms age, their capacity for cellular regulation and immune surveillance declines, allowing previously suppressed malignant cells to proliferate.

Following Lewis Thomas's articulation of the immune surveillance hypothesis in the late 1950s and 1960s—Burnet elaborated that the immune system plays a crucial role in detecting and destroying nascent tumor cells. According to this view, Burnet argued that cancer represents a failure of immune surveillance: the immune system, effective in youth, becomes less vigilant or less capable with age, permitting transformed cells to survive and expand. His framing of cancer as both a genetic and immunologic phenomenon anticipated later breakthroughs in tumor immunoediting, immune checkpoint biology and cancer immunotherapy.



Macfarlane Burnet, Intrinsic Mutagenesis, 1974 (inscribed by the author). From the author's medical library.

1992: Tasuku Honjo

Discovered the programmed cell death protein 1 (PD-1), a discovery substantially advanced cancer treatment through immune activation via PD-1 blockade antibodies. Honjo shared the 2018 Nobel Prize for this work in 2018 with Jim Allison.

Tasuku Honjo's seminal contribution to cancer biology centers on his 1992 discovery of programmed cell death protein 1 (PD-1), a receptor expressed on the surface of activated T cells. Initially identified while investigating mechanisms of immune regulation, PD-1 was later found to act as a critical inhibitory checkpoint—a molecular "brake" that prevents overactivation of the immune system. Honjo and colleagues elucidated that PD-1 binds to its ligands, PD-L1 and PD-L2, which are often expressed by tumor cells or within the tumor microenvironment. This interaction suppresses T-cell proliferation and cytokine production, thereby allowing cancer cells to evade immune destruction. Through a series of mouse model experiments in the 1990s and early 2000s, Honjo's group demonstrated that blocking the PD-1/PD-L1 pathway could restore antitumor immune responses, laying the scientific foundation for a completely new therapeutic approach—immune checkpoint blockade.

His work, together with that of James P. Allison on CTLA-4, transformed oncology by showing that the immune system could be harnessed to fight cancer effectively. Anti-PD-1 and anti-PD-L1 antibodies—such as nivolumab and pembrolizumab—became the cornerstone of modern immuno-oncology, producing durable responses across multiple cancers including melanoma, lung, breast, renal and head-and-neck carcinomas.

For these achievements, Honjo shared the 2018 Nobel Prize in Physiology or Medicine.

References: GMN 14268

Ishida Y, Agata Y, Shibahara K, Honjo T. 1992, "Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death," *EMBO Journal*, Nov;11(11):3887-95.

2006: James P. Allison

"Checkpoint blockade in cancer immunotherapy," Alan Korman, Karl Peggs and James P. Allison, *Advances in Immunology*, Volume 90, pp. 297-339. From the author's medical book library.

Described checkpoint blockade as a novel strategy to combat cancer.

James P. Allison (born 1948) is an American immunologist whose pioneering work on the immune checkpoint molecule CTLA-4 fundamentally changed cancer therapy. In the 1990s, while studying T-cell regulation, Allison discovered that CTLA-4 acts as a brake on immune activation, preventing T-cells from attacking normal tissue—but also limiting their ability to destroy cancer cells. In a landmark series of experiments, he demonstrated that blocking CTLA-4 with an antibody could unleash T-cells to mount a powerful antitumor response, leading to tumor regression in mice. This insight introduced the concept of immune checkpoint blockade, a completely new therapeutic paradigm distinct from chemotherapy, radiation, or targeted molecular therapy. Allison's discoveries culminated in the development of ipilimumab (Yervoy), the first CTLA-4 inhibitor, approved in 2011 for metastatic melanoma and earned him the 2018 Nobel Prize in Physiology or Medicine.

While Allison's most celebrated work centered on melanoma, his discoveries had far-reaching implications for breast cancer immunotherapy. The identification of CTLA-4 as a modulator of immune tolerance opened the door to combining checkpoint blockade with other modalities—chemotherapy, HER2-targeted therapy and PD-1/PD-L1 inhibitors—to overcome the immunosuppressive tumor microenvironment of breast cancer. In preclinical and clinical studies, CTLA-4 blockade has shown activity in "immunologically cold" breast cancers, particularly triple-negative subtypes when paired with PD-1 inhibitors or radiation. Allison's fundamental immunologic insights thus helped redefine breast cancer as a disease potentially responsive to immune modulation.

References: DeVita and Rosenberg (2012).

2020: Peter Schmid and Team

Showed that a PD1 inhibitor could make major inroads in early stage triple negative breast cancer.

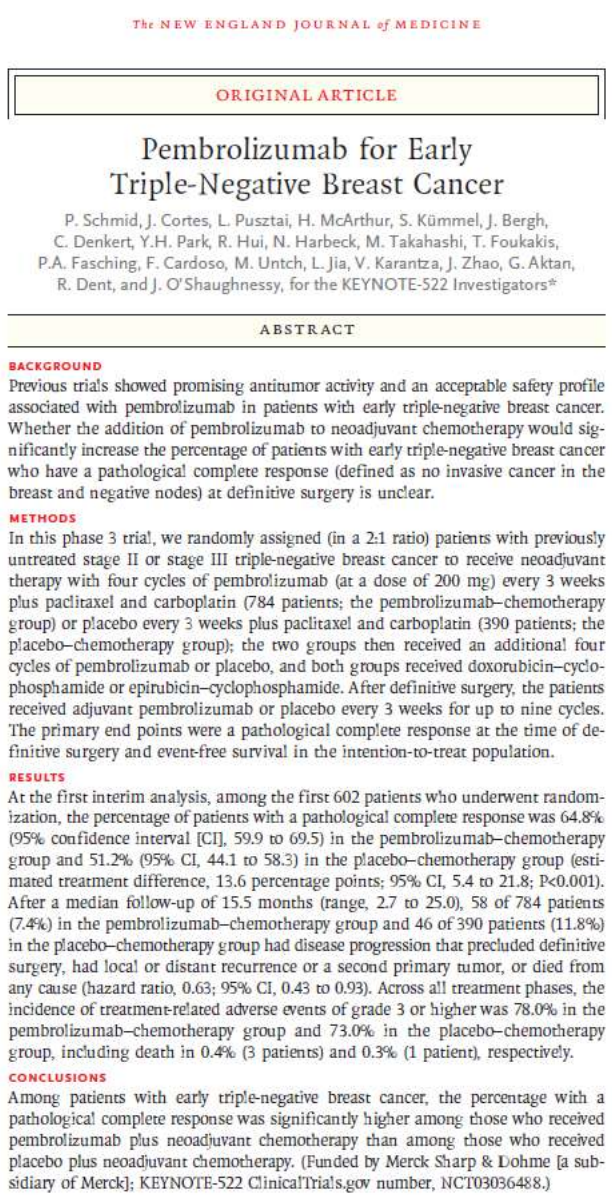
In this phase 3 study (known as KEYNOTE-522), women with previously untreated early-stage, high-risk triple-negative breast cancer (TNBC) were randomized to receive neoadjuvant chemotherapy (before surgery) with or without the addition of the anti-PD-1 immunotherapy agent Pembrolizumab, followed by surgery and then adjuvant treatment (including continued pembrolizumab in the experimental arm).

The primary endpoint was the pathological complete response (pCR) rate (i.e., no invasive cancer in the breast and lymph nodes at the time of surgery). The study found a significantly higher pCR rate in the pembrolizumab-plus-chemotherapy arm compared to chemotherapy alone: in the 2020 paper they reported roughly 64.8% vs 51.2% (experimental vs control) achieving pCR. Importantly, the benefit was observed regardless of PD-L1 expression status.

This study was a landmark because it shifted the paradigm for early-stage TNBC by demonstrating that adding immunotherapy prior to surgery (and continuing after) could improve the rate of complete response—a surrogate marker known to correlate with better long-term outcomes in TNBC.

In practical terms, it opened the door for pembrolizumab to become part of standard of care in high-risk early TNBC. Indeed, regulatory approvals followed.

Because TNBC has historically had fewer targeted therapy options and a worse prognosis than other breast-cancer subtypes, this study marked one of the first times immunotherapy was shown to meaningfully enhance outcomes in the curative (early-stage) rather than metastatic setting.



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab for Early Triple-Negative Breast Cancer

P. Schmid, J. Cortes, L. Pusztai, H. McArthur, S. Kümmel, J. Bergh, C. Denkert, Y.H. Park, R. Hui, N. Harbeck, M. Takahashi, T. Foukakis, P.A. Fasching, F. Cardoso, M. Untch, L. Jia, V. Karantza, J. Zhao, G. Aktan, R. Dent, and J. O'Shaughnessy, for the KEYNOTE-522 Investigators*

ABSTRACT

BACKGROUND

Previous trials showed promising antitumor activity and an acceptable safety profile associated with pembrolizumab in patients with early triple-negative breast cancer. Whether the addition of pembrolizumab to neoadjuvant chemotherapy would significantly increase the percentage of patients with early triple-negative breast cancer who have a pathological complete response (defined as no invasive cancer in the breast and negative nodes) at definitive surgery is unclear.

METHODS

In this phase 3 trial, we randomly assigned (in a 2:1 ratio) patients with previously untreated stage II or stage III triple-negative breast cancer to receive neoadjuvant therapy with four cycles of pembrolizumab (at a dose of 200 mg) every 3 weeks plus paclitaxel and carboplatin (784 patients; the pembrolizumab–chemotherapy group) or placebo every 3 weeks plus paclitaxel and carboplatin (390 patients; the placebo–chemotherapy group); the two groups then received an additional four cycles of pembrolizumab or placebo, and both groups received doxorubicin–cyclophosphamide or epirubicin–cyclophosphamide. After definitive surgery, the patients received adjuvant pembrolizumab or placebo every 3 weeks for up to nine cycles. The primary end points were a pathological complete response at the time of definitive surgery and event-free survival in the intention-to-treat population.

RESULTS

At the first interim analysis, among the first 602 patients who underwent randomization, the percentage of patients with a pathological complete response was 64.8% (95% confidence interval [CI], 59.9 to 69.5) in the pembrolizumab–chemotherapy group and 51.2% (95% CI, 44.1 to 58.3) in the placebo–chemotherapy group (estimated treatment difference, 13.6 percentage points; 95% CI, 5.4 to 21.8; P<0.001). After a median follow-up of 15.5 months (range, 2.7 to 25.0), 58 of 784 patients (7.4%) in the pembrolizumab–chemotherapy group and 46 of 390 patients (11.8%) in the placebo–chemotherapy group had disease progression that precluded definitive surgery, had local or distant recurrence or a second primary tumor, or died from any cause (hazard ratio, 0.63; 95% CI, 0.43 to 0.93). Across all treatment phases, the incidence of treatment-related adverse events of grade 3 or higher was 78.0% in the pembrolizumab–chemotherapy group and 73.0% in the placebo–chemotherapy group, including death in 0.4% (3 patients) and 0.3% (1 patient), respectively.

CONCLUSIONS

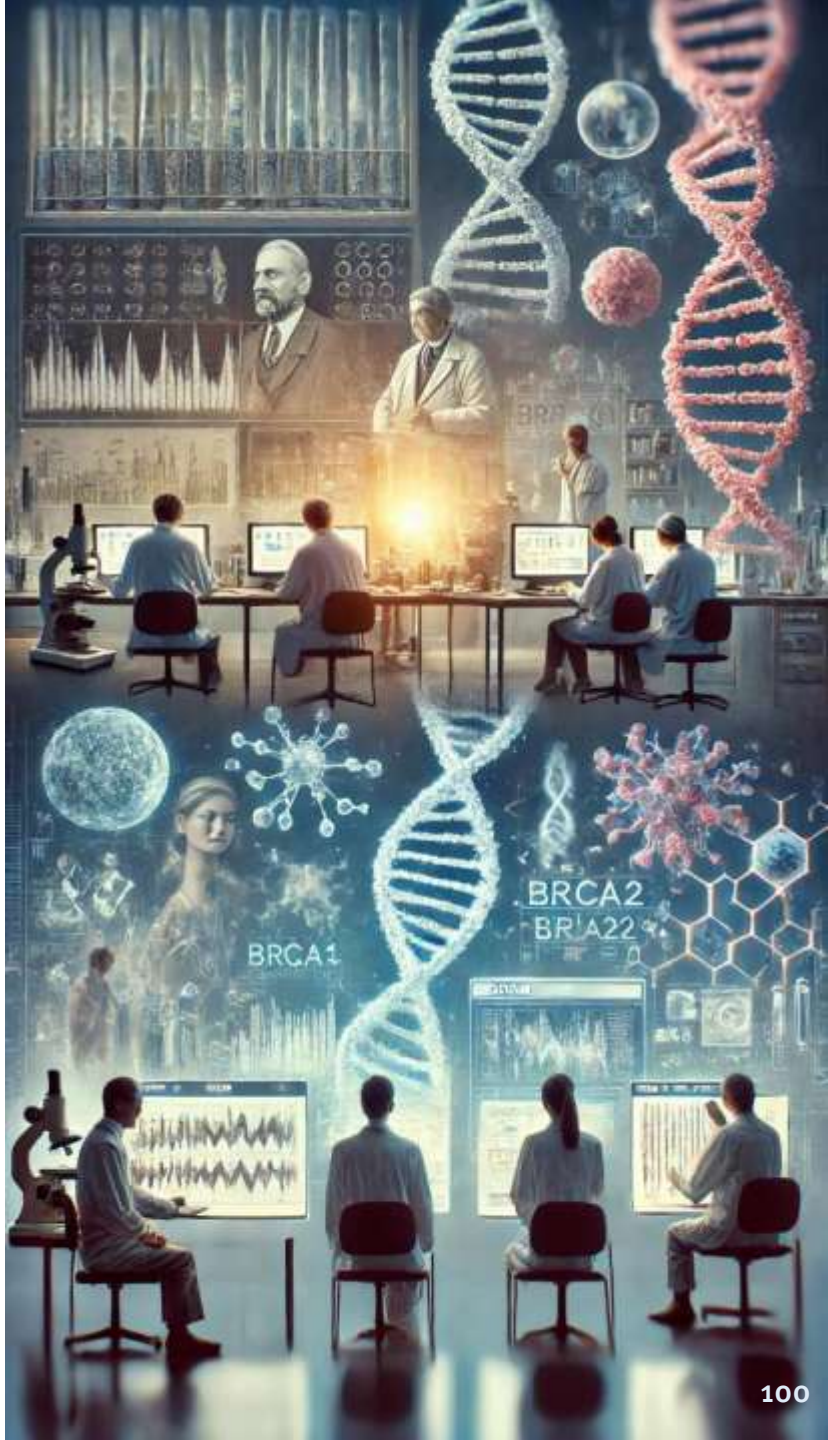
Among patients with early triple-negative breast cancer, the percentage with a pathological complete response was significantly higher among those who received pembrolizumab plus neoadjuvant chemotherapy than among those who received placebo plus neoadjuvant chemotherapy. (Funded by Merck Sharp & Dohme [a subsidiary of Merck]; KEYNOTE-522 ClinicalTrials.gov number, NCT03036488.)

Peter Schmid et al., "Pembrolizumab for Early Triple-Negative Breast Cancer," *New England Journal of Medicine*, Feb 26, , Volume 382, pp. 810-821. From the author's medical library.

Section 4.H: Precision Therapy

The study of genetics and breast cancer has evolved from descriptive family histories to molecular precision, reshaping both diagnosis and treatment. Early observations hinted at inherited cancer susceptibility, but it was not until the late 20th century that the genetic basis of hereditary breast cancer was revealed. In the 1990s, Mary-Claire King and colleagues identified mutations in the BRCA1 and later BRCA2 genes, showing that loss of DNA repair capacity could dramatically increase breast and ovarian cancer risk. These discoveries ushered in the era of genetic counseling and predictive testing, transforming not only risk assessment but also surgical and preventive strategies. Parallel advances in molecular biology and sequencing technologies enabled scientists to map entire cancer genomes, revealing that breast cancer was not a single disease but a constellation of molecular subtypes—luminal A, luminal B, HER2-enriched and basal-like—each with distinct gene expression profiles and clinical behaviors.

The dawn of precision therapy in breast cancer emerged from these genomic insights. Drugs targeting the estrogen receptor (e.g., tamoxifen) or HER2 amplification (e.g., trastuzumab) represented the first molecularly guided therapies, while later identification of PI3K, AKT and CDK4/6 pathway alterations provided additional targets for intervention. The discovery that BRCA-mutated tumors depend on defective DNA repair mechanisms led to the development of PARP inhibitors (such as olaparib and talazoparib), which exploit synthetic lethality to selectively kill cancer cells.



1990: Mary-Claire King

King and colleagues showed that breast cancer can be inherited through mutations in the BRCA1 gene which causes truncated protein which lacks normal tumor suppressor function.

Mary-Claire King's landmark contribution to breast cancer genetics culminated in her 1990 *Science* paper. In this study, King and her team used linkage analysis across multiple families with high incidences of early-onset breast and ovarian cancer to demonstrate that the susceptibility to these cancers could be traced to a single autosomal-dominant locus on the long arm of chromosome 17.

This was a groundbreaking finding because, until then, familial clustering of breast cancer had been recognized but not genetically explained. King's identification of this locus—later named BRCA1—provided the first molecular evidence that hereditary breast cancer has a specific genetic basis, paving the way for the positional cloning of BRCA1 in 1994. BRCA1 is a tumor suppressor gene that is responsible for repairing DNA.

King's work reframed breast cancer as a disease with both hereditary and sporadic dimensions, integrating genetics into oncology's clinical practice. Over subsequent decades, she became a leading advocate for population-based genetic testing, particularly for BRCA1 and BRCA2 mutations, emphasizing equity and access to testing for all women—not just those with a strong family history.

References: DeVita and Rosenberg (2012), Ekmektzoglou (2009), GMN 13966, Lukon (2017), Olson (2002, p. 254).

Linkage of Early-Onset Familial Breast Cancer to Chromosome 17q21

Jeff M. Hall, Ming K. Lee, Beth Newman, Jan E. Morrow, Lee A. Anderson, Bing Huey, Mary-Claire King

Human breast cancer is usually caused by genetic alterations of somatic cells of the breast, but occasionally, susceptibility to the disease is inherited. Mapping the genes responsible for inherited breast cancer may also allow the identification of early lesions that are critical for the development of breast cancer in the general population. Chromosome 17q21 appears to be the locale of a gene for inherited susceptibility to breast cancer in families with early-onset disease. Genetic analysis yields a lod score (logarithm of the likelihood ratio for linkage) of 5.98 for linkage of breast cancer susceptibility to *D17S74* in early-onset families and negative lod scores in families with late-onset disease. Likelihood ratios in favor of linkage heterogeneity among families ranged between 2000:1 and greater than 10^6:1 on the basis of multipoint analysis of four loci in the region.

Human disease genes can be located by linkage analysis of families in which the incidence of the disease is high. Linkage analysis can reveal the chromosomal location of the genes of interest by identifying polymorphic genetic markers of known location that are coinherited with the disease in families (*1*). Among the common cancers, breast cancer is particularly suited for this approach, because family history of the disease is a significant risk factor in all populations; epidemiological evidence consistently indicates that a woman's risk of breast cancer is increased by the occurrence of the disease in her mother or sisters. The younger the ages at diagnosis of her relatives, the greater the increase in a woman's risk (*2*).

unavoidable epidemiologic realities. The disease is common, but only a small proportion of cases in the general population are attributable to inherited susceptibility. Thus, families may have multiple cases of breast cancer without inherited susceptibility, and "sporadic" cases may occur even in families with inherited disease. In addition, the disease is not completely penetrant among susceptible persons, with expression depending on gender, age, and nongenetic risk factors. Finally, both epidemiological and molecular evidence suggests heterogeneity. We have tested simultaneously for genetic linkage and heterogeneity of breast cancer in families, and our results suggest both the presence of a gene for early-onset breast cancer on chromosome 17q21 and linkage heterogeneity of the disease.

Families and inheritance of susceptibility. Our genetic analysis is based on 23 extended families with 146 cases of breast cancer (Figs. 1 and 2). All persons in our analysis are Caucasian and from a variety of original ancestries. The 329 participating relatives now live in, and were therefore sampled from, 40 states of the United States, Puerto Rico, Canada, the United Kingdom, and Colombia. These families share the epidemiological features that are characteristic of familial, versus sporadic, breast cancer (*2*): younger age at diagnosis, frequent bilateral disease, and more frequent occurrence of disease among men.

Our statistical model for the inheritance of susceptibility to breast cancer was derived from our previous complex segregation analysis of a population-based series of 1500 families with breast cancer (*4*). Inherited susceptibility to breast cancer in that series could be fully explained by a rare autosomal dominant allele with a major effect on risk: risk of breast cancer in genetically susceptible women was estimated to be 0.37 by age 40, 0.66 by age 55, and 0.82 over the entire lifetime. In contrast, risk of breast cancer in women without

Jeff Hall et. al. "Linkage of early-onset familial breast cancer to chromosome 17q21, *Science*, Dec 21, Volume 250, pp. 1684-1689.

2000: Charles M. Perou et al.

Defined intrinsic subtypes (e.g., Luminal A/B, HER2-enriched, Basal-like), inaugurating the genomics era of classification. With over 13,000 citations, this is one of the most cited papers in breast cancer research history.

The 2000 paper by Charles M. Perou and colleagues, titled “Molecular Portraits of Human Breast Tumours”, reported one of the first large-scale efforts to catalogue breast cancer heterogeneity at the level of gene expression. The authors analyzed 65 surgical specimens from 42 women using cDNA microarrays covering ~8,102 genes, including paired samples taken before and after doxorubicin chemotherapy (20 pairs) and two primary tumour–lymph-node metastasis pairs. They found that (i) samples from the same individual clustered more closely than samples from different individuals; (ii) there were coherent gene-expression modules corresponding to proliferation, interferon signalling, stromal/lymphoid infiltration and epithelial lineage; and (iii) hierarchical clustering of these data allowed the tumours to be classified into distinct molecular sub-types rather than simply being variations on a common theme.

This work shifted the paradigm of breast cancer classification from purely morphological/histopathological categories (e.g., ductal vs. lobular, ER + vs. ER –) to a molecular taxonomy grounded in transcriptional programs. By demonstrating that breast tumours segregate into distinct expression-defined groups, the paper laid the groundwork for the “intrinsic subtypes” of breast cancer (later refined into Luminal A/B, HER2-enriched, Basal-like, etc.). This has had major downstream implications: the subtypes have been linked to prognosis, therapeutic response and biology of breast tumours. In short, the paper opened the door for gene-expression based prognostic/predictive assays and for precision oncology in breast cancer.

References: Lukong (2017), Sanli (2022).

Molecular portraits of human breast tumours

Charles M. Perou*†, Therese Sørlie*‡, Michael B. Eisen*, Matt van de Rijn§, Stefanie S. Jeffrey‖, Christian A. Rees*, Jonathan R. Pollack¶, Douglas T. Ross¶, Hilde Johnsen‡, Lars A. Akslen#, Øystein Fluge☆, Alexander Pergamenschikov*, Cheryl Williams*, Shirley X. Zhu§, Per E. Lønning**, Anne-Lise Børresen-Dale‡, Patrick O. Brown¶†† & David Botstein*

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† These authors contributed equally to this work

Human breast tumours are diverse in their natural history and i
their responsiveness to treatments[1]. Variation in transcriptiona
programs accounts for much of the biological diversity of huma
cells and tumours. In each cell, signal transduction and regulator
systems transduce information from the cell's identity to it
environmental status, thereby controlling the level of expressio
of every gene in the genome. Here we have characterized variatio
in gene expression patterns in a set of 65 surgical specimens o
human breast tumours from 42 different individuals, usin
complementary DNA microarrays representing 8,102 huma
genes. These patterns provided a distinctive molecular portrai
of each tumour. Twenty of the tumours were sampled twic
before and after a 16-week course of doxorubicin chemotherapy
and two tumours were paired with a lymph node metastasis fro
the same patient. Gene expression patterns in two tumou
samples from the same individual were almost always mor
similar to each other than either was to any other sample. Se
of co-expressed genes were identified for which variation i
messenger RNA levels could be related to specific features o
physiological variation. The tumours could be classified int
subtypes distinguished by pervasive differences in their gen
expression patterns.

Charles M. Perou et al., 2000, “Molecular portraits of human breast tumours, *Nature*, Aug 17, 2000, Volume 406, pp. 747-52. From the author’s medical library.

2013: St. Gallen Consensus Guidelines

Updated breast cancer classification of HR+ cancers into Luminal A and Luminal B, following the 2013 St. Gallen Consensus. Codified the precision approach used for the next decade by breast oncologists.

This paper summarizes the outcomes of the 13th St Gallen International Breast Cancer Conference 2013 Expert Panel and distils key recommendations for the management of early-stage breast cancer.

The Panel reviewed recent evidence on local/regional therapies (surgery, axillary management, radiation), systemic therapies (endocrine, chemotherapy, targeted agents) and recognized the increasing relevance of tumor biology (intrinsic subtypes) and multi-gene assays. Specifically, the document emphasizes a shift away from “one size fits all” to a biologically guided, risk-adapted approach: it supports less extensive axillary surgery and shorter or more tailored radiotherapy in appropriate patients, refines the management of luminal ($ER^+/HER2^-$) disease including the role of genomic assays and reaffirms existing strategies for HER2-positive and triple-negative disease.

The implications of this consensus were broad and enduring. By endorsing tumor subtype-based decision-making and encouraging the selective use of multi-gene prognostic/predictive assays, the paper advances the principle of personalized breast-cancer treatment—matching therapy intensity with individual risk and biology rather than relying solely on tumor size or nodal status. For clinicians, this means moving toward de-escalation of therapy when safe and escalation when indicated—thereby balancing efficacy, toxicity, patient preference and cost. At a system level, the consensus supports integrating newer diagnostic technologies into practice and encourages global consideration of resource constraints. In short, the Goldhirsch et al. 2013 paper helped translate emerging molecular and clinical evidence into practical, consensus-based guidance—a major step in the evolution from empiric to individualized early-breast-cancer care.

References: Sanli (2022).

Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013

A. Goldhirsch[1*], E. P. Winer[2], A. S. Coates[3], R. D. Gelber[4], M. Piccart-Gebhart[5], B. Thürlimann[6] & H.-J. Senn[7] Panel members[†]

introduction

St Gallen 2013: news and progress

Goldhirsch A, Winer EP, Coates AS, Gelber RD, Piccart-Gebhart M, Thürlimann B, Senn HJ; Panel members, “Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer,” 2013. *Ann Oncol.* Sep;24(9):2206-23.

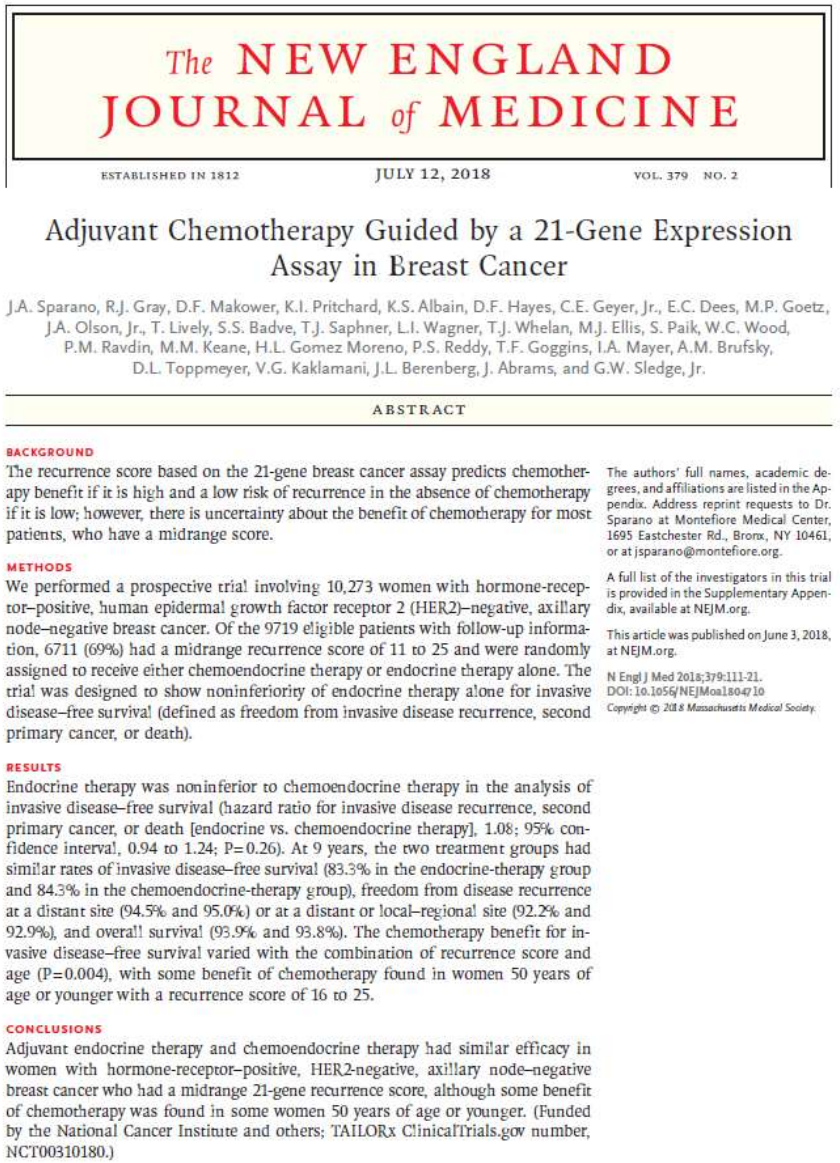
2018: Joseph Sparano

A precision assay was used to show that adjuvant chemotherapy is not always additive in managing HR+, Her2- patients with early breast cancer. This study validated the value of sophisticated gene testing in breast cancer.

In this large, prospective clinical trial (known as TAILORx), the investigators enrolled over 10,000 women with hormone-receptor positive, HER2-negative, axillary node-negative early breast cancer. Tumour tissue from each patient was evaluated using the 21-gene Recurrence Score assay (Oncotype DX) and patients with "intermediate" scores (11–25) were randomly assigned to receive either standard endocrine therapy alone or combined chemo-endocrine therapy. After a median follow-up of about 9 years, the study found that endocrine therapy alone was noninferior to chemo-endocrine therapy in terms of invasive disease-free survival, distant recurrence and overall survival: 83.3% vs. 84.3% for invasive disease-free survival, 94.5% vs. 95.0% for freedom from distant recurrence and 93.9% vs. 93.8% for overall survival in the endocrine vs chemo-endocrine arms respectively. Importantly, there was a statistically significant interaction of age with benefit of chemotherapy: women 50 years or younger with recurrence scores of 16–25 derived some benefit from chemotherapy (P=0.004).

The implications of this trial are substantial for the management of early breast cancer. First, it supports the use of a molecular assay (the 21-gene Recurrence Score) to guide adjuvant chemotherapy decisions in hormone-receptor positive, HER2-negative, node-negative disease by identifying a large subgroup of women who may safely forgo chemotherapy, thereby avoiding its costs and toxicities without compromising outcomes. It represents a major shift toward precision medicine—tailoring therapy intensity to tumour biology rather than using a one-size-fits-all approach. Second, by demonstrating that endocrine therapy alone was adequate for many women with intermediate scores, the paper has influenced clinical guidelines and practice.

References: Bonilla (2017), Lukong (2017).



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Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer

J.A. Sparano, R.J. Gray, D.F. Makower, K.I. Pritchard, K.S. Albain, D.F. Hayes, C.E. Geyer, Jr., E.C. Dees, M.P. Goetz, J.A. Olson, Jr., T. Lively, S.S. Badve, T.J. Saphner, L.I. Wagner, T.J. Whelan, M.J. Ellis, S. Paik, W.C. Wood, P.M. Ravdin, M.M. Keane, H.L. Gomez Moreno, P.S. Reddy, T.F. Goggins, I.A. Mayer, A.M. Brufsky, D.L. Toppmeyer, V.G. Kaklamani, J.L. Berenberg, J. Abrams, and G.W. Sledge, Jr.

ABSTRACT

BACKGROUND

The recurrence score based on the 21-gene breast cancer assay predicts chemotherapy benefit if it is high and a low risk of recurrence in the absence of chemotherapy if it is low; however, there is uncertainty about the benefit of chemotherapy for most patients, who have a midrange score.

METHODS

We performed a prospective trial involving 10,273 women with hormone-receptor–positive, human epidermal growth factor receptor 2 (HER2)–negative, axillary node–negative breast cancer. Of the 9719 eligible patients with follow-up information, 6711 (69%) had a midrange recurrence score of 11 to 25 and were randomly assigned to receive either chemoendocrine therapy or endocrine therapy alone. The trial was designed to show noninferiority of endocrine therapy alone for invasive disease–free survival (defined as freedom from invasive disease recurrence, second primary cancer, or death).

RESULTS

Endocrine therapy was noninferior to chemoendocrine therapy in the analysis of invasive disease–free survival (hazard ratio for invasive disease recurrence, second primary cancer, or death [endocrine vs. chemoendocrine therapy], 1.08; 95% confidence interval, 0.94 to 1.24; P=0.26). At 9 years, the two treatment groups had similar rates of invasive disease–free survival (83.3% in the endocrine-therapy group and 84.3% in the chemoendocrine-therapy group), freedom from disease recurrence at a distant site (94.5% and 95.0%) or at a distant or local–regional site (92.2% and 92.9%), and overall survival (93.9% and 93.8%). The chemotherapy benefit for invasive disease–free survival varied with the combination of recurrence score and age (P=0.004), with some benefit of chemotherapy found in women 50 years of age or younger with a recurrence score of 16 to 25.

CONCLUSIONS

Adjuvant endocrine therapy and chemoendocrine therapy had similar efficacy in women with hormone-receptor–positive, HER2-negative, axillary node–negative breast cancer who had a midrange 21-gene recurrence score, although some benefit of chemotherapy was found in some women 50 years of age or younger. (Funded by the National Cancer Institute and others; TAILORx ClinicalTrials.gov number, NCT00310180.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Sparano at Montefiore Medical Center, 1695 Eastchester Rd., Bronx, NY 10461, or at jsparano@montefiore.org.

A full list of the investigators in this trial is provided in the Supplementary Appendix, available at NEJM.org.

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DOI: 10.1056/NEJMoa1804710

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Sparano JA, et. al, "Adjuvant Chemotherapy Guided by a 21-Gene Expression Assay in Breast Cancer,," *N Engl J Med*. Jul 12;379(2):111-121.

Section 4.I: New Targets

Recent advances in molecular oncology have revealed a wealth of new therapeutic targets for breast cancer beyond the classical domains of hormone and HER2 signaling. One important breakthrough has come from targeting PARP in BRCA mutated cancers. We had the first FDA approval for olaparib for breast cancer in 2018. A further breakthrough has been the targeting of the PI3K–AKT–mTOR pathway, a central regulator of cell growth and metabolism frequently altered in breast tumors. Mutations in PIK3CA, encoding the PI3K-α catalytic subunit, occur in up to 40% of hormone receptor–positive breast cancers. The FDA approval of alpelisib (Piqray) in 2019 marked the first precision therapy directed at this pathway. Other inhibitors, such as capivasertib (AKT inhibitor) and everolimus (mTOR inhibitor), further expand this axis of intervention. Beyond PARP and PI3K, other targets such as HER3 (ERBB3), FGFR1/2, TROP-2, iNOS and Claudin6 are emerging as key actionable nodes, targeted by antibody–drug conjugates (e.g., sacituzumab govitecan, datopotamab deruxtecan) and bispecific antibodies that selectively deliver cytotoxins or immune activation to tumor cells.

Concurrently, new biological insights are redefining breast cancer as a disease deeply intertwined with metabolism, inflammation and the tumor microenvironment. Other promising targets include DNA damage repair proteins (ATR, CHK1 and WEE1), epigenetic regulators (such as EZH2 and BET bromodomains) and novel immune-metabolic checkpoints.

2004: Kurtis Bachman et. al.

PI3Kα mutations are common in breast cancers – suggesting a strategy for precision therapy.

The 2004 paper by Kenneth E. Bachman and colleagues at Johns Hopkins, titled “The PIK3CA gene is mutated with high frequency in human breast cancers” (*Cancer Research*, 64:7678–7681), was the first to establish that activating mutations in PIK3CA, encoding the catalytic subunit p110α of phosphatidylinositol 3-kinase (PI3K), occur frequently in human breast tumors. By sequencing tumor samples and cell lines, the authors found PIK3CA mutations in approximately 25% of breast cancers—particularly clustered in the helical (E542K, E545K) and kinase (H1047R) domains.

These “hotspot” mutations enhanced PI3K signaling, promoting downstream AKT activation and cellular proliferation. The findings linked the PI3K pathway—previously known for its role in growth factor signaling and oncogenic transformation—directly to endogenous driver mutations in human breast carcinoma, identifying it as one of the most common genetic lesions in the disease.

The implications were transformative. Bachman’s discovery reframed PI3K not just as a signaling mediator but as a mutated oncogene central to luminal A and B breast cancer subtypes. It spurred an international wave of research into PI3K pathway targeting, including the development of PI3K inhibitors such as alpelisib (approved in 2019 for PIK3CA-mutant HR+/HER2- metastatic breast cancer). Follow-up studies in the late 2000s (notably by Samuels, Hennessy and Baselga groups) confirmed PIK3CA mutations’ prevalence across multiple cancers and their role in endocrine resistance. Thus, the Bachman et al. paper stands as the pivotal bridge from molecular discovery to precision therapy, laying the groundwork for one of modern oncology’s most successful biomarker-driven treatment paradigms.

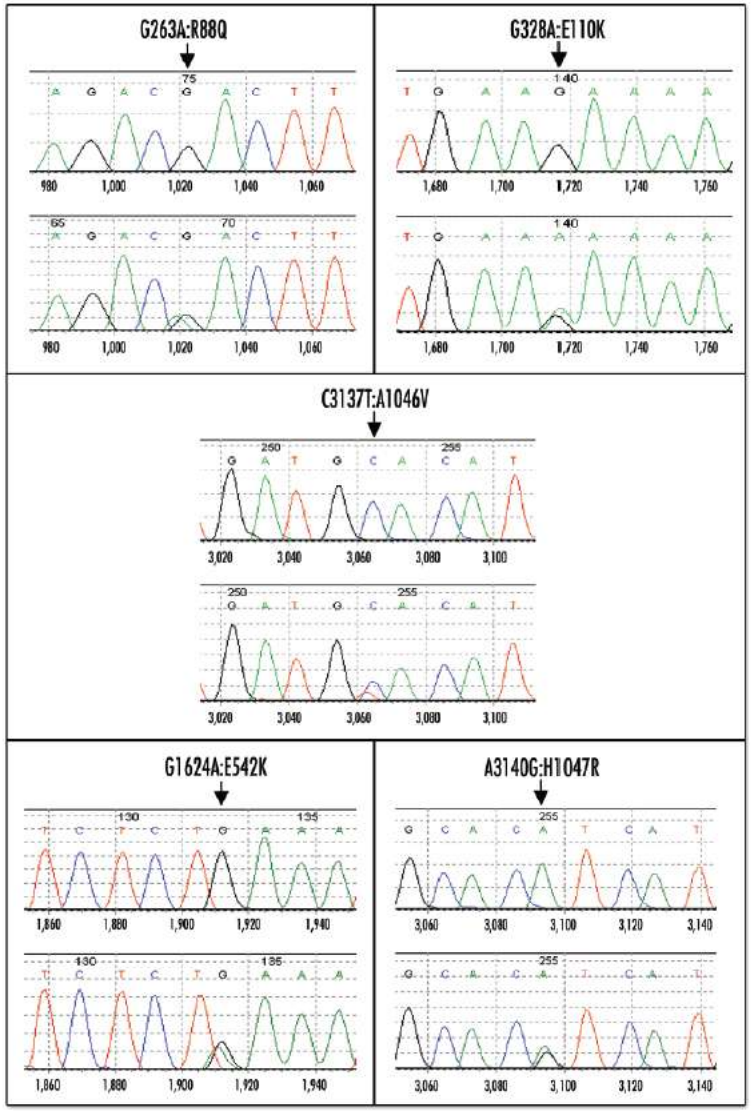

Figure 1. Somatic mutations found in the *PIK3CA* gene in primary breast cancers. Examples of somatic mutations found in the p85 binding domain, helical and kinase domain of PIK3CA. Top sequence in each chromatogram is derived from normal tissue and bottom sequence from tumor. Arrows indicate the position of the missense mutations. The nucleotide and amino acid changes are given above the arrows.

Bachman KE, Argani P, Samuels Y, Silliman N, Ptak J, Szabo S, Konishi H, Karakas B, Blair BG, Lin C, Peters BA, Velculescu VE, Park BH., 2004, “The PIK3CA gene is mutated with high frequency in human breast cancers,” *Cancer Biol Ther.* Aug;3(8):772-5.

2005: Alan Ashworth and Team

First to recognize that a PARP inhibitor could work in BRCA mutated breast cancers.

In the mid-1990s Stephen Jackson's lab at the ICR Cambridge explored DNA damage repair mechanisms; the idea of inhibiting PARP (poly ADP-ribose polymerase) first emerged from this basic research program.

Then, Jackson and an ICR colleague Alan Ashworth come up with the idea for a PARP inhibitor. ICR Press Release: "A vital breakthrough came from a conversation between Professor Ashworth and Professor Steve Jackson … They both realised that blocking another DNA-repair pathway in BRCA-defective cells that are already struggling to fix faults in their genetic material had the potential to tip them over the edge, making them unviable."

The first time the world saw this idea was in a 2005 paper where Ashworth, Jackson and his team discussed the idea of a PARP inhibitor for breast cancer. The authors wrote in the paper: "BRCA1 and BRCA2 are important for DNA double-strand break repair by homologous recombination and mutations in these genes predispose to breast and other cancers. Poly(ADP-ribose) polymerase (PARP) is an enzyme involved in base excision repair, a key pathway in the repair of DNA single-strand breaks. We show here that BRCA1 or BRCA2 dysfunction unexpectedly and profoundly sensitizes cells to the inhibition of PARP enzymatic activity, resulting in chromosomal instability, cell cycle arrest and subsequent apoptosis. This seems to be because the inhibition of PARP leads to the persistence of DNA lesions normally repaired by homologous recombination. These results illustrate how different pathways cooperate to repair damage and suggest that the targeted inhibition of particular DNA repair pathways may allow the design of specific and less toxic therapies for cancer."

Targeting the DNA repair defect in *BRCA* mutant cells as a therapeutic strategy

Hannah Farmer[1,2]*, Nuala McCabe[1,2]*, Christopher J. Lord[2]*, Andrew N. J. Tutt[2,3], Damian A. Johnson[2], Tobias B. Richardson[2], Manuela Santarosa[2]†, Krystyna J. Dillon[4], Ian Hickson[4], Charlotte Knights[4], Niall M. B. Martin[4], Stephen P. Jackson[4,5], Graeme C. M. Smith[4] & Alan Ashworth[1,2]

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[5]*Wellcome Trust and Cancer Research UK, Gurdon Institute of Cancer and Developmental Biology, and Department of Zoology, University of Cambridge, Tennis Court Road, Cambridge CB2 1QN, UK*

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† Present address: Division of Experimental Oncology1, CRO-IRCCS, Aviano 33081 PN, Italy

BRCA1 and BRCA2 are important for DNA double-strand break repair by homologous recombination[1], and mutations in these genes predispose to breast and other cancers[2]. Poly(ADP-ribose) polymerase (PARP) is an enzyme involved in base excision repair, a key pathway in the repair of DNA single-strand breaks[3]. We show here that BRCA1 or BRCA2 dysfunction unexpectedly and profoundly sensitizes cells to the inhibition of PARP enzymatic activity, resulting in chromosomal instability, cell cycle arrest and subsequent apoptosis. This seems to be because the inhibition of PARP leads to the persistence of DNA lesions normally repaired by homologous recombination. These results illustrate how different pathways cooperate to repair damage, and suggest that the targeted inhibition of particular DNA repair pathways may allow the design of specific and less toxic therapies for cancer.

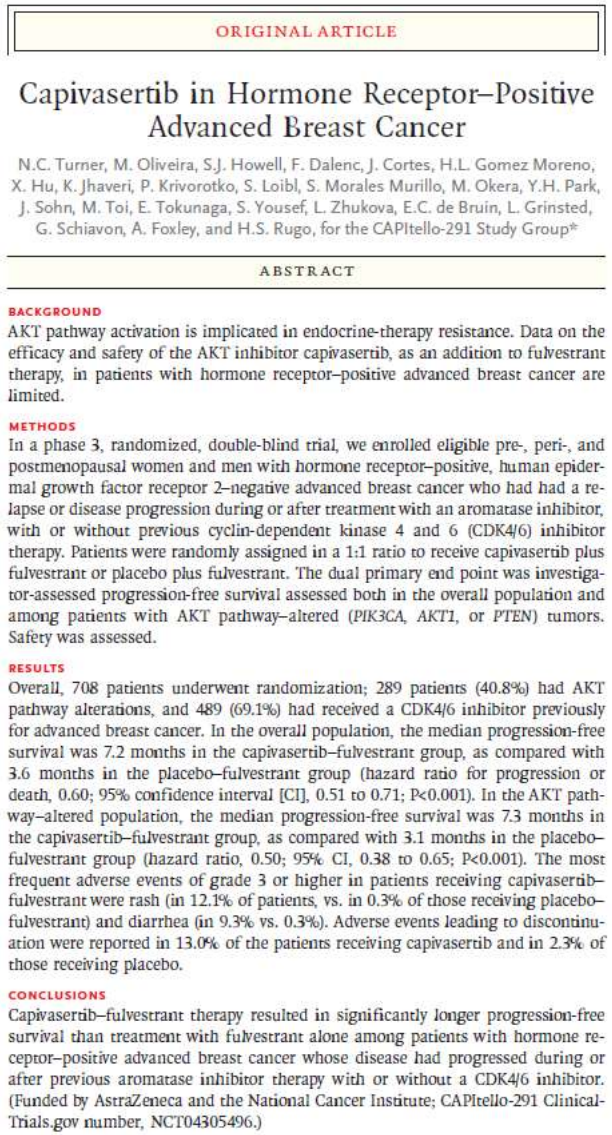
Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, Santarosa M, Dillon KJ, Hickson I, Knights C, Martin NM, Jackson SP, Smith GC, Ashworth A., 2005, "Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy," *Nature*. Apr 14;434(7035):917-21.

2023: Nicholas Turner

Showed high benefit of an oral AKT inhibitor in breast cancer for the first time.

In the 2023 *New England Journal of Medicine* study by Nicholas C. Turner and colleagues, the researchers reported the results of a phase III, double-blind, randomized trial evaluating capivasertib, an oral selective AKT inhibitor, in combination with fulvestrant for patients with hormone receptor–positive, HER2-negative advanced breast cancer who had relapsed or progressed after aromatase inhibitor therapy. The study enrolled 708 patients, stratified by tumor AKT pathway alterations (PIK3CA, AKT1, or PTEN). Patients receiving capivasertib + fulvestrant had a median progression-free survival (PFS) of 7.2 months, compared with 3.6 months in the placebo + fulvestrant group, representing a 40 percent reduction in the risk of progression or death. The benefit was particularly marked in patients whose tumors had AKT pathway alterations, in whom median PFS improved to 7.3 months vs 3.1 months, confirming the role of AKT activation as a driver of endocrine resistance.

The trial established capivasertib + fulvestrant as a new targeted therapeutic option for patients with endocrine-resistant, HR-positive metastatic breast cancer, expanding precision therapy beyond PI3K inhibition. Toxicities such as rash, diarrhea and hyperglycemia were consistent with AKT pathway inhibition but were generally manageable. Turner's study demonstrated that dual blockade of ER and AKT signaling can overcome key mechanisms of endocrine resistance and that molecular profiling to identify AKT pathway mutations can guide therapy selection. These findings reinforced the growing role of genotype-directed treatment in advanced breast cancer and paved the way for capivasertib's regulatory approval and incorporation into standard care for this patient population.



ORIGINAL ARTICLE

Capivasertib in Hormone Receptor–Positive Advanced Breast Cancer

N.C. Turner, M. Oliveira, S.J. Howell, F. Dalenc, J. Cortes, H.L. Gomez Moreno, X. Hu, K. Jhaveri, P. Krivorotko, S. Loibl, S. Morales Murillo, M. Okera, Y.H. Park, J. Sohn, M. Toi, E. Tokunaga, S. Yousef, L. Zhukova, E.C. de Bruin, L. Grinsted, G. Schiavon, A. Foxley, and H.S. Rugo, for the CAPItello-291 Study Group*

ABSTRACT

BACKGROUND

AKT pathway activation is implicated in endocrine-therapy resistance. Data on the efficacy and safety of the AKT inhibitor capivasertib, as an addition to fulvestrant therapy, in patients with hormone receptor–positive advanced breast cancer are limited.

METHODS

In a phase 3, randomized, double-blind trial, we enrolled eligible pre-, peri-, and postmenopausal women and men with hormone receptor–positive, human epidermal growth factor receptor 2–negative advanced breast cancer who had had a relapse or disease progression during or after treatment with an aromatase inhibitor, with or without previous cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor therapy. Patients were randomly assigned in a 1:1 ratio to receive capivasertib plus fulvestrant or placebo plus fulvestrant. The dual primary end point was investigator-assessed progression-free survival assessed both in the overall population and among patients with AKT pathway–altered (*PIK3CA*, *AKT1*, or *PTEN*) tumors. Safety was assessed.

RESULTS

Overall, 708 patients underwent randomization; 289 patients (40.8%) had AKT pathway alterations, and 489 (69.1%) had received a CDK4/6 inhibitor previously for advanced breast cancer. In the overall population, the median progression-free survival was 7.2 months in the capivasertib–fulvestrant group, as compared with 3.6 months in the placebo–fulvestrant group (hazard ratio for progression or death, 0.60; 95% confidence interval [CI], 0.51 to 0.71; P<0.001). In the AKT pathway–altered population, the median progression-free survival was 7.3 months in the capivasertib–fulvestrant group, as compared with 3.1 months in the placebo–fulvestrant group (hazard ratio, 0.50; 95% CI, 0.38 to 0.65; P<0.001). The most frequent adverse events of grade 3 or higher in patients receiving capivasertib–fulvestrant were rash (in 12.1% of patients, vs. in 0.3% of those receiving placebo–fulvestrant) and diarrhea (in 9.3% vs. 0.3%). Adverse events leading to discontinuation were reported in 13.0% of the patients receiving capivasertib and in 2.3% of those receiving placebo.

CONCLUSIONS

Capivasertib–fulvestrant therapy resulted in significantly longer progression-free survival than treatment with fulvestrant alone among patients with hormone receptor–positive advanced breast cancer whose disease had progressed during or after previous aromatase inhibitor therapy with or without a CDK4/6 inhibitor. (Funded by AstraZeneca and the National Cancer Institute; CAPItello-291 ClinicalTrials.gov number, NCT04305496.)

Nicholas Turner et al., 2023, "Capivasertib in Hormone Receptor–Positive Advanced Breast Cancer," *NEJM*, May 31, Volume 388, pp. 2058-2070. Boston: Massachusetts Medical Society, First edition. From the author's medical library.

2025: ASCENT-03 Investigators

Showed that TRODELVY®, a TROP2 ADC was associated with substantially longer PFS in advanced TNBC patients than chemo. Adverse event rates were similar across both classes of treatment.

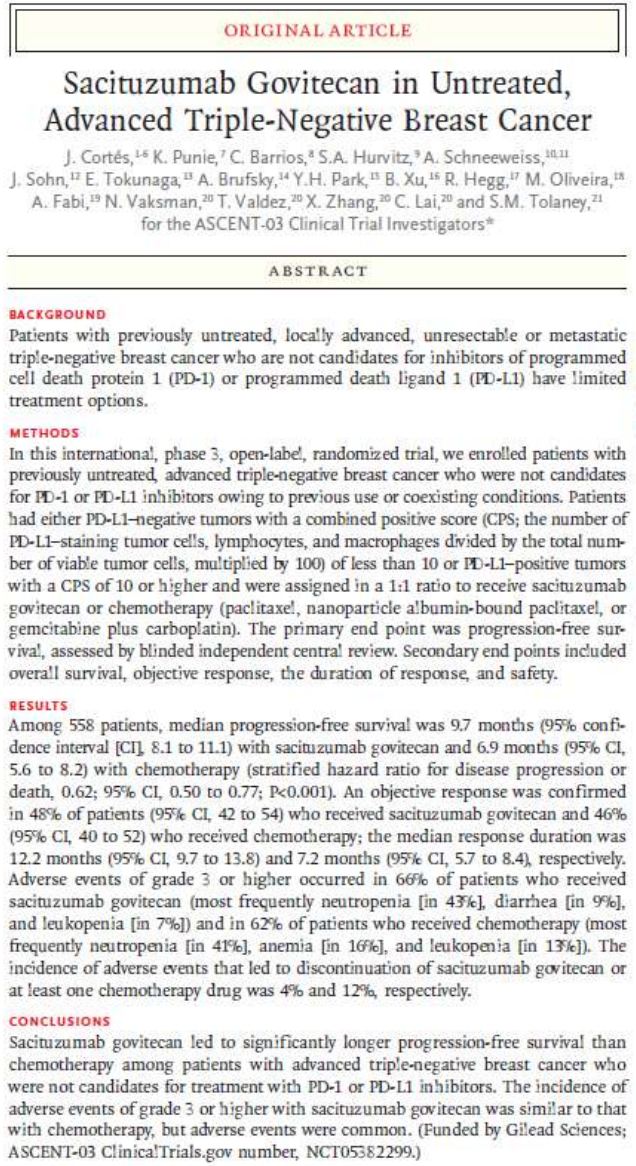
Sacituzumab govitecan (TRODELYVY®) led to significantly longer progression-free survival than chemotherapy among patients with advanced triple-negative breast cancer who were not candidates for treatment with PD-1 or PD-L1 inhibitors. The incidence of adverse events of grade 3 or higher with sacituzumab govitecan was similar to that with chemotherapy.

In the randomized ASCENT trial, 468 patients with metastatic triple-negative breast cancer (mTNBC), who had received at least two prior therapies (including a taxane) and had no brain metastases, were assigned to receive SG versus single-agent chemotherapy of physician's choice.

The median progression-free survival (PFS) in the SG arm was 5.6 months (95% CI 4.3–6.3) versus 1.7 months (95% CI 1.5–2.6) in the chemo arm (hazard ratio [HR] 0.41; 95% CI 0.32–0.52; P<0.001).

Median overall survival (OS) was 12.1 months (95% CI 10.7–14.0) with SG versus 6.7 months (95% CI 5.8–7.7) with chemotherapy (HR 0.48; 95% CI 0.38–0.59; P<0.001). The objective response rate (ORR) was 35% for SG vs. 5% for chemo.

The toxicity profile was higher for SG in terms of neutropenia (51% grade ≥3) and diarrhea (10% grade ≥3) but was manageable with supportive care.



ORIGINAL ARTICLE

Sacituzumab Govitecan in Untreated, Advanced Triple-Negative Breast Cancer

J. Cortés,[1,6] K. Punie,[7] C. Barrios,[8] S.A. Hurvitz,[9] A. Schneeweiss,[10,11] J. Sohn,[12] E. Tokunaga,[13] A. Brufsky,[14] Y.H. Park,[15] B. Xu,[16] R. Hegg,[17] M. Oliveira,[18] A. Fabi,[19] N. Vaksman,[20] T. Valdez,[20] X. Zhang,[20] C. Lai,[20] and S.M. Tolaney,[21] for the ASCENT-03 Clinical Trial Investigators*

ABSTRACT

BACKGROUND

Patients with previously untreated, locally advanced, unresectable or metastatic triple-negative breast cancer who are not candidates for inhibitors of programmed cell death protein 1 (PD-1) or programmed death ligand 1 (PD-L1) have limited treatment options.

METHODS

In this international, phase 3, open-label, randomized trial, we enrolled patients with previously untreated, advanced triple-negative breast cancer who were not candidates for PD-1 or PD-L1 inhibitors owing to previous use or coexisting conditions. Patients had either PD-L1–negative tumors with a combined positive score (CPS; the number of PD-L1–staining tumor cells, lymphocytes, and macrophages divided by the total number of viable tumor cells, multiplied by 100) of less than 10 or PD-L1–positive tumors with a CPS of 10 or higher and were assigned in a 1:1 ratio to receive sacituzumab govitecan or chemotherapy (paclitaxel, nanoparticle albumin-bound paclitaxel, or gemcitabine plus carboplatin). The primary end point was progression-free survival, assessed by blinded independent central review. Secondary end points included overall survival, objective response, the duration of response, and safety.

RESULTS

Among 558 patients, median progression-free survival was 9.7 months (95% confidence interval [CI], 8.1 to 11.1) with sacituzumab govitecan and 6.9 months (95% CI, 5.6 to 8.2) with chemotherapy (stratified hazard ratio for disease progression or death, 0.62; 95% CI, 0.50 to 0.77; P<0.001). An objective response was confirmed in 48% of patients (95% CI, 42 to 54) who received sacituzumab govitecan and 46% (95% CI, 40 to 52) who received chemotherapy; the median response duration was 12.2 months (95% CI, 9.7 to 13.8) and 7.2 months (95% CI, 5.7 to 8.4), respectively. Adverse events of grade 3 or higher occurred in 66% of patients who received sacituzumab govitecan (most frequently neutropenia [in 43%], diarrhea [in 9%], and leukopenia [in 7%]) and in 62% of patients who received chemotherapy (most frequently neutropenia [in 41%], anemia [in 16%], and leukopenia [in 13%]). The incidence of adverse events that led to discontinuation of sacituzumab govitecan or at least one chemotherapy drug was 4% and 12%, respectively.

CONCLUSIONS

Sacituzumab govitecan led to significantly longer progression-free survival than chemotherapy among patients with advanced triple-negative breast cancer who were not candidates for treatment with PD-1 or PD-L1 inhibitors. The incidence of adverse events of grade 3 or higher with sacituzumab govitecan was similar to that with chemotherapy, but adverse events were common. (Funded by Gilead Sciences; ASCENT-03 ClinicalTrials.gov number, NCT05382299.)

Cortés J, Punie K, Barrios C, Hurvitz SA, Schneeweiss A, Sohn J, Tokunaga E, Brufsky A, Park YH, Xu B, Hegg R, Oliveira M, Fabi A, Vaksman N, Valdez T, Zhang X, Lai C, Tolaney SM; ASCENT-03 Clinical Trial Investigators, 2025, "Sacituzumab Govitecan in Untreated, Advanced Triple-Negative Breast Cancer," *N Engl J Med*. Oct 19.

Section 4.J: Risk Factors

The recognition of breast cancer risk factors has evolved over centuries, from vague humoral notions to a precise understanding of hormonal, reproductive and metabolic determinants. By the mid-20th century, epidemiologic studies firmly established that lifetime exposure to estrogen—whether through early menarche, late menopause, or exogenous hormone use—plays a central role in driving risk.

Nulliparity and delayed childbearing, noted as early as the 16th Century, later confirmed in modern cohort studies is associated with elevated susceptibility to malignant transformation.

Obesity, particularly after menopause, emerged as another major risk factor because adipose tissue becomes the dominant source of estrogen production via aromatase activity, creating a hormonally rich microenvironment that fosters tumor growth.

Additional physiologic and environmental contributors—alcohol consumption, ionizing radiation, physical inactivity and high-fat diets—have been linked to increased incidence, while lactation, regular exercise and maintaining healthy body weight provide protective effects.

1997: Walt Willett and Colleagues

Found that weight gain and weight is a significant risk factor for post-menopausal breast cancer. Weight is a substantial risk factor and is very likely an important clue as to the etiology of breast cancer itself.

The 1997 paper by Walt Willett of Harvard's School of Public Health analyzed a cohort of 95256 US female nurses aged 30 to 55 years who were followed up for 16 years (the Nurses Health Study).

uring 1203498 person-years, 2517 incident breast cancers (60% postmenopausal) were documented. Higher current BMI was associated with lower breast cancer incidence before menopause and was minimally associated with incidence after menopause.

Weight gain after the age of 18 years was unrelated to breast cancer incidence before menopause, but was positively associated with incidence after menopause. This increased risk with weight gain was limited to women who never used postmenopausal hormones; among these women, the relative risk was 1.99 (95% confidence interval, 1.43-2.76) for weight gain of more than 20 kg vs unchanged weight (P for trend <.001). Current BMI and weight gain were even more strongly associated with fatal postmenopausal breast cancer. In this population, the percentage of postmenopausal breast cancer accounted for by weight gain alone was approximately 16% and by hormone replacement therapy alone was 5%,

Dual Effects of Weight and Weight Gain on Breast Cancer Risk

Zhiping Huang, MD, PhD; Susan E. Hankinson, ScD; Graham A. Colditz, MBBS, DrPH; Meir J. Stampfer, MD, DrPH; David J. Hunter, MBBS, ScD; JoAnn E. Manson, MD, DrPH; Charles H. Hennekens, MD; Bernard Rosner, PhD; Frank E. Speizer, MD; Walter C. Willett, MD, DrPH

Context.—Breast cancer is a major cause of mortality among women. It is important to identify modifiable risk factors for this disease.

Objective.—To examine body mass index (BMI) at the age of 18 years and at midlife and adult weight change in relation to breast cancer incidence and mortality.

Design.—Cohort study.

Setting.—A cohort of 95 256 US female nurses aged 30 to 55 years who were followed up for 16 years.

Main Outcome Measure.—Incident and fatal breast cancer.

Results.—During 1 203 498 person-years, 2517 incident breast cancers (60% postmenopausal) were documented. Higher current BMI was associated with lower breast cancer incidence before menopause and was minimally associated with incidence after menopause. However, a stronger positive relationship was seen among postmenopausal women who never used hormone replacement (relative risk=1.59 for BMI >31 kg/m² vs ≤20 kg/m²; 95% confidence interval, 1.09-2.32; *P* for trend <.001). Higher BMI at the age of 18 years was associated with lower breast cancer incidence both before and after menopause. Weight gain after the age of 18 years was unrelated to breast cancer incidence before menopause, but was positively associated with incidence after menopause. This increased risk with weight gain was limited to women who never used postmenopausal hormones; among these women, the relative risk was 1.99 (95% confidence interval, 1.43-2.76) for weight gain of more than 20 kg vs unchanged weight (*P* for trend <.001). Current BMI and weight gain were even more strongly associated with fatal postmenopausal breast cancer. In this population, the percentage of postmenopausal breast cancer accounted for by weight gain alone was approximately 16% and by hormone replacement therapy alone was 5%, but when the interaction between these variables was considered, together they accounted for about one third of postmenopausal breast cancers.

Conclusions.—Avoiding adult weight gain may contribute importantly to the prevention of breast cancer after menopause, particularly among women who do not use postmenopausal hormones.

JAMA. 1997;278:1407-1411

From the Departments of Nutrition (Drs Huang, Stampfer, and Willett), Epidemiology (Drs Hankinson, Colditz, Stampfer, Hunter, Manson, Hennekens, and Willett), and Biostatistics (Dr Rosner), Harvard School of Public Health, and the Channing Laboratory (Drs Hankinson, Colditz, Stampfer, Hunter, Manson, Rosner, Speizer, and Willett), Division of Preventive Medicine, Department of Medicine (Drs Manson and Hennekens), and Department of Ambulatory Care and Prevention (Dr Hennekens), Harvard Medical School and Brigham and Women's Hospital, Boston, Mass.

Reprints: Walter C. Willett, MD, DrPH, Channing Laboratory, 181 Longwood Ave, Boston, MA 02115.

THE RELATION OF body weight to breast cancer is complex. An inverse association between relative weight and breast cancer risk has been found among premenopausal women in most case-control and prospective studies.[1,2] A similar inverse association has been observed between relative weight at the age of 18 years and risk of premenopausal breast cancer.[3] The relation between body weight and postmenopausal breast cancer is less clear. In many case-control studies, body mass index (BMI) has been positively associated with postmenopausal breast cancer.[4,5] However, prospective studies have generally suggested only a weak, if any, positive association.[6,7] The lack of a clear and consistent positive association between body

For editorial comment see p 1448.

weight and breast cancer has been perplexing because among postmenopausal women endogenous estrogen levels, which are believed to increase breast cancer incidence, are 50% to 100% higher among heavy women compared with lean women.[8,9] This has suggested that some beneficial aspect of adiposity may counterbalance an adverse effect due to higher endogenous estrogen levels. It is also possible that the use of estrogen preparations after menopause, which appears to increase breast cancer incidence,[10] could obscure any relation of adiposity to breast cancer risk that was due to higher endogenous estrogen levels.

Few studies have examined weight change in relation to breast cancer risk. Adult weight gain, which largely reflects an increase in body fat, may be a better variable to assess adiposity and its metabolic consequences than body weight itself, which reflects both lean and fat mass.[11,12] Further, greater adiposity is associated with larger tumor size and nodal involvement at diagnosis of breast cancer,[13] as well as a poorer survival,[10] which suggests that obesity may relate differently to breast cancer incidence and mortality.

The objectives of this study were to examine prospectively BMI at the age of

JAMA, November 5, 1997—Vol 278, No. 17 Weight Gain and Breast Cancer Risk—Huang et al 1407

Huang Z, Hankinson SE, Colditz GA, Stampfer MJ, Hunter DJ, Manson JE, Hennekens CH, Rosner B, Speizer FE, Willett WC., 1997, "Dual effects of weight and weight gain on breast cancer risk," *JAMA*. Nov 5;278(17):1407-11.

2015: Natalie Engmann

Did a careful analysis of multiple determinants of breast cancer risk.

Engmann et al., JAMA Oncology (2017) analyzed data from over 18,000 women in the U.S. Breast Cancer Surveillance Consortium to quantify how much of breast cancer risk could be explained by known clinical factors.

The study found that traditional risk factors—such as family history, benign breast disease, breast density, BMI and reproductive history—accounted for roughly 39% of breast cancer cases among premenopausal women and 37% among postmenopausal women. Among these, mammographic breast density was the single strongest contributor, explaining 16–23% of population-attributable risk, followed by family history and prior benign biopsy.

In contrast, reproductive and hormonal variables (e.g., parity, age at first birth, hormone therapy use) had relatively smaller effects.

The authors concluded that while these factors collectively capture a meaningful fraction of breast cancer risk, the majority of individual susceptibility remains unexplained, emphasizing the need for improved biomarkers and genetic profiling to refine personalized risk prediction and screening strategies.

Engmann NJ, Golmakani MK, Miglioretti DL, Sprague BL, Kerlikowske K; Breast Cancer Surveillance Consortium., 2017,"Population-Attributable Risk Proportion of Clinical Risk Factors for Breast Cancer," *JAMA Oncol*. Sep 1;3(9):1228-1236.

Table 1. Characteristics of Women With Breast Cancer and Controls Included in the Study Population, Breast Cancer Surveillance Consortium (1996-2015)

Characteristic	Women, No. (%)			
	Premenopausal		Postmenopausal	
	Control (n = 52 860)	Invasive and In Situ Cancer (n = 5286)	Control (n = 131 449)	Invasive and In Situ Cancer (n = 13 151)
Age, y				
40-49	41 120 (77.8)	4114 (77.8)	4711 (3.6)	471 (3.6)
50-59	11 740 (22.2)	1172 (22.2)	48 868 (37.2)	4882 (37.1)
60-69	NA	NA	54 153 (41.2)	5415 (41.2)
70-74	NA	NA	23 717 (18.0)	2383 (18.1)
Race/ethnicity				
White	40 054 (75.8)	4091 (77.4)	104 157 (79.2)	10 832 (82.4)
Black	1295 (2.4)	122 (2.3)	3323 (2.5)	279 (2.1)
Asian	5670 (10.7)	548 (10.4)	11 177 (8.5)	894 (6.8)
Hispanic	2719 (5.1)	208 (3.9)	5105 (3.9)	395 (3.0)
Other/mixed	3122 (5.9)	317 (6.0)	7687 (5.8)	751 (5.7)
Family history of breast cancer				
No	46 070 (87.1)	4181 (79.1)	109 827 (83.6)	10 035 (76.3)
Yes	6840 (12.9)	1105 (20.9)	21 622 (16.4)	3116 (23.7)
History of benign breast biopsy				
No	45 658 (86.4)	4193 (79.3)	102 741 (78.2)	9252 (70.4)
Yes	7202 (13.6)	1093 (20.7)	28 708 (21.8)	3899 (29.6)
Age at first live birth, y				
Nulliparous	11 729 (22.2)	1240 (23.5)	20 236 (15.4)	2350 (17.9)
Age <30 y	29 060 (55.0)	2615 (49.5)	97 101 (73.9)	9168 (69.7)
Age ≥30 y	12 071 (22.8)	1431 (27.1)	14 112 (10.7)	1633 (12.4)
BMI				
<18.5	924 (1.7)	106 (2.0)	2223 (1.7)	173 (1.3)
18.5-24.9	23 739 (44.9)	2642 (50.0)	45 341 (34.5)	4194 (31.9)
25.0-29.9	15 123 (28.6)	1456 (27.5)	43 937 (33.4)	4476 (34.0)
30.0-34.9	7192 (13.6)	616 (11.7)	23 321 (17.7)	2493 (19.0)
≥35.0	5882 (11.1)	466 (8.8)	16 627 (12.6)	1815 (13.8)
BI-RADS breast density				
Almost entirely fat (a)	2764 (5.2)	95 (1.8)	16 852 (12.8)	1014 (7.7)
Scattered fibroglandular densities (b)	17 256 (32.6)	1248 (23.6)	62 743 (47.7)	5749 (43.7)
Heterogeneously dense (c)	24 479 (46.3)	2803 (53.0)	44 686 (34.0)	5448 (41.4)
Extremely dense (d)	8361 (15.8)	1140 (21.6)	7168 (5.5)	940 (7.1)
Type of cancer				
Invasive	NA	3890 (73.6)	NA	10 313 (78.4)
In situ		1396 (26.4)		2838 (21.6)
No. of risk factors				
None	9749 (18.4)	539 (10.2)	11 222 (8.5)	649 (4.9)
1	20 793 (39.3)	1759 (33.3)	49 661 (37.8)	3803 (28.9)
2	17 509 (33.1)	2039 (38.6)	46 076 (35.1)	4807 (36.6)
3	4365 (8.3)	821 (15.5)	19 744 (15.0)	2914 (22.2)
≥4	444 (0.8)	128 (2.4)	4746 (3.6)	978 (7.4)

Abbreviations: BI-RADS, Breast Imaging Reporting and Data System; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); NA, not applicable.

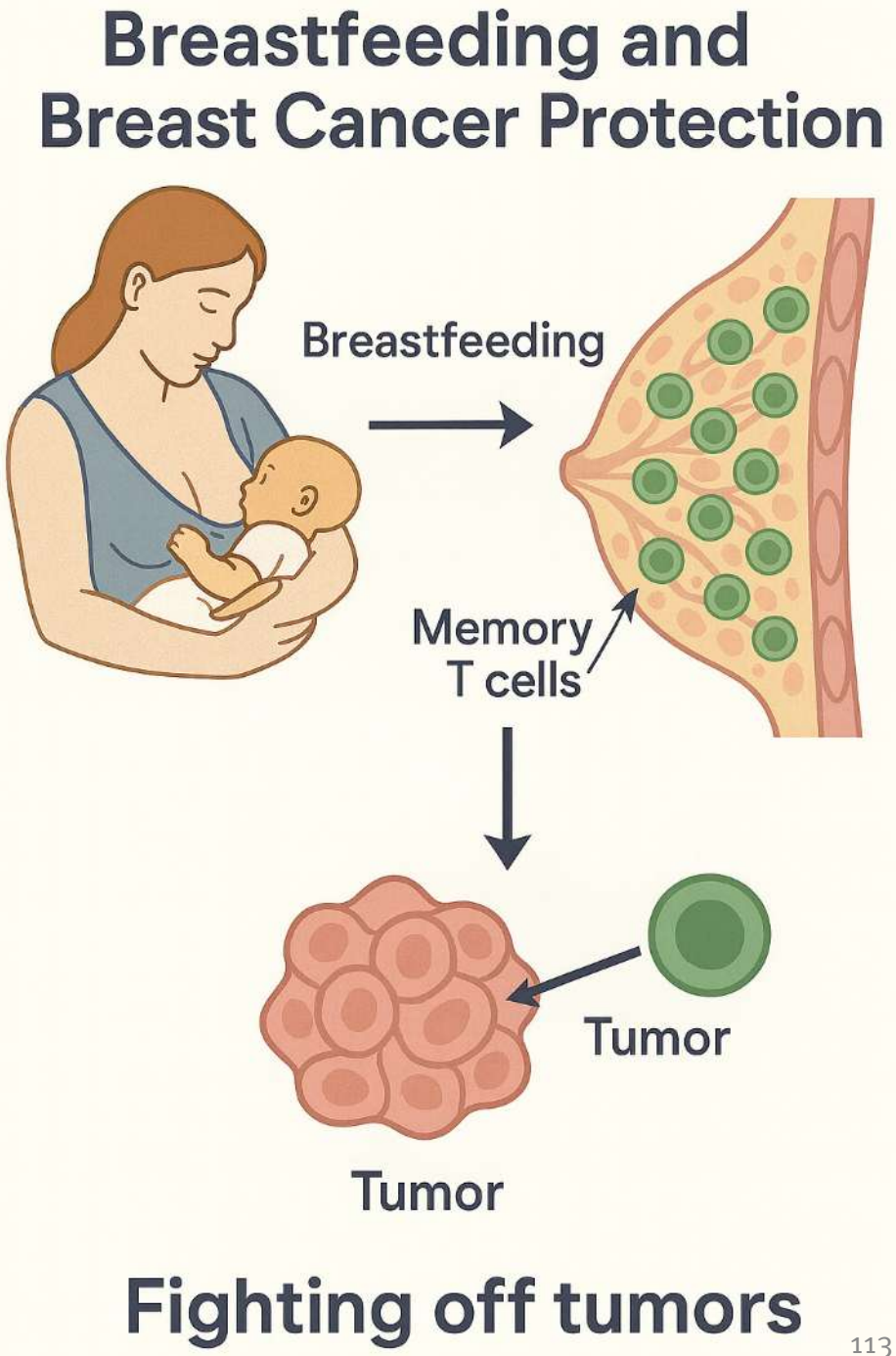
2025: Balaji Virassamy et al.

Link the centuries long understanding of the relationship between parity and breast cancer incidence to T-cell populations.

In 1713, Bernardino Ramazzini (1633–1714) noted a higher frequency of breast cancer in nuns in Italy than in married women. blamed the disparity on celibacy. More recent work has shown the breast-feeding is a key factor in reducing breast cancer risk. In Virassamy et al., "Parity and lactation induce T cell-mediated breast cancer protection" in *Nature* Oct 2025 the authors show that undergoing pregnancy, followed by a period of lactation and subsequent mammary gland involution, leads to the durable accumulation of $CD8^+$ T-cells—particularly those with a tissue-resident memory-like phenotype—in normal human breast tissue.

Using mouse models of mammary tumour challenge, they demonstrate that only the full sequence of pregnancy, lactation and involution confers significantly reduced tumour growth, enhanced intratumoural T-cell infiltration and that depletion of $CD8^+$ cells abolishes the protection. Analyses of more than a thousand human breast cancer specimens revealed that women with a history of both parity and breastfeeding had tumours with higher T-cell infiltration and better outcomes (notably in triple-negative breast cancer) compared with women without such history.

The findings explain the well-documented epidemiologic observation that parity and lactation reduce breast cancer risk. The study identifies adaptive immunity—more precisely mammary gland-resident $CD8^+$ T-cells—as a key mediator of this protective effect, rather than attributing it purely to hormonal changes or breast tissue differentiation. This paper opens up new prevention avenues, suggesting that mimicking or stimulating the protective T-cell population in women who did not breastfeed might yield benefit.



Virassamy B, et al., 2025, "Parity and lactation induce T cell mediated breast cancer protection," *Nature*, Oct 20.

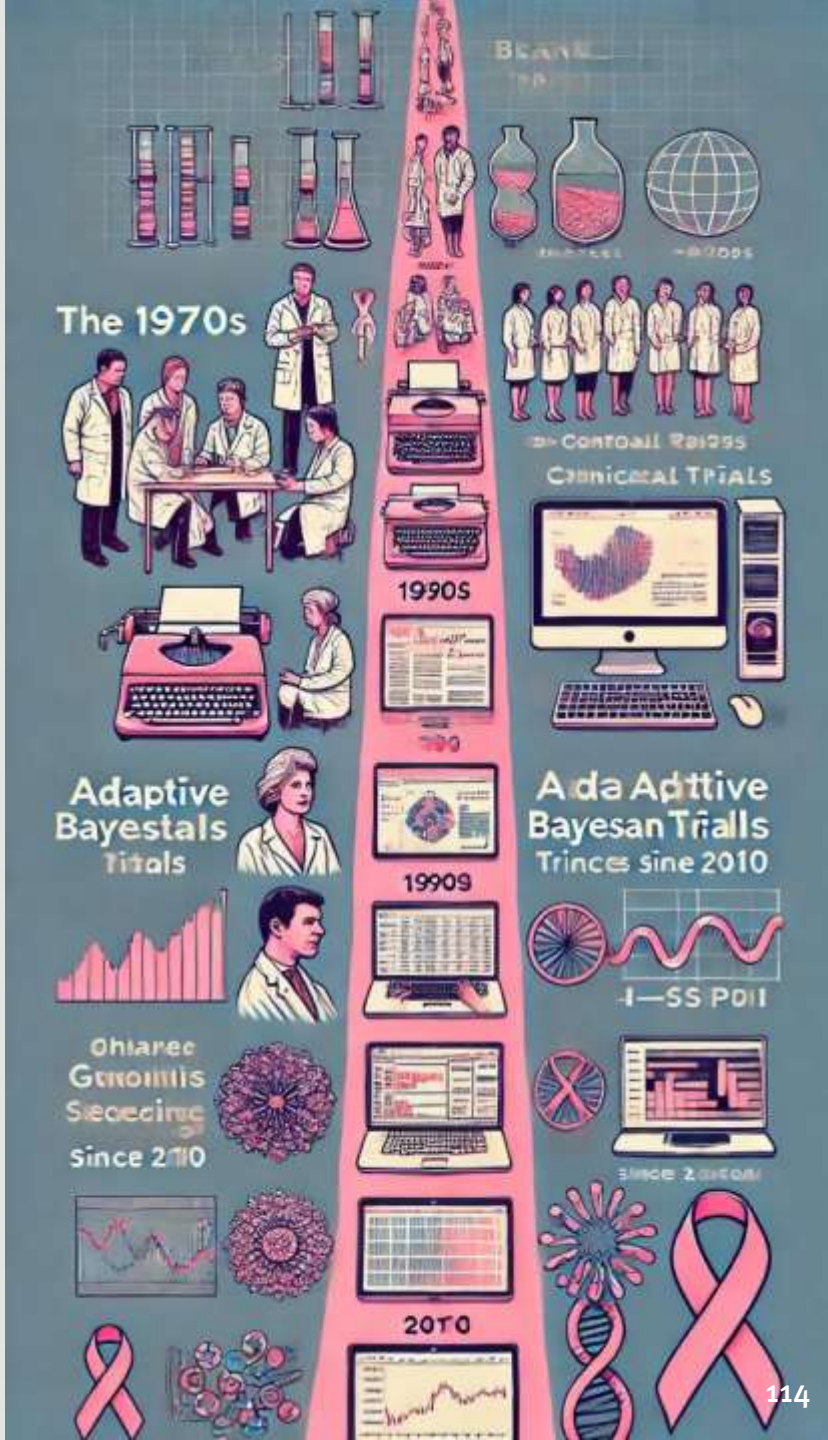
Section 4.K: Research Methods

The evolution of research methods in breast cancer has mirrored the broader transformation of oncology from empirical trial-and-error to data-driven precision. In the decades following World War II, progress accelerated through large-scale cooperative group studies, many coordinated by the National Cancer Institute (NCI) and its cooperative trial networks, such as the NSABP (National Surgical Adjuvant Breast and Bowel Project) and CALGB (Cancer and Leukemia Group B).

These research consortia pioneered randomized clinical trials that tested the role of adjuvant chemotherapy, hormonal therapy and radiation, establishing modern standards of care.

By the 1990s and early 2000s, the development of large multi-institutional collaborations—like ECOG-ACRIN, SWOG and Alliance—allowed the integration of correlative science, tissue banking and molecular profiling into prospective trials, transforming them from treatment tests into discovery platforms.

The 21st century has ushered in an era of adaptive, biomarker-driven trial design, enabling breast cancer research to evolve in real time. Notable examples include I-SPY 1 and I-SPY 2, innovative adaptive Bayesian platform trials sponsored by the NCI and the Quantum Leap Healthcare Collaborative.



2009: Laura Esserman

Introduced the I-SPY2 trial in breast cancer: a mature well-designed adaptive Bayesian clinical trial to better identify therapeutic opportunities in breast cancer.

The Barker et al., *2009* paper laid the conceptual foundation for the I-SPY 2 Trial, introducing one of the first fully adaptive, Bayesian, biomarker-driven clinical trial designs in oncology. The authors—an interdisciplinary team including Don Berry, Laura Esserman and leaders from the FDA and NCI—argued that traditional sequential phase I–III trials were too slow, costly and inefficient for an era of molecularly targeted therapies. Instead, they proposed a platform trial capable of simultaneously testing multiple experimental drugs across biologically defined patient subsets, using adaptive randomization to allocate more patients to promising agents based on early response signals (measured primarily by pathologic complete response, or pCR). This design allowed drugs to "graduate" early if they met a predefined Bayesian probability of success, enabling a continuous, learning system rather than isolated, static studies.

The paper was transformative because it moved oncology away from the "one-drug, one-trial" paradigm toward a learning-health-system model, in which molecular data, imaging and clinical endpoints feed into a live statistical engine that updates probabilities of benefit in real time. It emphasized collaboration among academia, regulators and industry, creating a precompetitive framework that accelerated drug development while maintaining rigor. Barker et al. also highlighted pCR as a suitable intermediate endpoint and described how imaging and genomic data would refine prediction models over time. The publication has since been recognized as a landmark in clinical-trial innovation—its principles now underlie not only I-SPY 2, but also modern adaptive platform trials in lung cancer (Lung-MAP), glioblastoma (GBM AGILE) and COVID-19 therapeutics—fundamentally reshaping the way precision oncology is conducted.

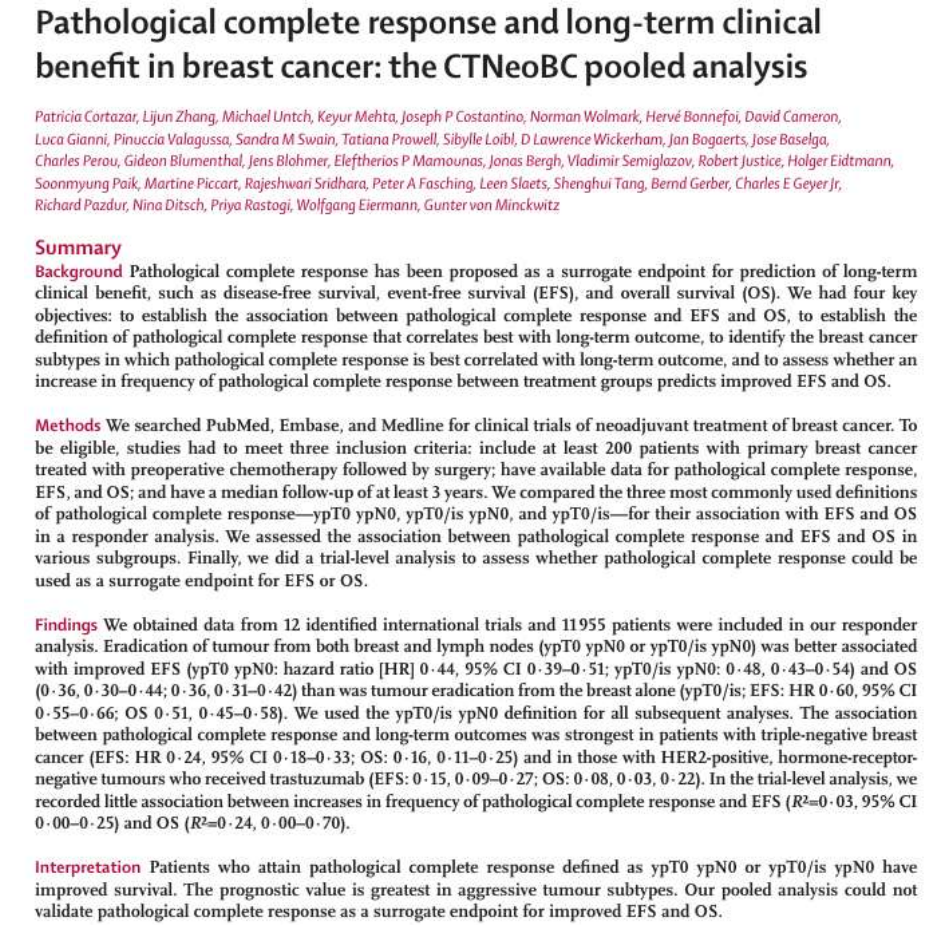
Barker AD, Sigman CC, Kelloff GJ, Hylton NM, Berry DA, Esserman LJ. , 2009, "I-SPY 2: an adaptive breast cancer trial design in the setting of neoadjuvant chemotherapy," *Clin Pharmacol Ther.* Jul;86(1):97-100.

2014: FDA + Academic Consortium Team

The CTNeoBC pooled analysis showed that achieving a pathologic complete response after neoadjuvant therapy predicts better long-term survival in aggressive breast cancer subtypes, establishing pCR as a key surrogate endpoint for evaluating treatment efficacy and an alternative to PFS.

The paper titled “Pathological Complete Response and Long-Term Clinical Benefit in Breast Cancer: The CTNeoBC Pooled Analysis” was led by Patricia Cortazar and a large team of international collaborators, including Lisa M. McShane, Hope Rugo, Martine Piccart, and Richard Pazdur from the U.S. Food and Drug Administration and global cooperative groups. Its purpose was to determine whether achieving a pathologic complete response (pCR) after neoadjuvant (pre-surgical) therapy could serve as a reliable surrogate endpoint for long-term outcomes such as event-free and overall survival in breast cancer. The investigators compiled individual patient data from more than 11,000 participants across 12 neoadjuvant clinical trials, representing all major breast cancer subtypes.

The study demonstrated that pCR—defined as no residual invasive cancer in the breast and lymph nodes—was strongly associated with better long-term outcomes. This link was most pronounced in biologically aggressive subtypes such as triple-negative and HER2-positive disease, where achieving pCR translated into a significant reduction in recurrence and mortality risk. In contrast, the association was weaker in hormone receptor–positive, HER2-negative cancers. These findings confirmed that pCR is not a universal surrogate for survival but is highly meaningful in certain molecular contexts, offering an earlier and more efficient way to evaluate treatment efficacy. Since the publication of this paper, pCR has become one of the most important endpoints in breast cancer research and regulatory science. It paved the way for accelerated FDA approvals of neoadjuvant therapies such as pertuzumab and pembrolizumab, fundamentally changing how new drugs are tested.



Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis

Patricia Cortazar, Lijun Zhang, Michael Untch, Keyur Mehta, Joseph P Costantino, Norman Wolmark, Hervé Bonnefoi, David Cameron, Luca Gianni, Pinuccia Valagussa, Sandra M Swain, Tatiana Prowell, Sibylle Loibl, D Lawrence Wickerham, Jan Bogaerts, Jose Baselga, Charles Perou, Gideon Blumenthal, Jens Blohmer, Efetherios P Mamounas, Jonas Bergh, Vladimir Semiglazov, Robert Justice, Holger Eidtmann, Soonmyung Paik, Martine Piccart, Rajeshwari Sridhara, Peter A Fasching, Leen Slaets, Shenghui Tang, Bernd Gerber, Charles E Geyer Jr, Richard Pazdur, Nina Ditsch, Priya Rastogi, Wolfgang Eiermann, Gunter von Minckwitz

Summary

Background Pathological complete response has been proposed as a surrogate endpoint for prediction of long-term clinical benefit, such as disease-free survival, event-free survival (EFS), and overall survival (OS). We had four key objectives: to establish the association between pathological complete response and EFS and OS, to establish the definition of pathological complete response that correlates best with long-term outcome, to identify the breast cancer subtypes in which pathological complete response is best correlated with long-term outcome, and to assess whether an increase in frequency of pathological complete response between treatment groups predicts improved EFS and OS.

Methods We searched PubMed, Embase, and Medline for clinical trials of neoadjuvant treatment of breast cancer. To be eligible, studies had to meet three inclusion criteria: include at least 200 patients with primary breast cancer treated with preoperative chemotherapy followed by surgery; have available data for pathological complete response, EFS, and OS; and have a median follow-up of at least 3 years. We compared the three most commonly used definitions of pathological complete response—ypT0 ypN0, ypT0/is ypN0, and ypT0/is—for their association with EFS and OS in a responder analysis. We assessed the association between pathological complete response and EFS and OS in various subgroups. Finally, we did a trial-level analysis to assess whether pathological complete response could be used as a surrogate endpoint for EFS or OS.

Findings We obtained data from 12 identified international trials and 11955 patients were included in our responder analysis. Eradication of tumour from both breast and lymph nodes (ypT0 ypN0 or ypT0/is ypN0) was better associated with improved EFS (ypT0 ypN0: hazard ratio [HR] 0·44, 95% CI 0·39–0·51; ypT0/is ypN0: 0·48, 0·43–0·54) and OS (0·36, 0·30–0·44; 0·36, 0·31–0·42) than was tumour eradication from the breast alone (ypT0/is; EFS: HR 0·60, 95% CI 0·55–0·66; OS 0·51, 0·45–0·58). We used the ypT0/is ypN0 definition for all subsequent analyses. The association between pathological complete response and long-term outcomes was strongest in patients with triple-negative breast cancer (EFS: HR 0·24, 95% CI 0·18–0·33; OS: 0·16, 0·11–0·25) and in those with HER2-positive, hormone-receptor-negative tumours who received trastuzumab (EFS: 0·15, 0·09–0·27; OS: 0·08, 0·03, 0·22). In the trial-level analysis, we recorded little association between increases in frequency of pathological complete response and EFS (R^2=0·03, 95% CI 0·00–0·25) and OS (R^2=0·24, 0·00–0·70).

Interpretation Patients who attain pathological complete response defined as ypT0 ypN0 or ypT0/is ypN0 have improved survival. The prognostic value is greatest in aggressive tumour subtypes. Our pooled analysis could not validate pathological complete response as a surrogate endpoint for improved EFS and OS.

Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, Bonnefoi H, Cameron D, Gianni L, Valagussa P, Swain SM, Prowell T, Loibl S, Wickerham DL, Bogaerts J, Baselga J, Perou C, Blumenthal G, Blohmer J, Mamounas EP, Bergh J, Semiglazov V, Justice R, Eidtmann H, Paik S, Piccart M, Sridhara R, Fasching PA, Slaets L, Tang S, Gerber B, Geyer CE Jr, Pazdur R, Ditsch N, Rastogi P, Eiermann W, von Minckwitz G., 2014, “Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis,” *Lancet*. Jul 12;384(9938):164-72.

2020: UK Age Trial

We have seen large consortia trials but how about a clinical trial run at the country level? The UK did just that through the NHS. This is one of the largest clinical studies we have ever seen.

The UK Age Trial, launched in 1991 and coordinated by the UK Medical Research Council and National Health Service Breast Screening Programme, was a landmark randomized study investigating whether starting mammography screening at age 40 (a decade earlier than standard NHS screening) could reduce breast cancer mortality. Over 160,000 women aged 39–41 were randomly assigned to either annual mammography from age 40 to 48 or usual care (screening beginning at age 50).

After 17 years of follow-up, results published in Lancet Oncology in 2020 showed a 25% reduction in breast cancer mortality in the intervention group during the first 10 years after entry, though the benefit waned thereafter.

The trial also confirmed that early screening led to earlier-stage cancer detection but at the cost of increased overdiagnosis and false positives. Its design—long-term, population-based and with robust mortality endpoints—made it one of the most rigorous tests ever conducted of early screening efficacy.

By size and duration, the UK Age Trial stands among the largest clinical trials ever run. It was bigger even than the US PLCO study which have around 155,000 subjects.

Duffy SW, Vulkan D, Cuckle H, Parmar D, Sheikh S, Smith RA, Evans A, Blyuss O, Johns L, Ellis IO, Myles J, Sasieni PD, Moss SM., 2020, “Effect of mammographic screening from age 40 years on breast cancer mortality (UK Age trial): final results of a randomised, controlled trial,” *Lancet Oncology*, Sep;21(9):1165-1172.

Section 4.L: Patient Advocacy

The modern history of patient advocacy in breast cancer is deeply intertwined with the women's health movement and the fight for medical transparency and autonomy. In the 1960s and 1970s, the Boston Women's Health Collective, authors of *Our Bodies, Ourselves*, helped transform how women understood their bodies and demanded a greater voice in medical decision-making.

Around the same time, journalist Rose Kushner, after undergoing breast cancer surgery, publicly denounced the prevailing "one-step" procedure in which diagnosis and radical mastectomy were performed without consent. The open disclosure by First Lady Betty Ford of her own breast cancer and mastectomy in 1974 further broke social taboos, encouraging early detection and conversation about women's health. These pioneering efforts reframed breast cancer from a private ordeal into a public cause—one centered on knowledge and dignity.

In the 1980s and 1990s, patient advocacy matured into a coordinated global movement that reshaped research, policy and funding. The Susan G. Komen Breast Cancer Foundation - founded in 1982 by Nancy Brinker - became one of the most influential advocacy organizations in medical history. The Breast Cancer Research Foundation (BCRF), established by Evelyn Lauder in 1993, further institutionalized the partnership between philanthropy and science.

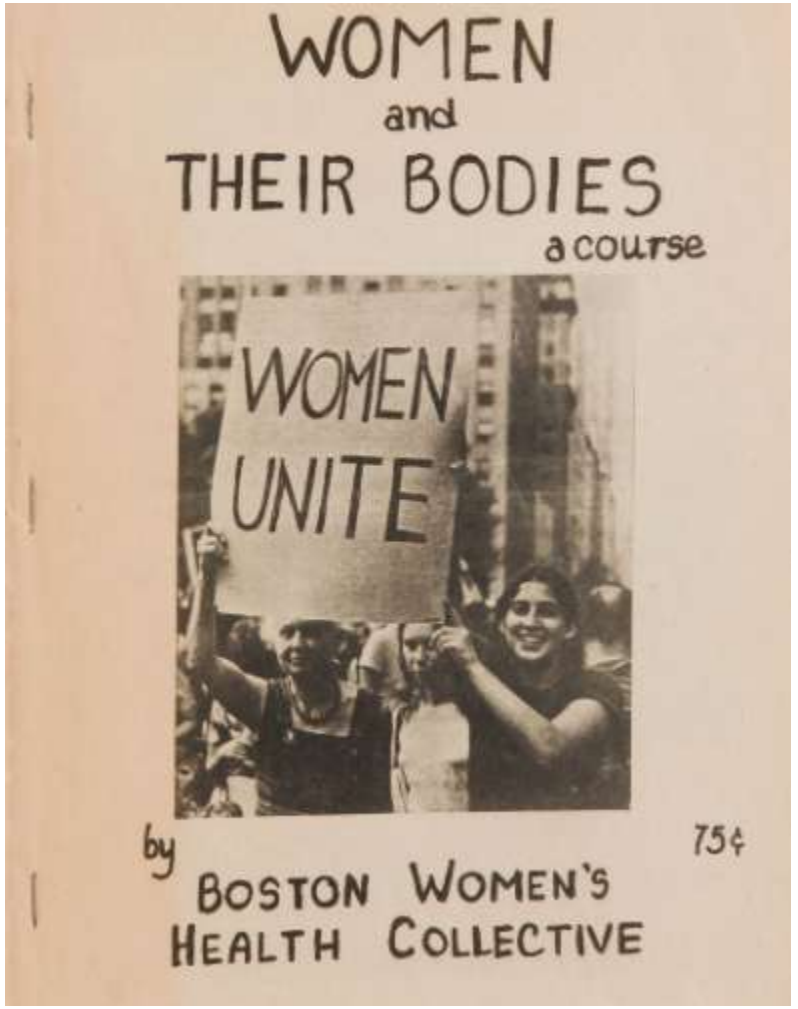
1970: Boston Women's Health Collective

The manifesto of the women's health movement of the 1970's. Argued for female autonomy over personal health decisions, particularly breast cancer.

Our Bodies, Ourselves—first published by the Boston Women's Health Book Collective in 1970 as "Women and Their Bodies" and updated repeatedly over the following decades—approached breast cancer as both a medical and social issue, deeply intertwined with women's autonomy, body awareness and the politics of medicine.

The book emphasized that breast cancer should not be viewed merely as a biological disease but also as a reflection of how women were treated within the healthcare system. It criticized the medical paternalism that had long dominated breast cancer care—especially the practice of performing radical mastectomies without informed consent—and urged women to ask questions, seek second opinions and understand their options. The authors encouraged readers to learn breast self-examination techniques, become familiar with normal breast anatomy and participate actively in screening and treatment decisions. In later editions, *Our Bodies, Ourselves* incorporated the growing evidence from the 1970s and 1980s that challenged the Halsted radical mastectomy as standard treatment, citing the work of advocates like Rose Kushner and studies demonstrating that less invasive surgeries (lumpectomy with radiation) could offer equivalent outcomes. The text presented breast cancer not only as a medical condition but as a feminist health issue, demanding transparency, compassionate care and respect for women's voices in clinical settings.

Note: The first edition of this title is scarce. While over 4 million copies of the title *Our Bodies, Ourselves* eventually sold, the first printing, *Women and Their Bodies* was issued on newsprint in five thousand copies. Copies were largely given away at rallies and may not have been kept by recipients. Today, only two copies can be found in a library (Boston Public Library & Harvard University).



Boston Women's Health Collective, 1970, *Women and Their Bodies,* Boston. From the author's medical library.

References: Lukong (2017), Pearson (2025).

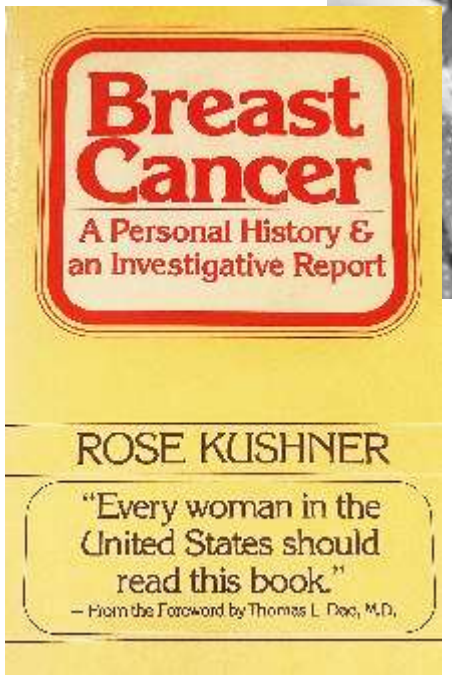
1975: Rose Kushner

One of the leaders of the women's movement for better breast cancer care.

Rose Kushner (1929–1990) was a pioneering journalist, author and patient advocate who transformed the landscape of breast cancer awareness, patient rights and surgical decision-making in the 1970s and 1980s. Following her own diagnosis of breast cancer in 1974, Kushner challenged the medical establishment's standard practice of performing a one-step procedure—in which a woman underwent biopsy and, if cancer was found, an immediate radical mastectomy under the same anesthesia, without her consent. Drawing on her investigative skills, she meticulously studied surgical literature and concluded that the radical Halsted procedure was excessively disfiguring and not always necessary. Her 1975 book, "Breast Cancer: A Personal History and an Investigative Report," exposed the paternalism and lack of patient autonomy in breast cancer treatment. Through her writing, she became the first widely recognized patient voice demanding informed consent and choice, insisting that women have the right to participate in decisions about their bodies. This book coincided with greater awareness of breast cancer associated with Betty Ford's frank 1974 conversation about her cancer and the 1970 book advocating women's autonomy in health (Woman and their Bodies – Later Our Bodies Ourselves).

Kushner's activism profoundly influenced both medical practice and public perception. She served on the National Cancer Advisory Board under Presidents Carter and Reagan, where she advocated for evidence-based, humane approaches to breast cancer care and helped shape national screening and treatment guidelines. Her outspoken criticism of overtreatment and her support for clinical trials validating breast-conserving surgery contributed to the eventual shift away from automatic radical mastectomy toward more individualized, patient-centered care. Beyond clinical reform, Kushner helped redefine breast cancer as a public and feminist issue, inspiring generations of advocacy organizations that emphasized education, early detection and patient empowerment.

References: Lerner (2001), Lukong (2017), Olson (2002, p. 171), Pearson (2025).



Rose Kushner, 1975, *Breast Cancer: A Personal History & an Investigative Report* (inscribed by the author), New York: Harcourt Brace Jovanovich. From the author's medical library.

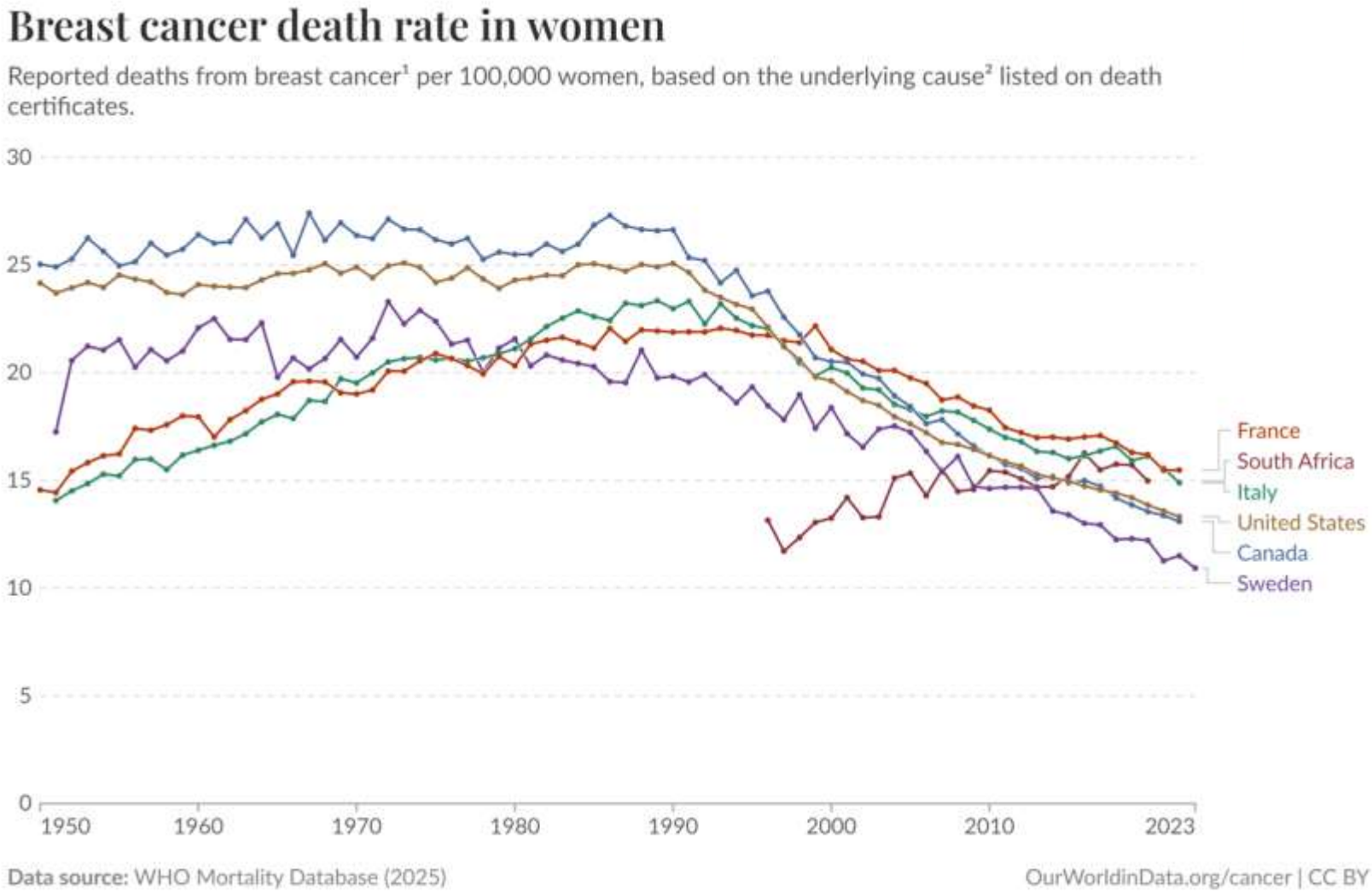
Section 5:

Where Next?

How Does Breast Cancer Treatment Evolve From Here?

Agatha – Patron Saint of Breast Cancer Sufferers
National Shrine of the Immaculate Conception

The Good News: Death Rates Are Down 40% to 60%

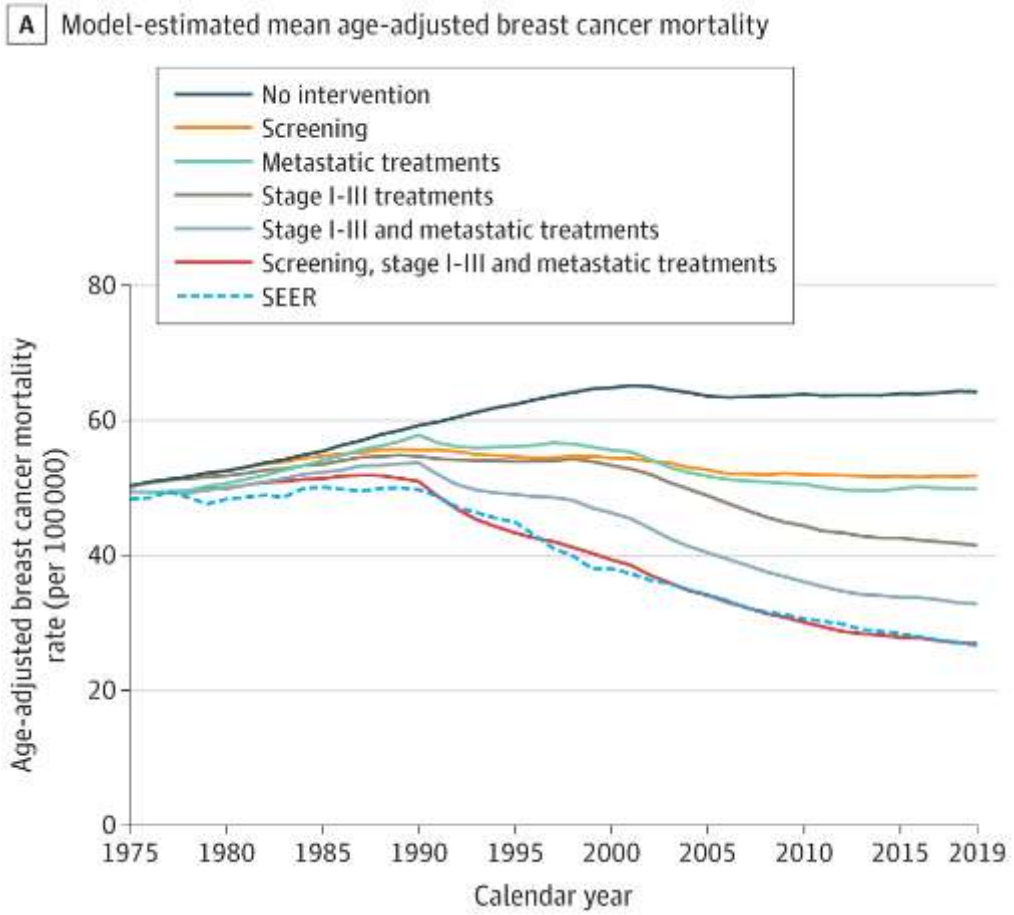


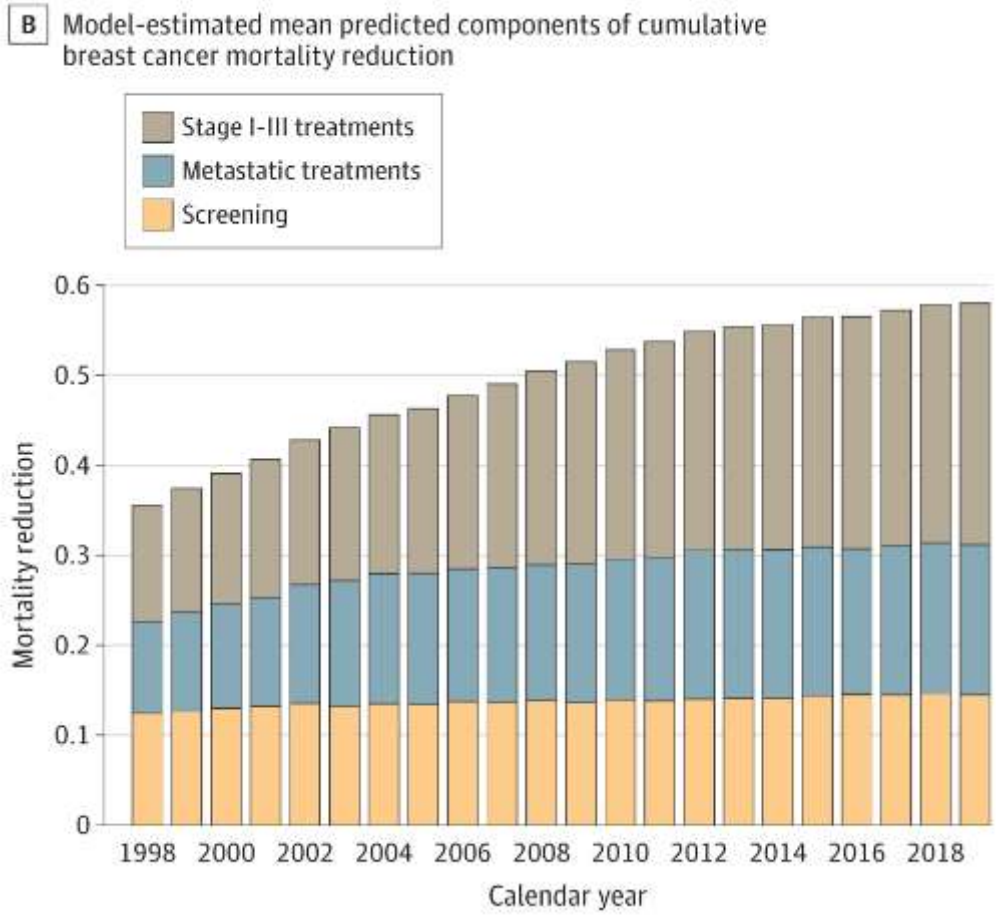
Between increased screening and improvements in treatment breast cancer mortality is down 40% to 60% since 1950 on a per capita basis.

This reflects an enormous social commitment to reduce the burden of this disease.

Further Good News: Screening and Treatments Matter

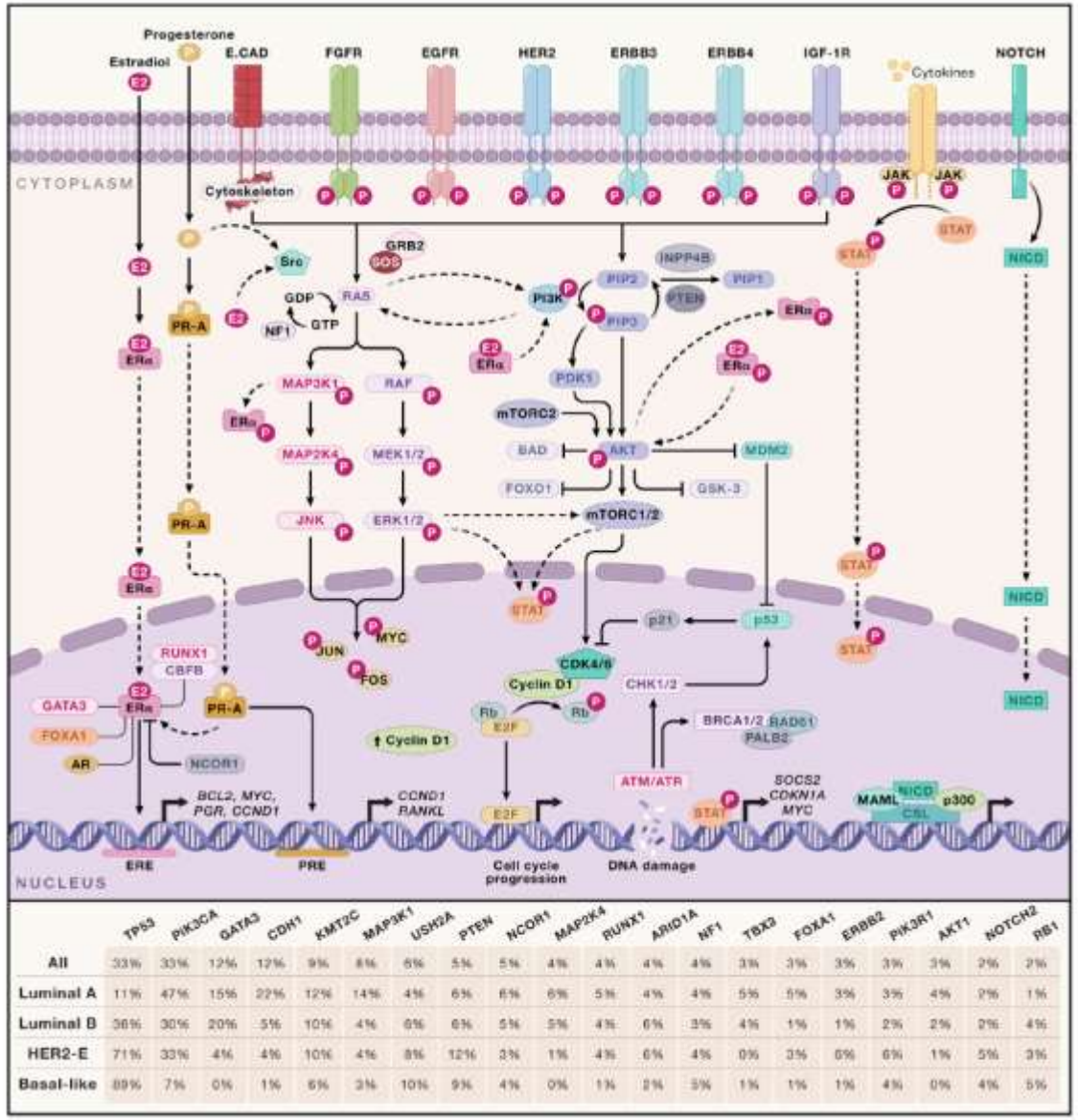
This study by Jennifer Caswell-Jin in *JAMA* in Jan 2024 shows that screening and new treatments are making a major difference in breast cancer mortality in the United States.





Source: https://jamanetwork.com/journals/jama/fullarticle/2813878

Further Good News: Deepening Biological Insight



	TP53	PIK3CA	GATA3	CDH1	KMT2C	MAP3K1	USH2A	PTEN	NCOR1	MAP2K4	RUNX1	ARID1A	NF1	TBX3	FOXA1	ERBB2	PIK3R1	AKT1	NOTCH2	RB1
All	33%	33%	12%	12%	9%	8%	6%	5%	5%	4%	4%	4%	4%	3%	3%	3%	3%	3%	2%	2%
Luminal A	11%	47%	15%	22%	12%	14%	4%	6%	6%	6%	5%	4%	4%	5%	5%	3%	3%	4%	2%	1%
Luminal B	36%	30%	20%	5%	10%	4%	6%	6%	5%	5%	4%	6%	3%	4%	1%	1%	2%	2%	2%	4%
HER2-E	71%	33%	4%	4%	10%	4%	8%	12%	3%	1%	4%	6%	4%	0%	3%	0%	6%	1%	5%	3%
Basal-like	89%	7%	0%	1%	6%	3%	10%	9%	4%	0%	1%	2%	5%	1%	1%	1%	4%	0%	4%	5%

Source: Emma Nolan, Geoffrey Lindeman and Jane Visvander (2023).

The signalling pathways involved in cancer are far better understood today than they were 25 years ago. Decades of research and associated support has associated specific subtypes of breast cancer with certain membrane receptors and intracellular pathways and their associated transcriptional activity inside the nucleus.

In general, we understand today why certain therapies stop working (treatment resistance) and which pathways for that tumor type might be targeted next.

Summary of major signaling pathways in breast cancer, highlighting pathway crosstalk and the intersection of common genetic alterations on key signaling nodes. The average mutation rate for 20 significantly mutated genes in each tumor subtype is indicated. Data are taken from analysis of the PanCancer dataset (n = 1,066 tumors) using cBioPortal. E2, estradiol; P (yellow), progesterone; P (pink), phosphorylation; ER, estrogen receptor; PR, progesterone receptor; ERE, estrogen response element; PRE, progesterone response element; ECAD, E-cadherin; FGFR, fibroblast growth factor receptor; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; IGF-1R, insulin-like growth factor type 1 receptor; NICD, Notch intracellular domain.

The Bad News: Plenty of Room to Improve

For all of the remarkable progress that has been made in breast cancer research there is plenty of room to improve.

Mortality has fallen by roughly 40% since the 1990s, yet over 40,000 women still die from the disease each year in the U.S. alone.

The global burden is large and growing. In 2022 there were ~2.3 million new breast cancer cases worldwide and ~670,000 deaths, making breast cancer one of the most commonly diagnosed cancers on the planet.

As note at right, sadly, breast remains the cancer most likely to kill a woman.

Demographic aging, urbanization and lifestyle risk factors (obesity, alcohol, physical inactivity) are pushing incidence upward in many regions.

And the burden of the disease often hits those who are least able to pay for its treatment.

WHO's Global Breast Cancer Initiative highlights that earlier diagnosis and access to timely treatment remain the biggest levers to reduce deaths.

While Mortality is Falling, Incidence is Rising

In the United States, incidence has been inching upward—about 1% per year from 2012–2021, with a somewhat faster rise in women under 50—while mortality has continued a long decline thanks to earlier detection and improved therapies.

Current SEER summaries show an age-adjusted incidence around 131 per 100,000 women and a death rate near 19 per 100,000, reflecting progress but also the large absolute number of affected people.

Globally, incidence has also trended upward over the last decade, with especially rapid growth in countries undergoing epidemiologic transition.

In addition, the number of young people with breast cancer is rising fast. Factors like obesity drive the disease and mammograms are not used in this population.

The sheer number of people living with a history of breast cancer is rising, not falling—both because more people are being diagnosed and because survival keeps improving.

Today, there are over 4 million breast cancer survivors in the U.S. – which all need to be monitored for recurrence.

The number of breast cancer survivors in the U.S. is projected to exceed 5.3 million by 2035

The Big Unmet Needs

The biggest areas for improvement are:

(1) stopping metastatic relapse (dormancy/immune escape/brain mets)

(2) cracking endocrine and ADC resistance with better biology and real-time monitoring

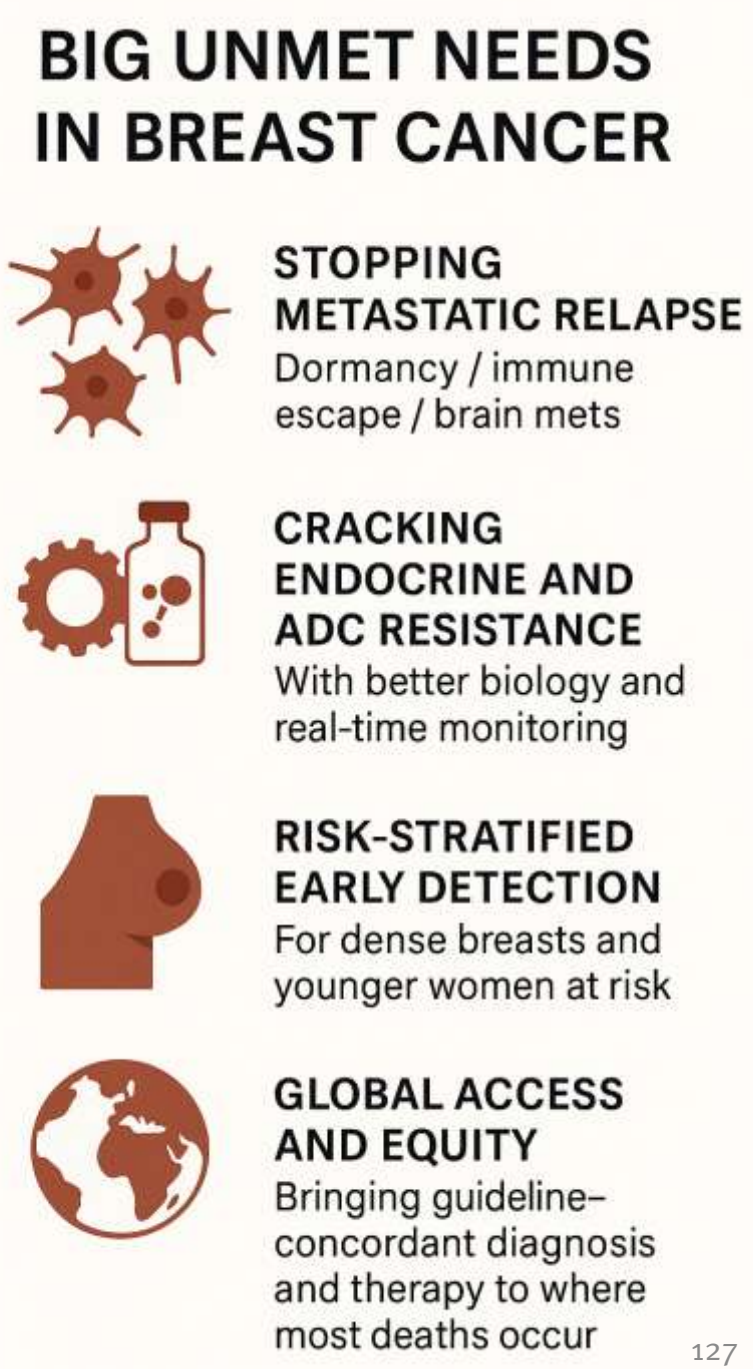
(3) risk-stratified early detection for dense breasts and younger women at risk and

(4) global access and equity—bringing guideline-concordant diagnosis and therapy to where most deaths occur.

A huge issue is that too many women are still dying with common types of cancer such as ER+ / HER2- due to resistance mutations associated with SERMs and CDK4/6 inhibitors.

There is a major need to upgrade therapeutics to be able to overcome the various types of resistance mutations seen all too often today.

Progress will hinge on integrating multi-omics and liquid biopsy into trials, designing adaptive studies that learn faster and scaling WHO-aligned systems for earlier diagnosis and timely treatment across all settings.



Early Detection, Prevention and Screening Could be Better

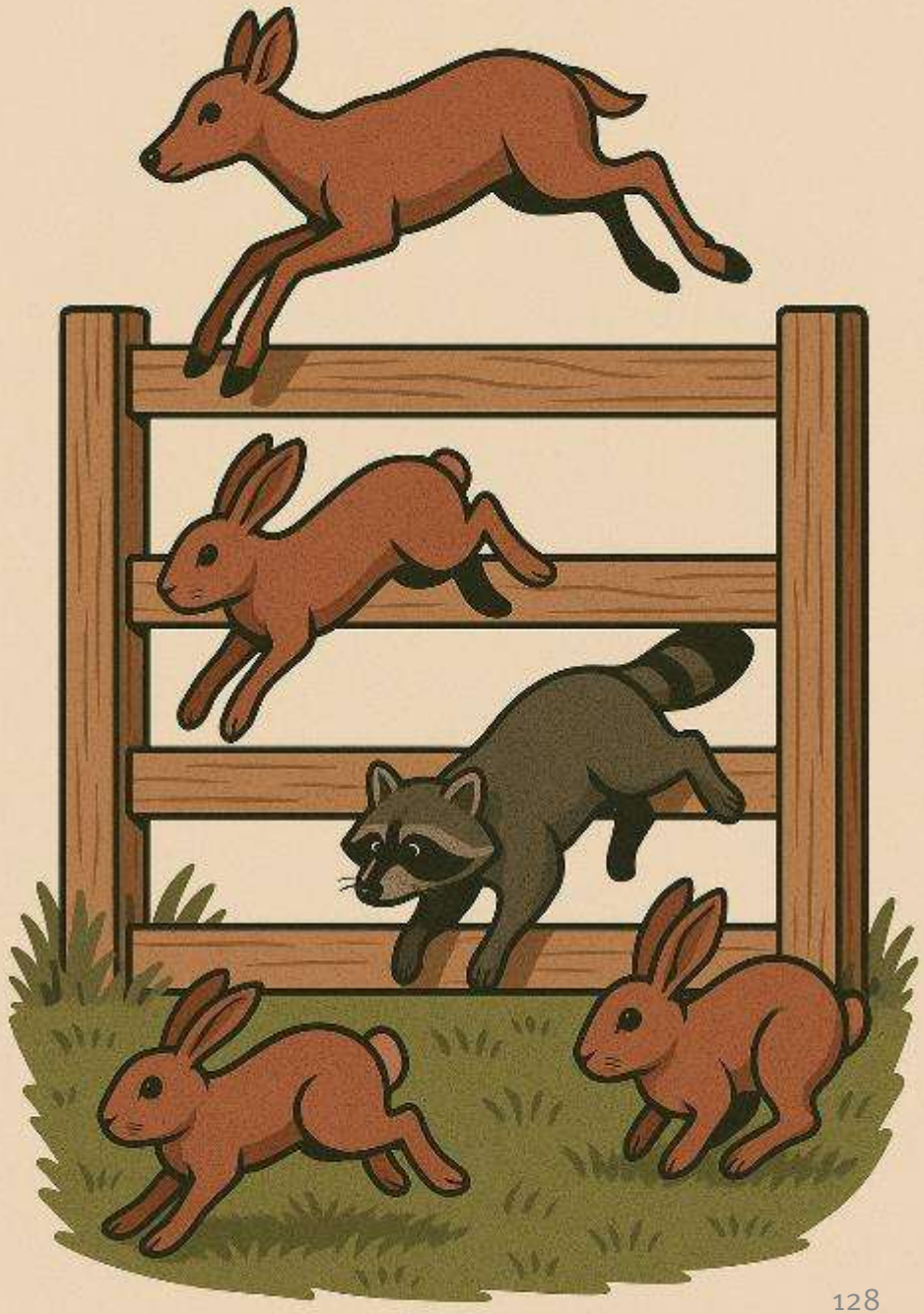
Survivorship and prevention research lag behind therapeutic advances. It seems unfathomable to us that incidence of breast cancer is *going up* despite all the progress.

We do not wish to sound too dire. After all, increases in mammography use should cause more cases of breast cancer to be found.

Yet, underlying pathological fires in our society continue ablaze. The biological links between obesity and inflammation are increasingly recognized but not well targeted.

Early detection also needs innovation—current mammography technology misses many aggressive cancers in dense breast tissue and we still lack validated biomarkers for recurrence risk beyond genetic predisposition. There are no widely used blood-based screening tests either. While available, circulating tumor cell and cell-free DNA technologies are not routinely used to monitor recurrence risk.

The future of breast cancer research depends on integrating multi-omic biology, digital data and global equity to move from reactive treatment toward genuine prevention and durable cure.



Is Precision Medicine Missing the Mark?

So many deaths today arise from metastatic recurrence—often years after initial remission—reflecting our incomplete understanding of tumor dormancy, microenvironmental escape and immune evasion.

Precision medicine has helped segment patients by receptor status (ER, PR, HER2, BRCA, etc.), but tumoral heterogeneity remains a formidable barrier.

Liquid biopsies, spatial genomics and single-cell sequencing promise to deepen insight into evolution and resistance, yet these technologies have not fully translated into real-time therapeutic adaptation.

Among the largest unmet needs are therapies for triple-negative breast cancer (TNBC), metastatic disease and endocrine-resistant ER-positive tumors.

In ER-positive cancers, resistance to endocrine therapy and CDK4/6 inhibitors drives most deaths; unraveling the epigenetic and metabolic underpinnings of this resistance is crucial.

TNBC lacks good targets, leaving chemotherapy and emerging antibody-drug conjugates (like Trodelvy®) as primary tools. A major issue is that traditional drugs that block growth factors may not be enough. The issues in TNBC may run much deeper.

Experts Agree: Modern Precision Therapies Facing Resistance Challenges

Emma Nolan, Geoffrey Lindeman and Jane Visvander (2023):

"The emergence of drug resistance continues to pose a major barrier to the efficacy of therapies. Branching evolution is a major source of clonal diversification in breast cancer, with subclonal populations playing a prominent role in treatment failure and disease recurrence. As the majority of resistant clones may be pre-existing, it will be crucial to develop better strategies to detect and target these cells before they undergo multi-step adaptation."

Sameer Khan, MD Anderson, Article (2024)

"Cancer treatment faces many hurdles and resistance is one among them. Anti-cancer treatment strategies are evolving due to innate and acquired resistance capacity, governed by genetic, epigenetic, proteomic, metabolic, or microenvironmental cues that ultimately enable selected cancer cells to survive and progress under unfavorable conditions."

William Gradishar, a medical oncologist at the Robert H. Lurie Comprehensive Cancer Center in Chicago, quoted in *Cancer Today*, Mar 13, 2025:

"Eradicating metastatic breast cancer completely is not an option. But several new therapies, including hormone treatments and drugs that target specific molecular features that drive cancer growth, have made it possible to keep the disease in check for longer periods of time. The inevitability of disease progression remains a difficult reality for people with metastatic breast cancer, Gradishar acknowledges, but he remains optimistic that the number of treatment options for advanced-stage breast cancer will continue to grow. 'Even if we can't cure the disease, the promise is we'll be able to switch from one treatment approach to another and have a series of therapies that may be helpful to extend life and hopefully maintain quality of life,' he says."

Experts Agree: Metastatic TNBC is a Particularly Tough Area in Which to Move Forward

Emma Nolan, Geoffrey Lindeman and Jane Visvander (2023):

"Given the massively parallel sequencing of 1,000s of breast tumors to date, it seems probable that most driver genes have been elucidated. In TNBC, there appears to be a notable lack of recurrently mutated and targetable pathways. For such cancers where **chromosomal instability** is a driving force, targeting mechanisms that underlie genomic instability may be necessary."

Sarat Chandarlapaty, MSK, BCRF interview, 2020):

"For cancers that have spread, that are stage IV or metastatic, most of them, I would say, on the order of 80 to 90 percent will eventually figure out and become resistant to the therapy we give. The timing of that is quite variable and remarkably so. So for one patient, on a very common regimen of a hormone and a targeted therapy combined, one person, their cancer might respond and then develop resistance in six months and another person treated with the same regimen with the same characteristics might respond and then develop resistance six years later."

Professor Neta Erez, Tel Aviv University, Israel, Worldwide Cancer Research, 2025:

Since advanced metastatic cancers are incurable, understanding the biology of tumor metastasis is the most significant challenge in cancer research today.
Metastasis is a complex multistep process. The early stages of metastasis, between the resection of primary tumor and diagnosis of clinically evident metastasis are currently a "black box" in patients, limiting our ability to predict or prevent metastatic relapse.
Reaching a comprehensive understanding of the mechanisms underlying the early stages of the metastatic process is the most significant and urgent quest in cancer research today.

Where From Here?

Key aspects of the current agenda of the breast cancer community is laid out in the next section – which reviews ongoing efforts to address unmet needs in breast cancer.

Relapse is particularly common among women with HR+/HER2- breast cancer (more than half of relapses in this category). At some point SERMS and CDK4/6's may stop working. it's not uncommon to discover a new metastatic tumor appear five to seven years after initial treatment.

In such cases, researchers are now working on improved CDK inhibitors, particularly the CDK2 class. We are also seeing very good work underway on improved PI3Ka mutation drugs, particularly following Eli Lilly's recent acquisition of Scorpion and ongoing work at Relay Therapeutics. We are also tracking other approaches including SERDs and the KAT6's.

HER2 failures also happen but are less common. The new classes of HER2 ADCs and bispecifics are looking quite good, particularly for HER2 low expressors.

Triple negative breast cancer is increasingly under attack by researchers and the recent successes with TROP2 ADC's at ESMO are quite impressive.

A big need is to improve upon mammography. Access is still clearly an issue and breast cancers crop up all the time in women who get mammograms. The technology is fallible. Issues are dense breasts, fast-moving cancers, reader variability and cancers that happen before age 40. Potential solutions in the works include AI-aided screening, blood-based screening, breast MRI and contrast-enhanced mammograph (for dense breasts).

One senses that AI will be important in breast cancer care in ways that go well beyond mammography. One early reader of this report wrote that AI could positively impact the clinical management of the disease.

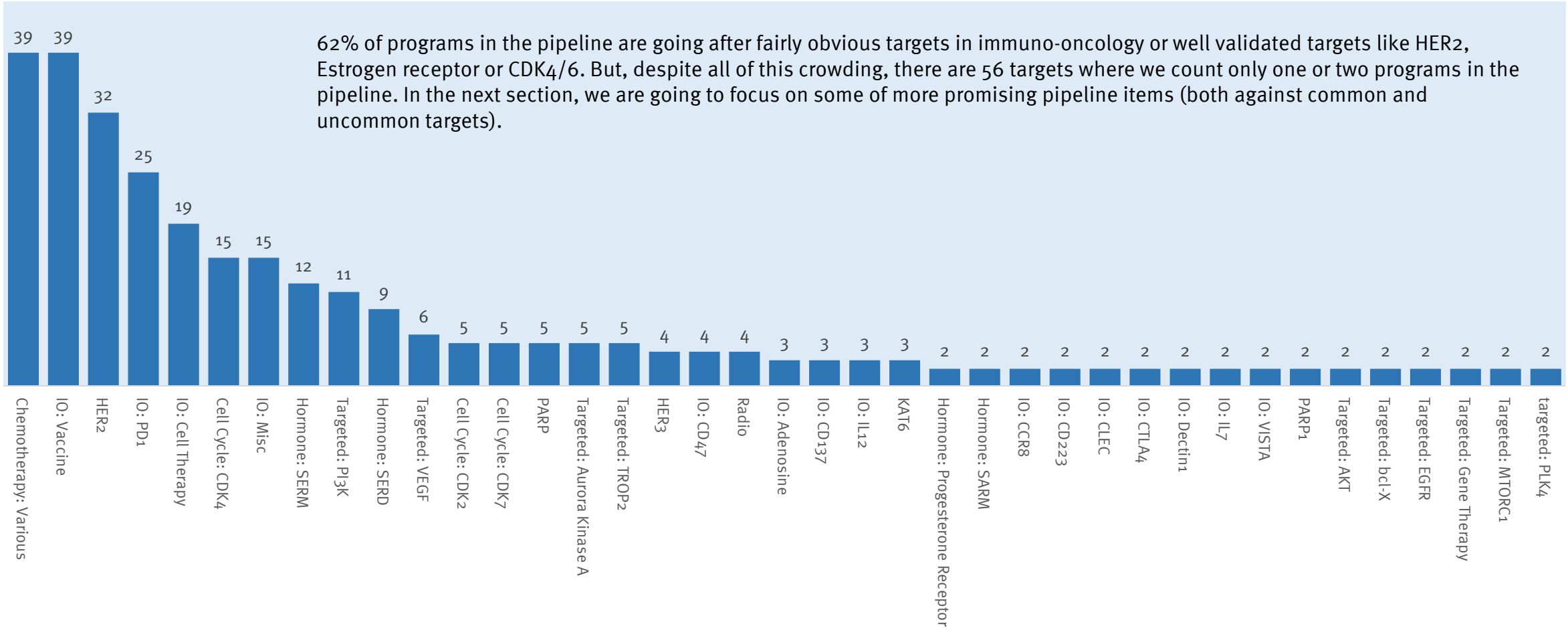
Perhaps the most interesting thing to contemplate is the unexpected. Rumsfeld's famous "unknown, unknowns". The history of the last 150 years is full of unexpected findings that have led to much better therapies. Today, we can only imaging what these might look like.

To quote Winston Churchill again (this time from a 1943 speech at Harvard):

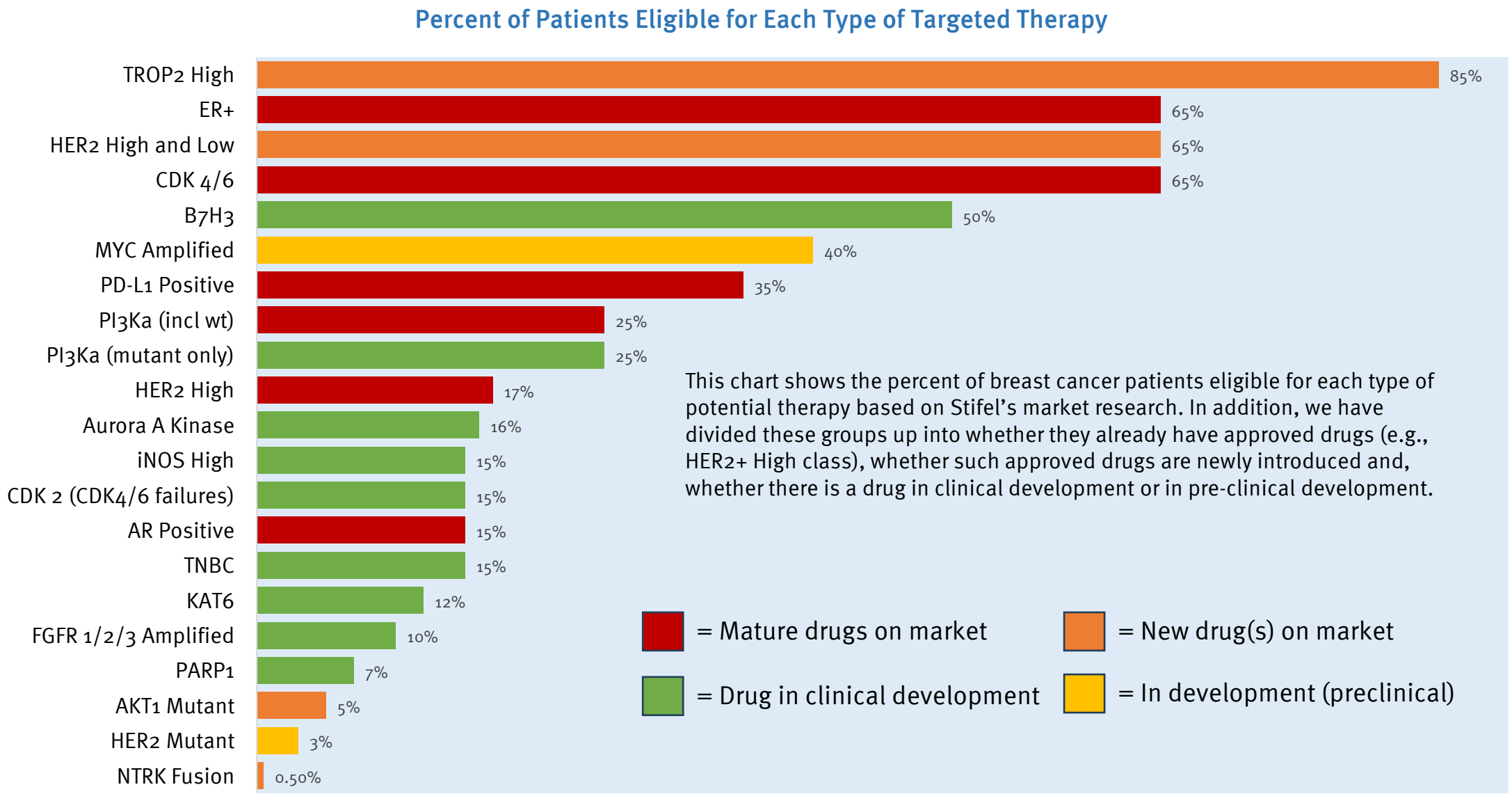
"The empires of the future are the empires of the mind."

Breast Cancer Drug Pipeline, by Target

Breast Cancer Pipeline, October 2025, DealForma Database (N=348)



Market Sizing of Target Space

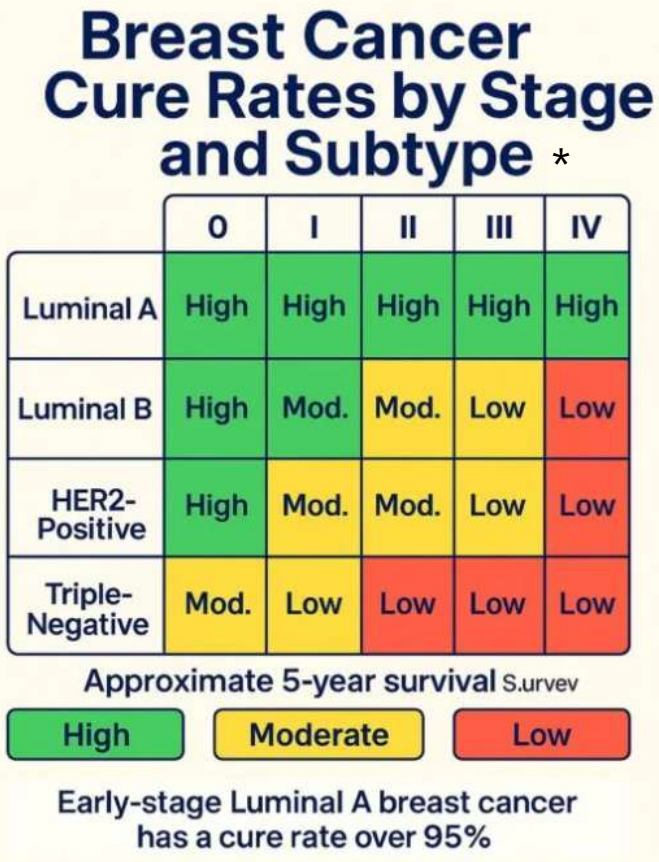


Source: Stifel Investment Banking

Section 6:

Promising Prospects

Thirteen organizations pursing projects that have the potential to transform breast cancer care in the next decade



* Luminal A breast cancers are characterized by higher levels of the estrogen receptor (ER) and lower levels of the Ki-67 gene, an established indicator of how quickly cells grow and divide to make new cells. They tend to be progesterone receptor (PR)–positive and HER2-negative and are more likely to be lower grade, meaning that the tumor cells look more like normal breast cells. Luminal A tumors differ from luminal B tumors, which are also ER-positive but often have higher levels of Ki-67 and lower levels of PR, and may be HER2-positive. Luminal B breast cancers tend to grow faster and have a worse prognosis than luminal A.

#1: AstraZeneca

AstraZeneca's breast-cancer strategy is built around three interlocking bets: expanding the impact of antibody–drug conjugates (ADCs), pushing next-generation endocrine therapies to outmaneuver resistance and layering precision cell-cycle/DNA-repair agents to prolong control in HR-positive disease. The company's ADC franchise—anchored by ENHERTU (trastuzumab deruxtecan) and Dato-DXd (datopotamab deruxtecan)—targets the full spectrum from HER2-overexpressing to HER2-low/ultralow and TROP2-positive tumors, with an emphasis on moving active agents earlier and pairing them rationally with endocrine backbones. In parallel, AstraZeneca is investing in oral SERDs such as camizestrant to directly address ER signaling and ESR1-mutant disease, aiming to re-establish endocrine sensitivity where standard therapies falter.

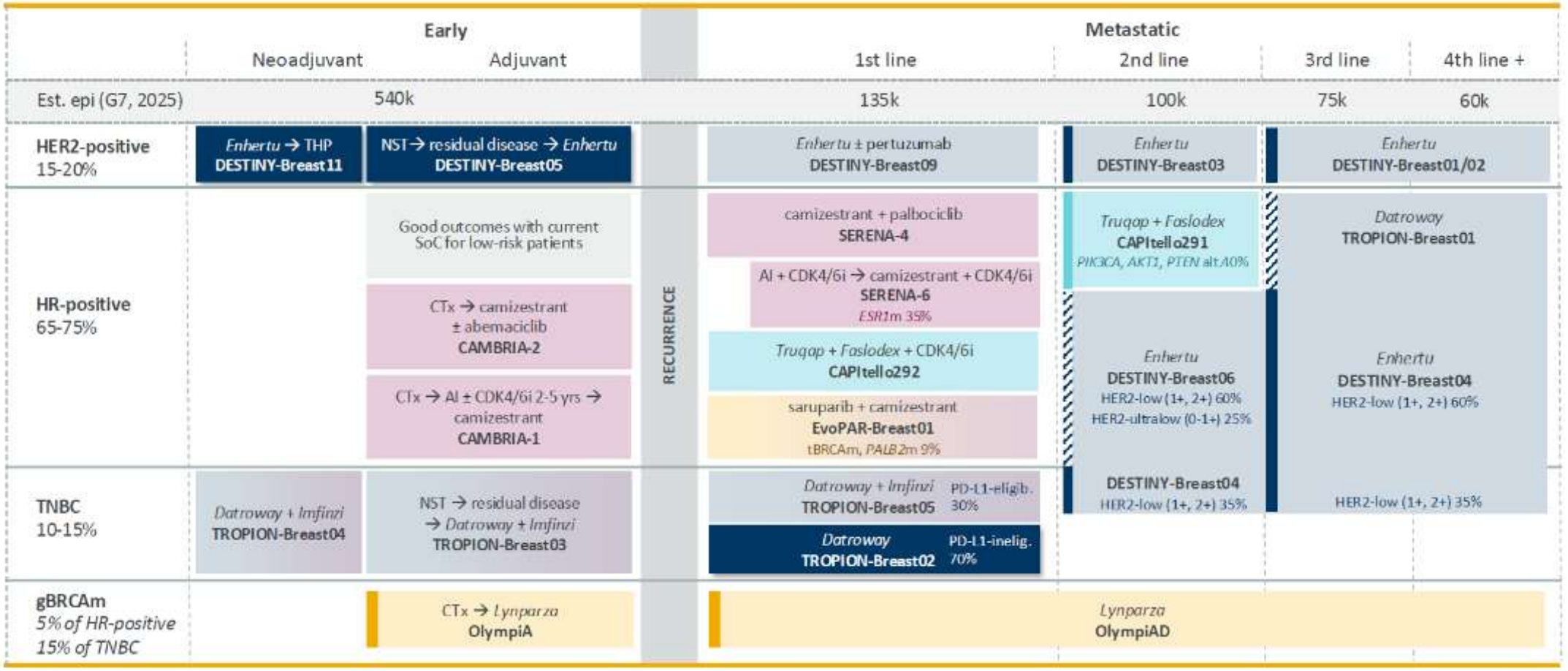
ENHERTU is the tip of the spear for the ADC strategy. Its strong activity across HER2-positive and HER2-low settings reframed segmentation beyond classic IHC categories and AstraZeneca is leveraging that momentum to test broader lines of therapy and combinatorial regimens. Dato-DXd ("Datroway") extends the ADC play to TROP2, a highly expressed target in HR-positive/HER2-negative breast cancer.

Together, these two DXd-based platforms give AstraZeneca levers across histologies and biomarker tiers, with room to optimize dose, sequence and partner drugs (for example, pairing ADCs with endocrine therapy or targeted agents to delay resistance and improve durability).

On the endocrine front, camizestrant represents a next-generation SERD designed to degrade ER more completely and to retain potency against ESR1 mutations that commonly drive resistance after AI or SERD exposure. The development plan emphasizes use with standard backbones (CDK4/6 inhibitors) and with targeted agents that attack parallel survival pathways (such as AKT inhibition), with the goal of extending progression-free intervals and delaying the need for chemotherapy. The broader theme is to keep tumors in an endocrine-sensitive state for longer, then hand off to ADCs when disease biology shifts—rather than bouncing prematurely to cytotoxics.

Looking earlier in the pipeline, AstraZeneca is placing intriguing bets on novel targets and smarter precision combinations. A selective PARP1 inhibitor (e.g., AZD5305) aims to deliver the DNA-damage benefits of PARP blockade with a cleaner safety/efficacy profile, opening combination windows with endocrine agents or CDK inhibitors in biomarker-defined subsets. Additional exploration includes next-wave ADC engineering (payloads, linkers and target choices that may capture HER2-ultralow or heterogeneous TROP2 expression) and combinations that knit together ER degradation, PI3K/AKT/mTOR signaling control and DNA-repair stress. The through-line is clear: use potent ADCs to widen eligibility and deepen responses, use modern endocrine therapy to control ER-driven biology and ESR1 mutations and layer precision agents to delay resistance—turning breast cancer into a longer-managed, modularly treated disease.

AZ Has an Exceptional and Deep Breast Cancer Drug Pipeline

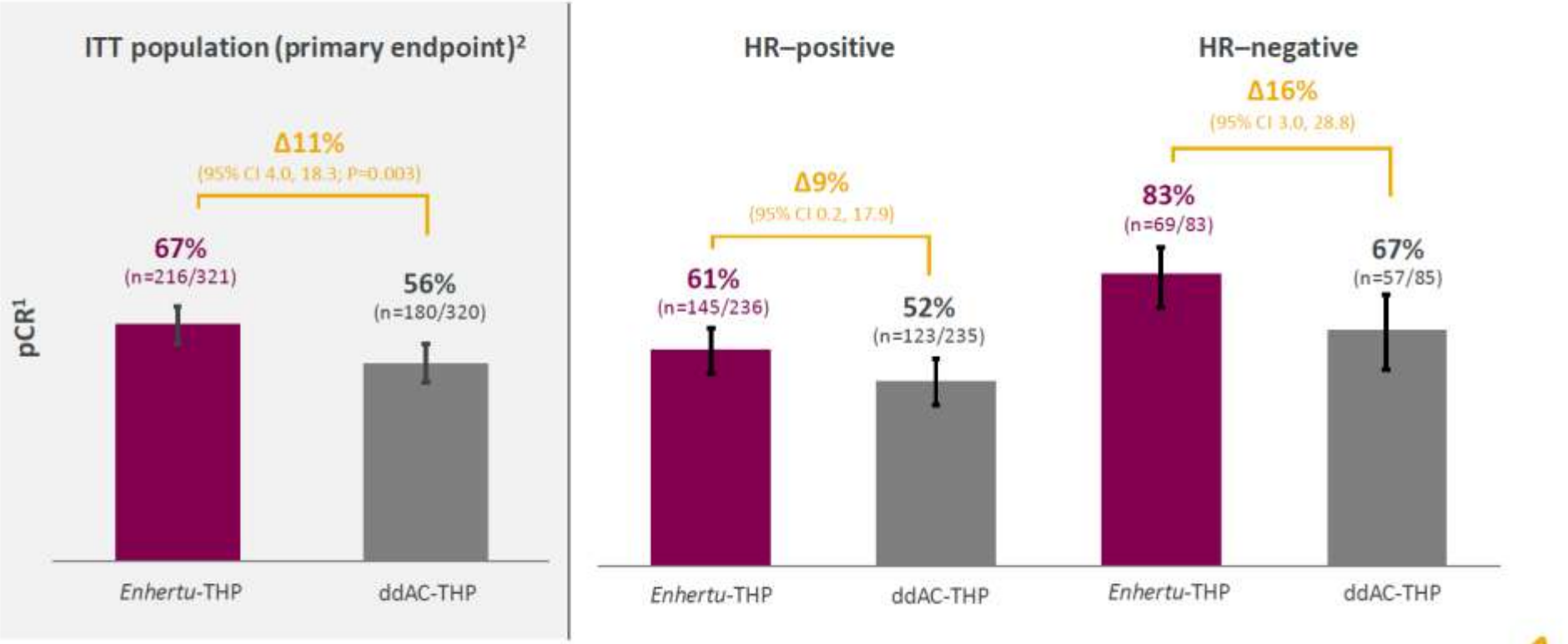


All numbers are approximate. Illustrative settings and populations, not to scale. Breast Cancer map reflects Phase III/pivotal trials.
Collaboration partners: Daiichi Sankyo (*Enhertu, Datroway*), Merck & Co., Inc. (*Lynparza*).

Source: AZ ESMO Presentation, October 2025

AZ (with Daiichi): Exceptional CR Rate with ENHERTU in Early Stage HER2+ Breast Cancer Study

DESTINY-Breast11: Highest reported pCR rate in registrational neoadjuvant HER2+ eBC trial



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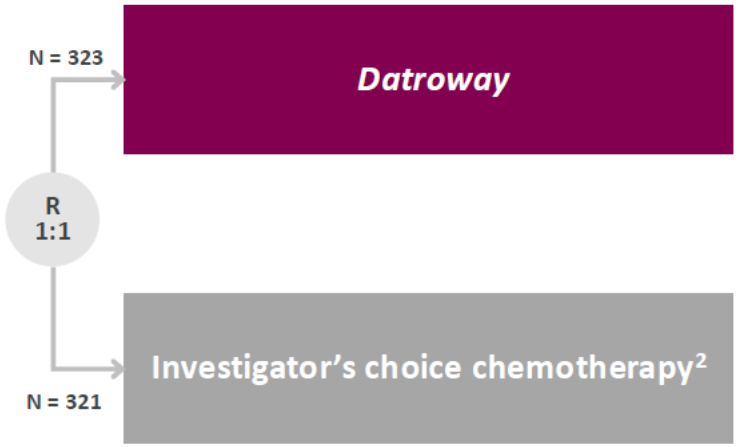
1. By blinded central review.2. pCR responders were defined as patients who only received randomised study treatment (at least one dose) and had pCR.
Harbeck N et al. Abstract 2910 presented at the European Society of Medical Oncology 2025. Collaboration partner: Daiichi Sankyo (*Enhertu*). Appendix Glossary

Source: AZ ESMO Presentation, October 2025

AZ (with Daiichi): TROP2 ADC for Front Line TNBC

TROPION-Breast02: Establishing *Datroway* in 1L TNBC with positive overall survival data

- Locally recurrent inoperable or metastatic TNBC
- No prior chemotherapy or targeted systemic therapy in the locally recurrent inoperable or metastatic setting
- Immunotherapy not an option[1]
- ECOG PS 0 or 1
- No minimum DFI



Dual primary endpoints:
PFS (BICR), OS

Secondary endpoints included:
- ORR, DoR
- PFS (inv)
- Safety

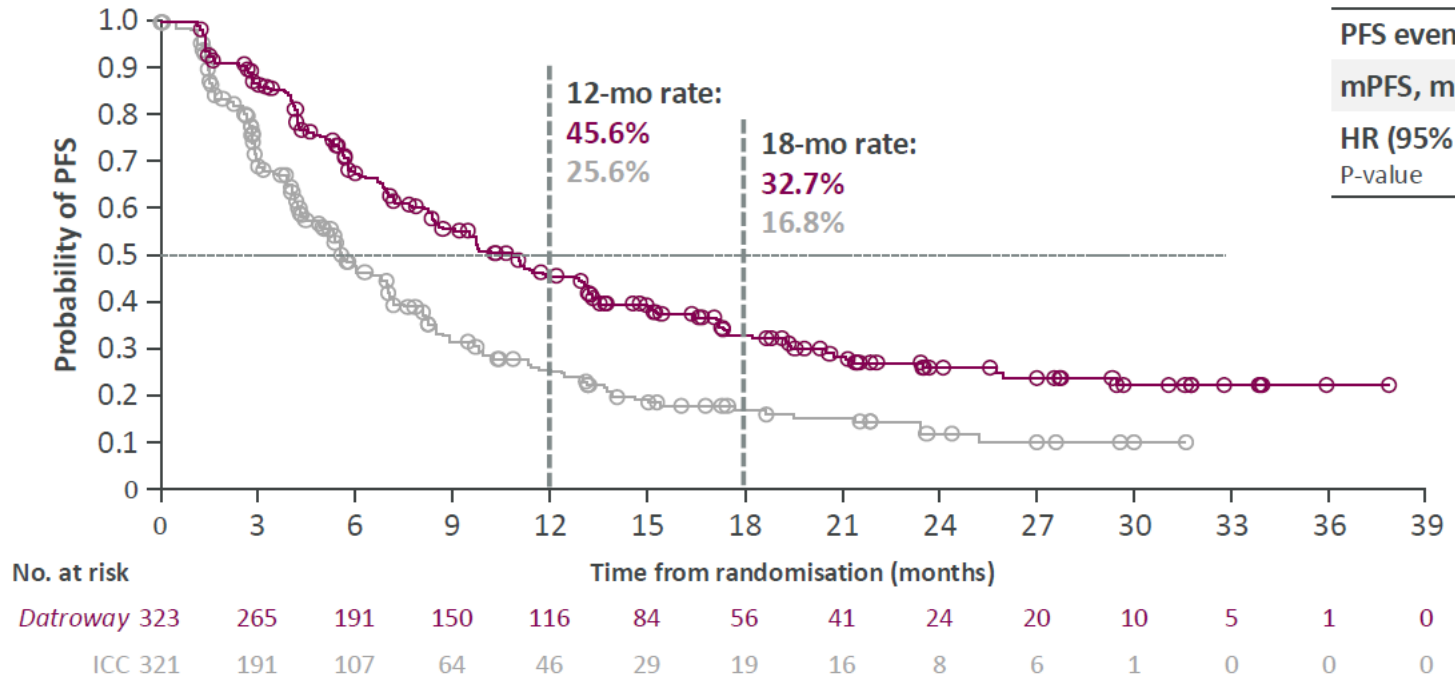
Stratification factors
- Geographic region (US/Canada/Europe vs other geographic regions)
- DFI history (*de novo* vs prior DFI 0-12 months vs prior DFI >12 months)
- PD-L1 status (high [CPS ≥10] vs low [CPS <10])

1. Including patients with PD-L1 low tumours, or patients with PD-L1 high tumours with (a) disease relapse after prior PD-(L)1 inhibitor therapy for early-stage breast cancer, (b) comorbidities precluding PD-(L)1 inhibitor therapy, or (c) no regulatory access to PD-(L)1 inhibitor therapy. 2. If no prior taxane, or prior taxane in the (neo)adjuvant setting and DFI >12 months: paclitaxel 80 mg/m² IV, D1, 8, 15, Q3W, or nab-paclitaxel 100mg/m² IV, D1, 8, 15, Q4W; if prior taxane and DFI 0–12 months: capecitabine 1000 or 1250 mg/m² orally twice daily, D1–14, Q3W (dose determined by standard institutional practice), or eribulin mesylate 1.4 mg/m² / eribulin 1.23 mg/m² IV, Day 1, 8, Q3W, or carboplatin AUC6 IV, D1, Q3W. Dent R et al. Abstract LBA21 presented at the European Society of Medical Oncology 2025. Collaboration partners: Daiichi Sankyo (*Datroway*). Appendix: Glossary.

Source: AZ ESMO Presentation, October 2025

TROP2 ADC Showing Good Results in 1L TNBC

TROPION-Breast02: *Datroway* reduced the risk of progression or death by 43% vs chemotherapy



	Datroway	ICC
PFS events, n (%)	199 (62)	209 (65)
mPFS, mo	10.8	5.6
HR (95% CI)	0.57 (0.47–0.69)	
P-value	<0.0001	

PFS by investigator assessment was consistent with PFS by BICR

Source: AZ ESMO Presentation, October 2025

#2: Avenzo Therapeutics

Avenzo Therapeutics is building a cell-cycle–centric $HR^+/HER2^-$ strategy around two selective small molecules—AVZO-021 (CDK2) and AVZO-023 (CDK4)—with the explicit aim to (1) overcome CDK4/6-inhibitor resistance driven by cyclin E–CDK2 activation and (2) maximize target coverage while sparing CDK6-linked myelosuppression.

The company's plans concentrate on $ER^+/HER2^-$ metastatic breast cancer and CCNE1-amplified tumors, i.e., the two settings where CDK2 dependence is strongest.

What's distinctive is Avenzo's combination architecture: it is positioning its CDK2 + CDK4 doublet as a potential next-gen backbone in HR^+ disease (front-line and adjuvant over time).

Avenzo is also advancing a HER3 x EGFR ADC and a NECTIN-4/TROP2 bispecific ADC, with potential plan to pair rational cell-cycle inhibitors and ADCs in breast cancer at a later time.

There is quite substantial upside from both of these potentially best-in-class ADC's in various types of cancer.

Spotlight on AVZO-021 (CDK2)

AVZO-021 (in-licensed, clinical) is a selective CDK2 inhibitor being developed for $HR^+/HER2^-$ breast cancer and CCNE1-amplified tumors. The idea here is carry out rational combination trials of AVZO-021 with AVZO-023 (CDK4) to attack both CDK2-driven resistance in breast cancer and maintain robust G1 blockade without CDK6 liability—an approach few competitors can match internally.

Strong Leadership Team

Avenzo's CEO, Dr. Athena Countouriotis is a proven oncology company builder, best known for leading Turning Point Therapeutics from through IPO and its $4 billion acquisition. At Avenzo, she applies the same "fast-to-clinic" model. Her leadership style is entrepreneurial, decisive and capital-efficient.

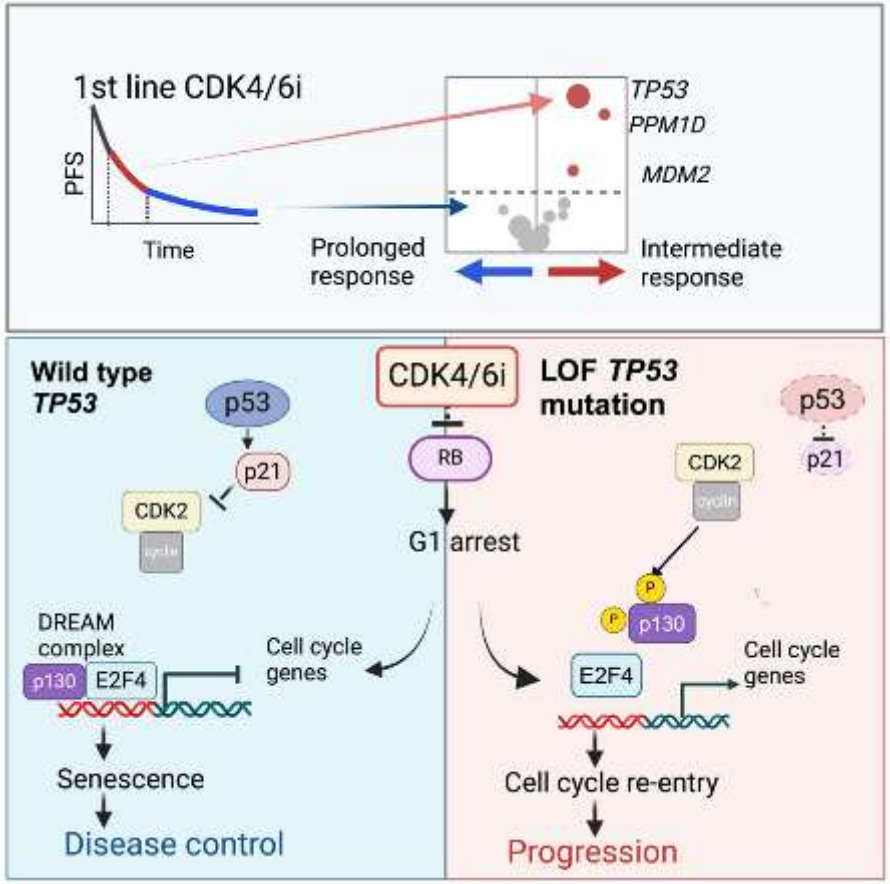
Avenzo's CMO, Dr. Mohammed Hirmand, is an experienced oncology drug developer with CMO tenures at Turning Point, Peloton and Medivation, where he guided key programs like enzalutamide through late-stage development. At Avenzo, he emphasizes data-driven, biomarker-focused clinical execution.

Why CDK2 Inhibitors Can Solve the CDK Drug Resistance Problem

To understand why resistance emerges to CDK drugs, a research team led by physician-scientist Sarat Chandarlapaty, MD, PhD, analyzed samples from thousands of breast cancer patients receiving the combined therapy. They found that tumors with a short-lived response to treatment had a mutation in the p53 gene. The researchers discovered that CDK2 plays a key role in allowing the p53-mutated tumors to begin growing again. Further, they found that blocking CDK2 and CDK4/6 together could put these p53-mutated tumors into a deep, arrested state.

Sarat Chandarlapaty et al., "Long-term breast cancer response to CDK4/6 inhibition defined by TP53-mediated geroconversion," *Cancer Cell*. 2024 Nov 11;42(11):1919-1935.e9.

Inhibition of CDK4/6 kinases has led to improved outcomes in breast cancer. Nevertheless, only a minority of patients experience long-term disease control. Using a large, clinically annotated cohort of patients with metastatic hormone receptor-positive (HR+) breast cancer, we identify TP53 loss (27.6%) and MDM2 amplification (6.4%) to be associated with lack of long-term disease control. Human breast cancer models reveal that p53 loss does not alter CDK4/6 activity or G1 blockade but instead promotes drug-insensitive p130 phosphorylation by CDK2. The persistence of phospho-p130 prevents DREAM complex assembly, enabling cell-cycle re-entry and tumor progression. Inhibitors of CDK2 can overcome p53 loss, leading to geroconversion and manifestation of senescence phenotypes. Complete inhibition of both CDK4/6 and CDK2 kinases appears to be necessary to facilitate long-term response across genomically diverse HR+ breast cancers.



CDK2 Inhibitor Competitive Landscape

The strategies being pursued by Avenzo Therapeutics and Nikang Therapeutics strike us as particularly promising.

Company	Asset	Stage / BC Setting	Development Strategy	Selectivity / Binding	Notes
Avenzo Therapeutics	AVZO-021	Phase 1/2; $HR^+/HER2^-$ and CCNE1-amp cohorts	Built for CDK4/6-resistant ER^+ disease; early ADC combination (with TROP2-ADC); paired with in-house CDK4 partner (AVZO-023)	Highly selective CDK2 built by Allorion	Differentiates via ADC pairing + same-sponsor CDK2+CDK4 'doublet' plan
BeOne Medicines	BG-68501	Phase 1a/b; $HR^+/HER2^-$ and solid tumors	Post-CDK4/6 resistance; Cyclin-E–high subsets; mono + endocrine combos	Strong CDK2 preference	Exploring CDK2 degraders as next-wave backups
Incyclix Bio	INX-315	Phase 1/2; $ER^+/HER2^-$ and CCNE1-amp cohorts	Targets CDK4/6-resistant ER^+ and CCNE1-amp disease; mono + combo	Large selectivity margin vs CDK1	Benchmark for CDK2 selectivity profile
Incyte	INCB123667	Phase 1/2; $HR^+/HER2^-$ and CCNE1-amp expansion	Biomarker-forward; potential path in CCNE1-amp; breast cohorts included	Highly selective CDK2	Combo expansions anticipated
Novartis	ECI830	Phase 1/2; $HR^+/HER2^-$ and CCNE1-amp	From-day-one combinations (with CDK4/6 + endocrine) to address CDK2-driven resistance	Selectivity data not disclosed	Integrates with ribociclib/endocrine ecosystems
Pfizer	Tegtociclib	Phase 1b/2; $HR^+/HER2^-$	Post-CDK4/6 setting; mono + endocrine/targeted combos	CDK2-selective; multi-log preference vs CDK1;	Big-pharma comparator for class safety/efficacy
Nikang Therapeutics	NKT3447 (CDK2 inhibitor); NKT5097 (CDK2/4 dual degrader)	Early clinical for inhibitor and degrader programs; solid-tumor/HR^+ cohorts	Degrader-led strategy for deep CDK2 suppression; focus on Cyclin-E–driven and HR^+ disease; pairing with endocrine/targeted agents	Slow-off kinetics and high CDK2 selectivity; degraders highly selective; impressive IC_{50}'s.	Unique mix of inhibitor + degrader + dual-degrader gives multiple shots on goal within CDK2 axis

Source: Stifel Investment Banking

#3: Eikon Therapeutics

Eikon Therapeutics is a next-generation biotechnology company that merges advanced engineering and cell biology to accelerate drug discovery. Its core technology—based on single-molecule tracking and live-cell imaging—allows scientists to observe how individual proteins behave in real time inside living cells. This approach enables Eikon to identify novel targets, optimize drug selectivity and understand mechanisms of resistance far earlier than traditional screening methods. The company's strategy focuses on oncology and DNA damage–repair pathways, where precise molecular control and resistance mapping can translate into substantial clinical advantage.

At the center of its clinical pipeline is **EIK1003**, a highly selective **PARP1 inhibitor** that has entered Phase 1 trials for solid tumors. Unlike first-generation pan-PARP inhibitors that block both PARP1 and PARP2, Eikon's compound was engineered to spare PARP2, thereby reducing bone marrow toxicity and enabling higher dosing or combination therapy. The company is also advancing a brain-penetrant PARP1 inhibitor, designed for cancers that metastasize to the brain—a setting where most existing PARP drugs have limited utility. Together, these assets position Eikon as a front-runner in the race to create the first clinically validated, truly selective PARP1 inhibitor in class.

Beyond PARP biology, Eikon's discovery pipeline spans several emerging cancer targets, including WRN helicase (for microsatellite instability–high tumors) androgen receptor antagonists and toll-like receptor agonists designed to enhance immune activation. The integration of imaging-based discovery tools with chemistry and AI analytics underpins this portfolio, giving the company a unique feedback loop between biophysics, pharmacology and clinical design.

Strong Leadership Team

Eikon is led by Roger Perlmutter, M.D., Ph.D., one of the most respected figures in modern drug development. Formerly head of R&D at Merck and Amgen, Perlmutter oversaw the creation and global rollout of blockbuster drugs such as pembrolizumab (Keytruda). His leadership style combines rigorous scientific vision with operational discipline, emphasizing the fusion of engineering, quantitative biology and translational science. Eikon's Chief Medical Officer, Roy Baynes, M.D., Ph.D., is a highly accomplished physician–scientist best known for leading global clinical development at Merck, where he oversaw the late-stage programs for Keytruda and multiple other oncology blockbusters.

Selective PARP1 Inhibitor Competitive Landscape

These all look promising. We like the idea of the brain-selective molecules at Eikon and Nerviano given the problem of brain metastases in advanced breast cancer. PARP1 skeptics note that AZ's Saruparid has already reported out some Phase 1 data and that it doesn't look that much better than what we have seen from PARP1/2's before.

Company	Asset	Selectivity notes	Stage	Key development focus / notes
Acerand Therapeutics	ACE-86225106	PARP1-selective	Ph 1/2 solid tumors	Early clinical data emphasize tolerability and combo potential
AstraZeneca	Saruparib (AZD5305)	PARP1-selective; limited PARP2 activity in preclinical models	Multiple Ph 1/2 and randomized Ph 3 (incl. $ER^+/HER2^-$ combos)	Broad HRD strategy; moving into pivotal settings.
Eikon Therapeutics	EIK1003 (IMP-1734) / EIK1004	PARP1-selective / EIK1004 is brain penetrant	Both in Ph 1/2 solid tumors (U.S. FIH 2024; global co-dev)	Mono and combo strategy; separate brain-penetrant follow-on program for brain mets.
Gilead	GS-0201 (program from XinThera acquisition)	Company states intent for PARP1-selective profile to enable cleaner combos	Early clinical/IND-stage program in solid tumors (incl. TNBC and $HR^+/HER2^-$ per external trackers)	Strategic aim: pair with Trodelvy® and other DNA-damaging agents; builds an in-house DDR partner for ADCs.
Nerviano Medical Sciences	NMS-293	PARP1-selective, non-trapping, brain-penetrant	Ph 1/2 mono and combo starts in 2025 (e.g., SCLC, BRCA-wt ovarian; temozolomide GBM)	Positioning around better marrow tolerability; CNS access; combination with DNA-damaging agents/ADCs.

Source: Stifel Investment Banking

#4. Eli Lilly

Eli Lilly's strategy in breast cancer therapeutics centers on building a comprehensive, precision-based portfolio that spans both established hormonal therapies and next-generation targeted agents. The company's foundation remains Verzenio (abemaciclib), a CDK4/6 inhibitor that has become a key treatment for hormone-receptor–positive, HER2-negative early and metastatic breast cancer. With strong survival data in high-risk adjuvant populations, Verzenio anchors Lilly's position in this segment. The company is now extending beyond CDK4/6 inhibition to tackle the mechanisms of resistance and mutation-driven progression that limit long-term efficacy, aiming to address emerging molecular targets such as ESR1 and PIK3CA.

A cornerstone of this next phase is Lilly's acquisition of Scorpion Therapeutics and its highly selective PI3Kα inhibitor, STX-478. This compound is designed to inhibit mutant PI3Kα while sparing the wild-type enzyme, potentially overcoming the tolerability and metabolic challenges that hindered earlier drugs in this class. The acquisition reflects Lilly's commitment to precision oncology and its intention to integrate STX-478 into combination regimens with endocrine and CDK4/6 therapies, especially for patients with PIK3CA-mutant HR-positive disease—a large and well-defined subset of breast cancer.

Strategically, Lilly is using the strength of its broader pharmaceutical portfolio to reinvest in oncology innovation, targeting high-value, mutation-driven niches that complement its hormonal backbone. The company envisions combining selective PI3Kα inhibition with existing therapies to achieve deeper, more durable tumor control, while expanding into earlier-stage and adjuvant treatment settings.

A recent article in *ApexOnco* by Madeleine Armstrong contrasted Lilly's approach with its PI3ka drug to that of Relay Therapeutics. She wrote: "While Relay's phase 3 trial, unveiled several months ago, is evaluating RLY-2608 in second-line breast cancer, Lilly has gone straight for the front line with its Scorpion-originated asset, tersolisib, a new clinicaltrials.gov listing has revealed. Meanwhile, Relay seems to be taking a more measured approach. That group's phase 3 trial, ReDiscover-2, will enrol post-CDK4/6 inhibitor patients and test RLY-2608 plus Faslodex, versus AstraZeneca's AKT inhibitor Truqap plus Faslodex."

Overall, Lilly's breast-cancer approach is shifting from a single-agent, class-focused strategy toward a multi-layered model that blends hormonal control, cell-cycle regulation and precision targeting. The Scorpion acquisition symbolizes this evolution—a move toward highly selective, tolerable and combinable agents that can transform outcomes for patients with genomically defined breast cancers.

Mutant Selective PI3Kα Inhibitors Competitive Landscape

Industry participants inform us that the Eli Lilly / Scorpion drug is exquisitely selective for PI3kα mutants – which is what is required to avoid the side effects seen with today's drugs from Novartis and Roche. Relay's drug is also very good. Others, like Haihe, Junshi, Onkure and Totus claim that they also have highly selective drugs. Others speak very favorably of BridgeBio Oncology's approach inhibiting RAS-driven PI3Kα-AKT signaling in tumors.

Company	Lead Asset	Selectivity / Type	Modality	Clinical Stage	Mutation Coverage	Combination Partners	Key Notes
BridgeBio Oncology	BBO-10203	RAS:PI3Kα Breaker	Small molecule inhibitor	Phase 1	Broad coverage – inhibits PPI not isoforms	Various	Promising preclinical package. Clinical data upcoming
Eli Lilly	STX-478 (Scorpion)	Mutant-selective, WT-sparing	Small molecule inhibitor	Phase 1/2	Broad hotspot coverage (helical + kinase mutants)	Endocrine + CDK4/6 combo	Good tolerability profile / strong monotherapy response in Phase 1 study. Running a 1L Phase 3 study
Haihe Biopharma	CYH33	PI3Kα-selective	Small molecule inhibitor	Phase 1/2	PIK3CA-mutant cancers	Fulvestrant, chemo, PD-1	Manageable safety, partial responses seen so far
Junshi Biosciences	JS105	WT-sparing PI3Kα inhibitor	Small molecule inhibitor	Preclinical /IND	PIK3CA mutants	Planned combo with fulvestrant	Preclinical BC activity reported
Novartis	Alpelisib (Piqray)	PI3Kα-selective, not mutant-specific	ATP-competitive inhibitor	Approved	WT + mutant PI3Kα	Fulvestrant	Hyperglycemia, rash common / side effects limit the sales of this drug substantially
OnKure Therapeutics	OKI-219	H1047R-selective (~100× vs WT)	Small molecule inhibitor	IND/Phase 1	H1047R hotspot	Single-agent, future endocrine combo	Minimal WT inhibition toxicity
Relay Therapeutics	RLY-2608	Mutant-selective, WT-sparing	Allosteric small molecule	Phase ½	E542, E545, H1047 mutants	Fulvestrant	Improved safety, early efficacy signals. Running a Second Line pivotal study
Roche	Inavolisib (GDC-0077)	PI3Kα-selective, mutant-preferring, induces mutant degradation	Small molecule inhibitor / degrader	Approved	PIK3CA mutants	Fulvestrant + Palbociclib	Favorable tolerability vs alpelisib but still does not just hit PI3Ka mutants.
Totus Medicines	TOS-358	Covalent, mutant-selective	Covalent small molecule	Phase 1	PIK3CA mutants	Fulvestrant (planned)	Strong target engagement, mild toxicity

Source: Stifel Investment Banking

#5. Memorial Sloan Kettering

Memorial Sloan Kettering Cancer Center

Dr. Pedram Razavi, a medical oncologist and physician-scientist at Memorial Sloan Kettering Cancer Center (MSKCC), is working to uncover how breast cancers evolve resistance to targeted and hormonal therapies with a key collaborator Sarat Chandarlapaty. His research integrates liquid biopsy, circulating tumor DNA (ctDNA) analysis and multi-omics profiling to map the dynamic genetic landscape of metastatic tumors in real time. Razavi's group has shown that resistant clones—bearing mutations in pathways such as ESR1, PIK3CA, HER2 and RB1—can emerge under selective pressure from endocrine therapy or CDK4/6 inhibitors. By sequencing thousands of tumor and plasma samples longitudinally, his team demonstrated that resistance is rarely binary: instead of single mutations conferring failure, cancers often evolve polygenic and adaptive escape routes, such as transcriptional rewiring or bypass signaling.

Building on this foundation, Razavi's current work focuses on predicting resistance trajectories before clinical progression occurs. Using ultra-sensitive ctDNA assays, his lab is developing algorithms to detect emerging resistant subclones months before imaging can reveal them—offering a window for preemptive treatment adjustment. He collaborates widely on AI-driven models that integrate genomic, proteomic and imaging data to personalize therapy and forecast therapeutic failure. His goal is to make resistance a predictable and preventable event, not an inevitable one. Razavi's research has redefined how clinicians think about metastatic breast cancer—not as a static disease with fixed mutations, but as a dynamic, evolving system that demands continuous molecular monitoring and adaptive therapeutic strategies.

Source: https://www.mskcc.org/news/latest-research-into-overcoming-resistance-to-breast-cancer-targeted-therapies

Pedram Razavi, Memorial Sloan Kettering Cancer Center is trying to outsmart treatment resistance with real time genetic mapping of metastatic tumors to get at ahead of mutations before they fully set the course of a patient's tumor.

Illustrative MSK Work: APOBEC3 Mutations Associated with Failures of CDK Inhibitors and Hormonal Therapy

nature genetics

Article

https://doi.org/10.1038/s41588-025-02187-1

APOBEC3 mutagenesis drives therapy resistance in breast cancer

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Check for updates

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Acquired genetic alterations drive resistance to endocrine and targeted therapies in metastatic breast cancer; however, the underlying processes engendering these alterations are largely uncharacterized. To identify the underlying mutational processes, we utilized a clinically annotated cohort of 3,880 patient samples with tumor-normal sequencing. Mutational signatures associated with apolipoprotein B mRNA-editing enzyme catalytic polypeptide-like 3 (APOBEC3) enzymes were prevalent and enriched in post-treatment hormone receptor-positive cancers. These signatures correlated with shorter progression-free survival on antiestrogen plus CDK4/6 inhibitor therapy in hormone receptor-positive metastatic breast cancer. Whole-genome sequencing of breast cancer models and paired primary-metastatic samples demonstrated that active APOBEC3 mutagenesis promoted therapy resistance through characteristic alterations such as *RB1* loss. Evidence of APOBEC3 activity in pretreatment samples illustrated its pervasive role in breast cancer evolution. These studies reveal APOBEC3 mutagenesis to be a frequent mediator of therapy resistance in breast cancer and highlight its potential as a biomarker and target for overcoming resistance.

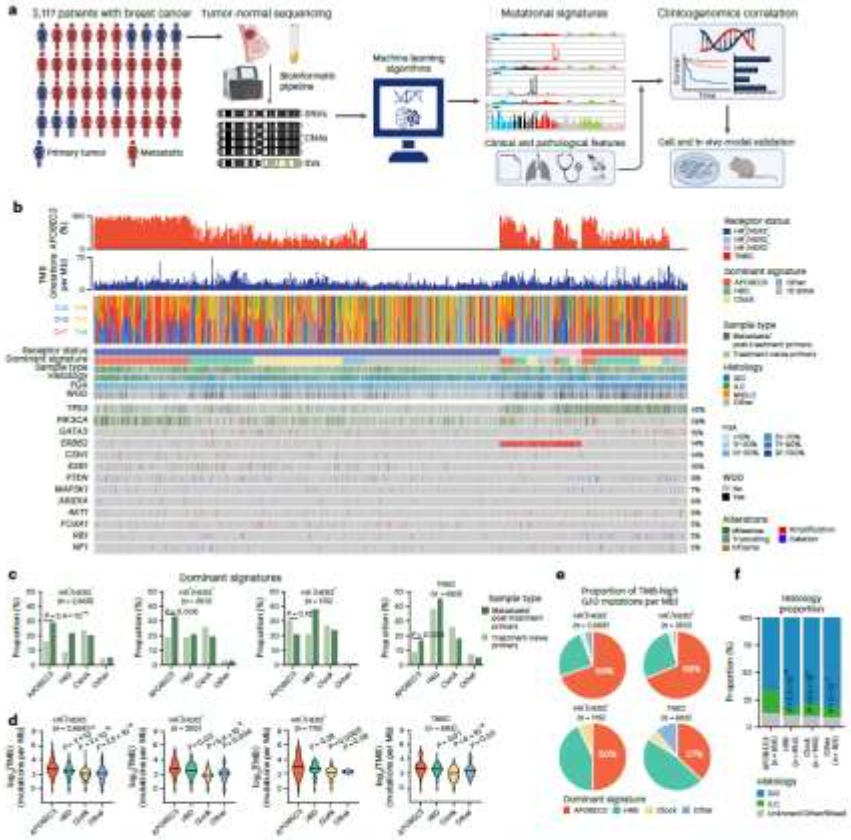


Fig. 1 | APOBEC3 mutational signatures are prevalent in breast cancers. **a**, Schematic of analysis pipeline of MSK-IMPACT breast cancer cohort. **b**, Summary of genomic characteristics of the clinical cohort demonstrating percentage contribution of APOBEC3 mutational signature (first panel), TMB (second panel), SNV change (third panel) and OncoPrint of select genes in samples. **c**, Barplots displaying the proportion of samples with indicated dominant mutational signature categorized by sample type and receptor status. Groups were compared using the two-tailed Pearson's chi-squared test. **d**, Violin plots representing TMB in samples categorized by receptor status. Groups were compared with APOBEC3-dominant samples using the two-tailed Wilcoxon test. **e**, Proportion of TMB-high samples with different dominant mutational signatures categorized by receptor status. **f**, Proportion of samples categorized by dominant mutational signature and histology. Groups were compared with APOBEC3-dominant samples using the two-tailed Pearson's chi-squared test. IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; MDLC, mixed invasive ductolobular breast cancer. Panel **a** created using BioRender.com.

This is but one of the examples of work being done at MSK to get in front of resistance mutations before they shut down a therapeutic strategy.

What is particularly interesting here is that there are likely to be specific therapeutic strategies to address APOBEC3 mutant tumors.

See Gupta, A., Gazzo, A., Selenica, P. *et al.* APOBEC3 mutagenesis drives therapy resistance in breast cancer. *Nat Genet* **57**, 1452–1462 (2025)

#6. Merck

Merck & Co. has taken a multifaceted approach to the breast-cancer space that combines immune-oncology innovation with precision and foundational therapies. At the heart of its strategy is the immune checkpoint inhibitor Keytruda (pembrolizumab), which Merck has developed across a broad range of breast-cancer subtypes, including triple-negative breast cancer (TNBC) and early-stage high-risk settings. Recognizing that immune responsiveness in breast cancer has historically been more modest compared to melanoma or lung cancer, Merck has pushed to identify combinations and biomarker-defined groups where immunotherapy will add meaningful value, rather than rely on monotherapy. This deliberate tilt toward combination regimens underscores a sophisticated view of the tumor microenvironment-driven resistance hurdles in breast cancer.

Parallel to the immuno-oncology axis, Merck is advancing precision approaches and antibody–drug conjugates (ADCs) or bispecifics in partnership and internal programs. The company recognizes that as standard care pushes earlier (adjuvant/neoadjuvant) and combinations solidify, differentiation will come from novel mechanisms and better targeting. For example, Merck has invested in programs that exploit DNA-damage repair vulnerabilities, immune microenvironment modulation and non-ER/HER2 driven subtypes—areas where unmet need remains high. A key pipeline asset is Sacituzumab Tirumotecan, which is in Phase 3 studies for treatment failures in HR+/HER2- metastatic breast cancer.

Merck is also exploring other ADCs in breast cancer including ones targeting B7H3 and CDH6.

A key pillar of Merck's strategy is move to front line treatment settings with highly efficaciouss drugs.

Merck aims to shift successful therapies from refractory metastatic settings into earlier-phase disease, including neoadjuvant and adjuvant trials, thereby developing long-term proprietary value, expanding addressable patient populations and potentially increasing regulatory/market access durability.

By doing so, Merck also positions itself to influence standard-of-care paradigms rather than follow them.

This forward-looking posture acknowledges that breast-cancer treatment is increasingly shifting to combination regimens in earlier stages and that capturing earlier disease settings is both clinically and commercially strategic.

Merck's longstanding company's willingness to invest in large phase-III trials, share data publicly and engage payers on real-world outcomes is indicative of a commitment to lead in breast-cancer care rather than tertiary follower status.

Merck Takes on the TROP2 Leaders in Breast Cancer

Madeleine Armstrong, ApexBIO, Feb 26, 2025

Merck & Co has just added to the huge programme for its Kelun-originated TROP2-targeting ADC, sacituzumab tirumotecan, with another new pivotal study, this time in first-line triple-negative breast cancer.

The TroFuse-011 trial, which seeks to enrol 1,000 patients, could pit saci-T against the two approved TROP2 ADCs, Gilead's Trodelvy and AstraZeneca/Daiichi Sankyo's Datroway. The study, just unveiled on clinicaltrials.com, is Merck's 12th phase 3, taking its total target patient population to nearly 10,000 – without even counting the Asian focused trials being carried out by Kelun.

Early TNBC has been transformed by Keytruda, which is approved front line in patients whose tumours express PD-L1 at ≥10%, as well as in the perioperative setting as part of a chemo combo.

Gilead's Trodelvy is approved in late-line TNBC, while saci-T recently got a green light here in China.

Source: https://www.oncologypipeline.com/apexonco/merck-takes-trop2-leaders-again-breast-cancer

TNBC delays

Trodelvy and Datroway are also being tested in front-line TNBC, in the Ascent-03 and Tropion-Breast02 trials respectively. Results from both studies had been expected last year, but have now been delayed until the first half of 2025; the imminent readouts could therefore set the bar for saci-T.

However, there are differences. For example, TroFuse-011 mandates PD-L1 expression below 10%, while Ascent-03 and Tropion-Breast02 have broader inclusion criteria, enrolling patients with PD-L1 <10%, as well as PD-L1-positive subjects who received (neo)adjuvant Keytruda and those with comorbidities preventing checkpoint inhibitors. Tropion-Breast02 also allows PD-L1-positive patients in countries where Keytruda isn't available.

Ascent-03 and Tropion-Breast02 are testing TROP2 ADC monotherapy versus physician's choice of chemo, while TroFuse-011 will evaluate saci-T, with or without Keytruda, versus physician's choice.

Another clash could come in adjuvant TNBC, where all three assets are being evaluated: saci-T in the TroFuse-012 trial; Trodelvy in Ascent-05; and Datroway in Tropion-Breast-03.

As for relapsed ER-positive, HER2-negative breast cancer, Merck is lagging behind. Datroway recently got the go ahead here, following Trodelvy's 2023 approval, while the TroFuse-010 trial of saci-T is due to complete in 2027.

#7. Nikang Therapeutics

Developing a CDK2/4 Degrader for Breast Cancer

Source: Nikang Therapeutics Investor Presentation, Zurich Switzerland, October 2025

NKT5097 is CDK2/CDK4 Selective Degrader in Phase 1

Being developed in breast cancer for patients that have progressed on CDK4/6 drugs like IBRANCE®.

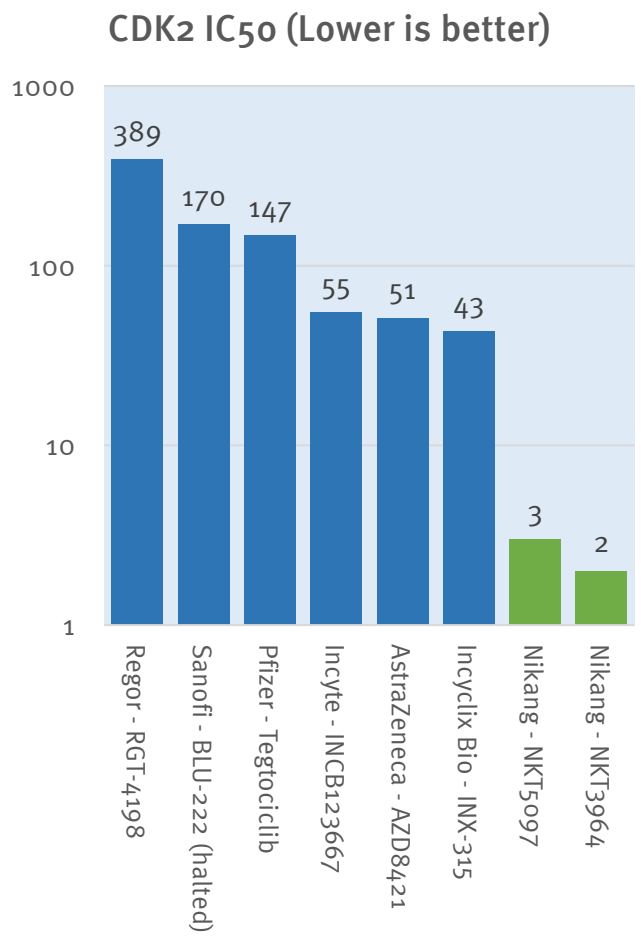
Has dosed first cohort of its Phase 1 SAD Study

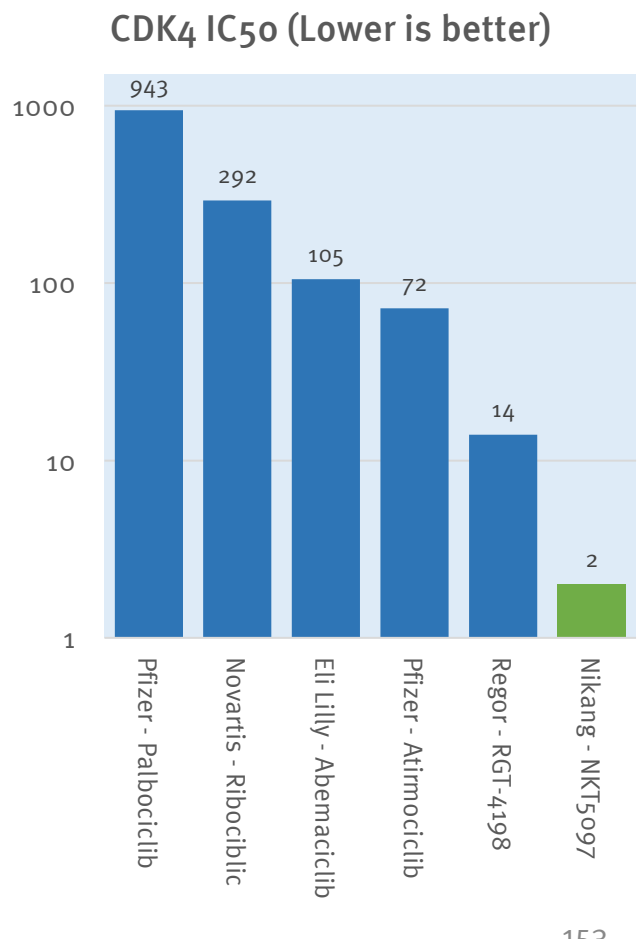
Sep 8, 2025: WILMINGTON, Del.--(BUSINESS WIRE)--NiKang Therapeutics® Inc. ("NiKang"), a clinical stage biotech company focused on developing innovative small molecule oncology medicines to bring transformative therapies to patients in need, announced today the successful completion of dosing in the first cohort of its phase 1 dose-escalation study evaluating NKT5097 as a single agent. NKT5097 is a first-in-class, orally bioavailable small molecule designed to selectively degrade CDK2 and CDK4 simultaneously, offering potential therapeutic benefits for patients with HR+ breast cancer and cancers with aberrant CDK2/cyclin E pathway activation.

"We are pleased to achieve this significant milestone expeditiously after IND clearance," said Zhenhai Gao, Ph.D., co-founder, president, and CEO of NiKang. "Initial PK data from the first cohort indicated favorable oral exposure consistent with human PK projections. In addition, initial PD data from the first cohort showed deep reduction of TKa level in HR+HER2- breast cancer patients previously treated with CDK4/6 inhibitors. NKT5097 has been well-tolerated to date. Due to its superior selectivity against CDK1 and CDK6, NKT5097 has the potential to mitigate neutropenia and/or diarrhea associated with existing CDK2 or CDK4/(6) inhibitors. These early findings underscore the potential of our dual degrader approach targeting both CDK2 and CDK4 - two key regulators of the cell cycle frequently dysregulated in various cancers including breast cancer. Our innovative, first-in-class CDK2/4 dual degrader holds the promise to replace currently approved CDK4/6 inhibitors as the new leader in treating HR+ breast cancer."

Source: Nikang website and investor presentation, October 2024

Impressive Target Selectivity vs. Competition





NKT3694 is CDK2 Selective Degrader in Phase 1

Being developed first for Cyclin E1 amplified ovarian cancer. Currently in POC testing.

Discovery of NKT3964: a first-in-class, highly potent and selective, orally bioavailable CDK2 PROTAC degrader for cancer therapy

ENA24-0307

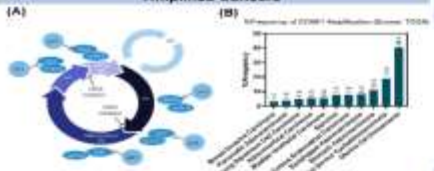
Jianlin Geng, Ke Liu, Zhiyong Yu, Wenfeng Sun, Yu-Te Yeh, Hairong Wei, Wenjun Li, Jing Lu, Juan Deng, Chenguang Yang, Liqing Geng, Xiao Luo, Zhihong Liu, Zhenhai Gao and Yan Lou
NiKang Therapeutics® Inc., Wilmington, DE 19803, USA

NKT™ NIKANG

Introduction

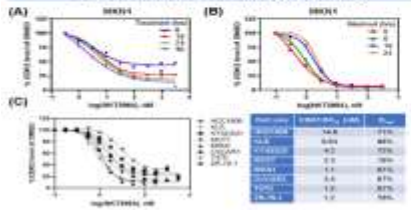
- CDK2 is a promising novel target for CCNE-amplified cancers as well as HR+HER2- breast cancer.
- Development of traditional ATP-competitive CDK2 inhibitors has been challenging due to the high homology between CDK2 and CDK1. Most CDK2 inhibitors currently in clinical trials show sub-optimal selectivity for CDK1 and can paradoxically increase cyclin E levels, resulting in off-target toxicities and pathway hyperactivation after drug clearance.
- PROTACs technology has emerged as a novel therapeutic paradigm, offering several advantages over traditional small molecule inhibitors such as enhanced potency and selectivity, a broader target range and the ability to overcome drug resistance.
- Here we report the discovery of NKT3964, a first-in-class oral CDK2 selective degrader with superior potency and selectivity, causing prolonged CDK2 pathway inhibition without cyclin E accumulation. NKT3964 has the potential to maximally inhibit the CDK2 pathway, fully harnessing the therapeutic benefits of CDK2 inhibition.

CDK2 is a Well-validated Oncogenic Driver in CCNE1 Amplified Cancers



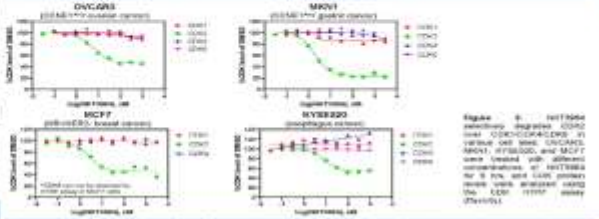
Results

NKT3964 Exhibits Rapid, Potent and Sustained Degradation of CDK2 Across Cell Lines

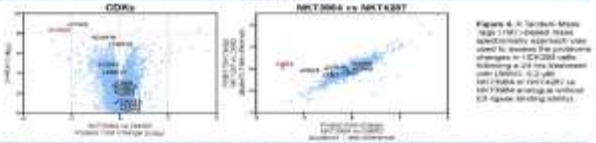


Results

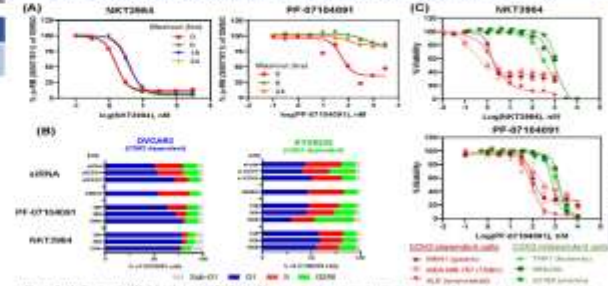
NKT3964 Achieves Highly Selective Degradation of CDK2



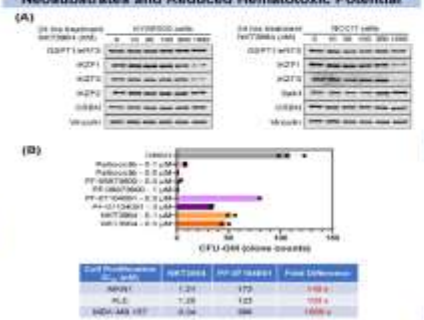
Proteomics Profiling Confirms High Selectivity for CDK2 as a Primary Target of NKT3964



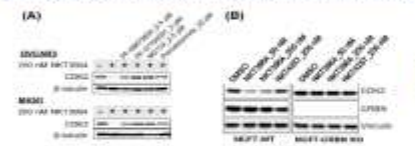
NKT3964 Treatment Leads to Prolonged Pathway Inhibition, Specific G1 Cell Cycle Arrest, and Enhanced Selective Inhibition of Cell Proliferation



NKT3964 Has Minimal Effect on Known Thalidomide Neosubstrates and Reduced Hematotoxic Potential



NKT3964-mediated Degradation of CDK2 Requires Both CDK2/Cereblon Binding and Proteasome Activity

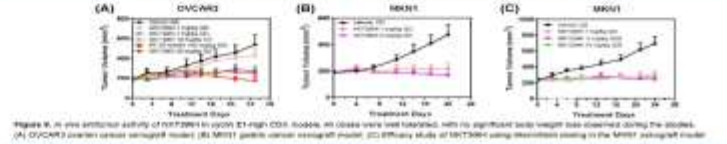


NKT3964 Is Orally Bioavailable Across Preclinical Species

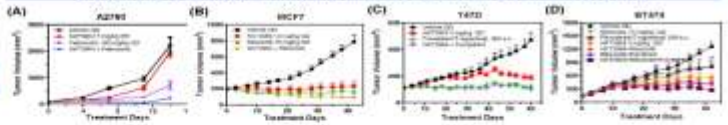
NKT3964	Mouse (10 mg/kg, PO)	Rat (5 mg/kg, PO)	Dog (2 mg/kg, PO)
PK	$T_{1/2}$ (h)	3.7	4.4	15.6
PO	F%	45	59	28

NKT3964 Demonstrates Robust PD Effect in MKN1 Tumor Model, Recapitulating *in vitro* Cellular Profiles

NKT3964 Inhibits CCNE1-amplified Tumor Growth *in Vivo*



Combination of NKT3964 with Other Therapeutic Agents Shows Improved TGI



Summary

- NKT3964 is a first-in-class oral CDK2-selective degrader. Treatment with NKT3964 in various cancer cell lines leads to more potent (10-100 times greater potency than traditional ATP-competitive CDK2 inhibitors) and more sustained inhibition of CDK2 pathway, without causing cyclin E accumulation.
- NKT3964 exhibits superior selectivity for CDK2, with minimal off-target degradation of CDK1 and other CDK family members. This excellent selectivity profile has been validated through unbiased proteomics analysis.
- In preclinical studies, NKT3964 treatment results in dose-dependent tumor growth inhibition or regression in CCNE1-amplified OVCAR3 and MKN1 tumor models. In addition, combining NKT3964 with a CDK4/6 inhibitor or fulvestrant enhances anticancer effects across multiple mouse xenograft tumor models.
- NKT3964 shows great potential for treating patients with aberrant CDK2/Cyclin E pathway activation, including those with ovarian, endometrial, gastric, as well as HR+HER2- breast cancers. NKT3964 is currently being investigated in a Phase 1 clinical trial for patients with advanced solid tumors (NCT05563857).

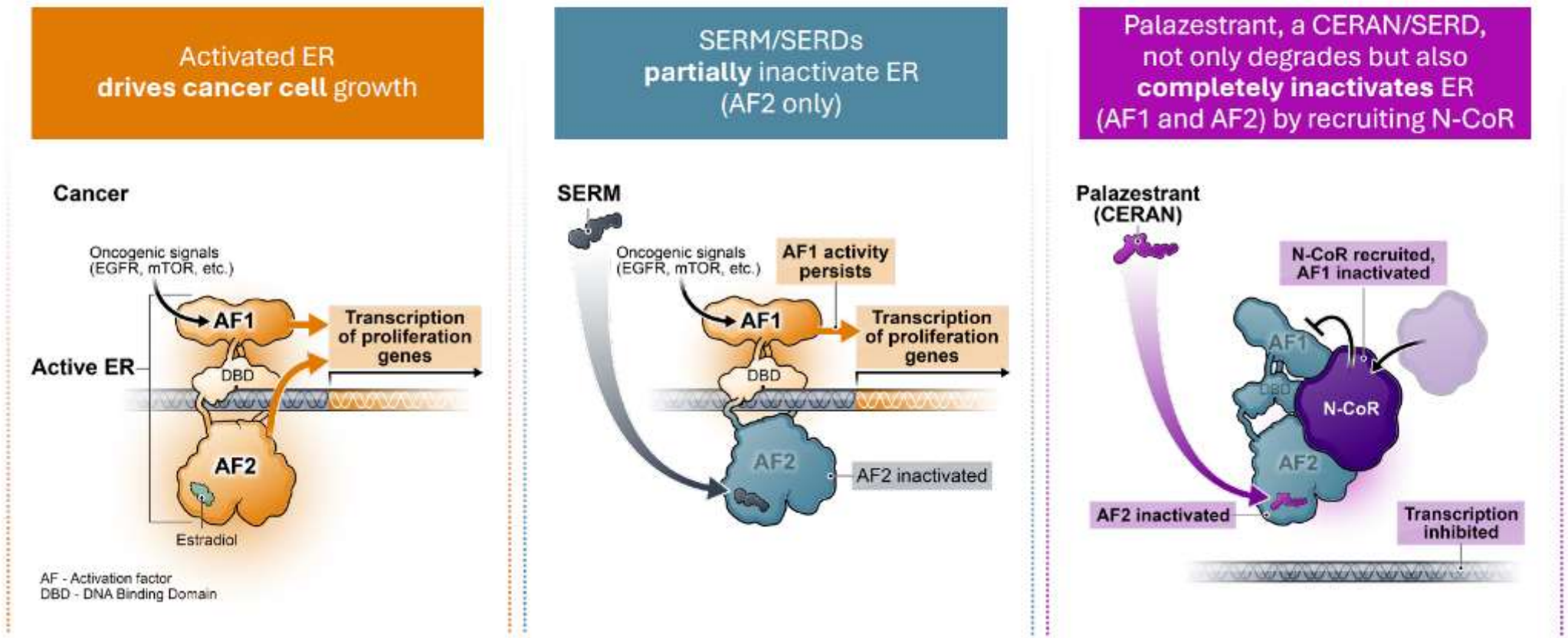
Reference

(1) Sakamoto Takitaka, et al. Drug Discov Today. 2022; 27(2): 490-513. (2) Mikkilineni L, et al. Nat Rev Drug Discov. 2022; 21: 501-502. (3) Chen Chu, et al. Transl Cell Biol. 2021; 11(2): 192-199. (4) Kevin Freedman-Cass, et al. Cancer Cell. 2021; 39(10): 1404-1421. (5) Rinath Jeselsohn, et al. Cancer Cell. 2021; 39(10): 1362-1368.

#8. Olema Oncology

Palazestrant is a dual SERM / SERD with high binding to its target of interest.

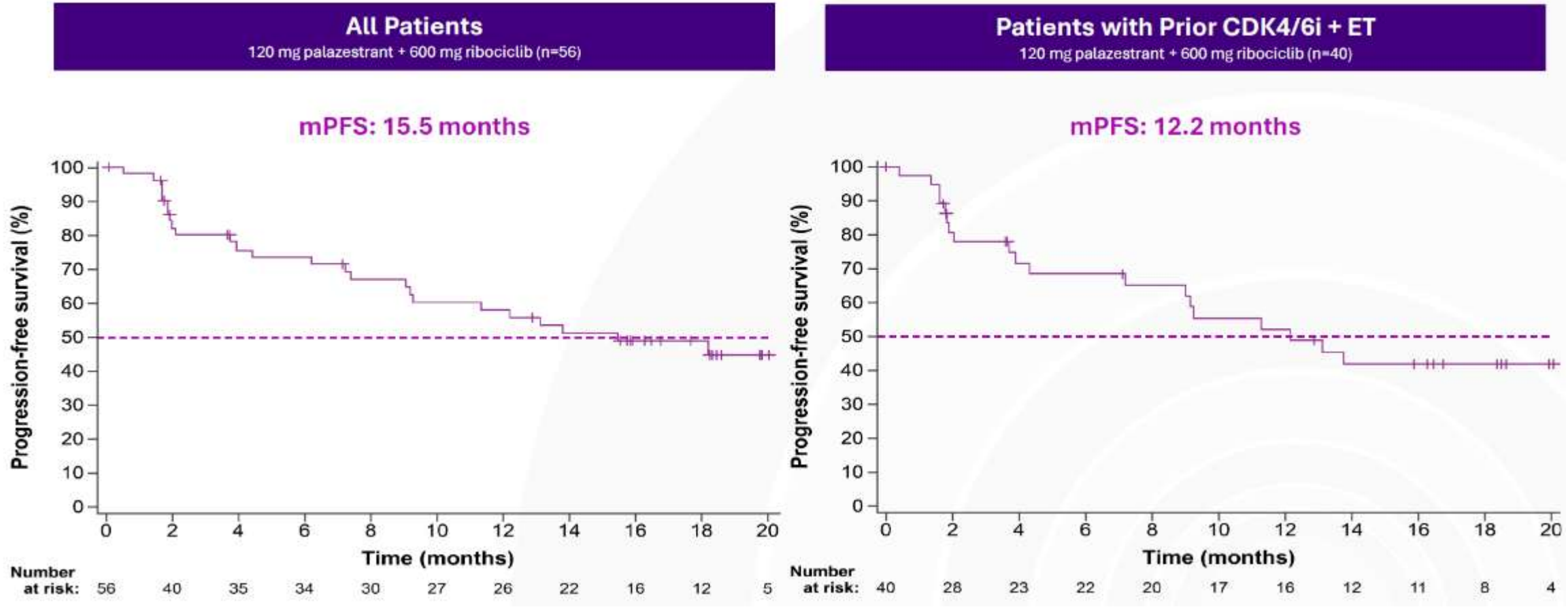
Palazestrant is a differentiated oral CERAN/SERD targeting the growth and proliferation mechanism driving ER+ breast cancer



Source: Olema Oncology Investor Presentation, October 2025

Olema Oncology

Now, in a Phase 3 registrational program based upon excellent performance in a prior Phase 1b/2a studies.



Source: Olema Oncology Investor Presentation, October 2025

#9. Pfizer

Pfizer is doubling-down on breast cancer as a key frontier in its oncology strategy despite the upcoming patent expiry for palbociclib. The company has set a target of delivering eight blockbuster cancer drugs by 2030 and has identified breast cancer as one of its four major disease-areas of focus.

Within that, Pfizer's play is two-fold: (1) advancing next-generation targeted therapies (e.g., PROTACs, selective CDK inhibitors, epigenetic modulators) and (2) moving existing and new agents earlier in the treatment line (e.g., earlier than second/third-line and combination strategies) to expand addressable population and prolong therapeutic benefit.
but
In practice, this means Pfizer is building a stacked portfolio: new CDK4-selective or CDK2 inhibitors, next-gen estrogen receptor degraders/targeters (e.g., PROTACs), epigenetic targets (e.g., KAT6A/B inhibitor) and antibody-drug conjugates (ADCs) via its acquisition of Seagen.

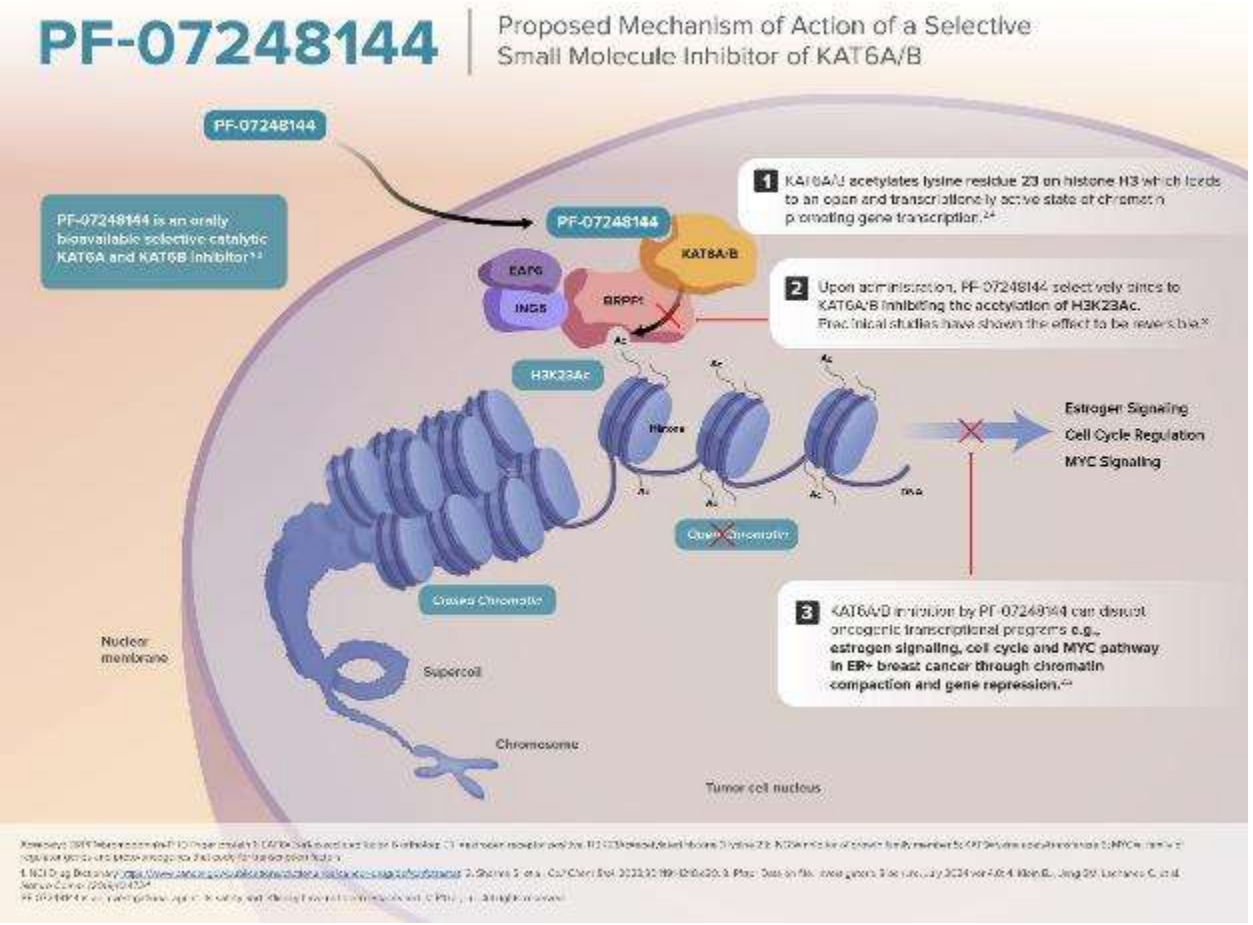
This layered approach is designed to both address resistance (e.g., ER+/HER2- after CDK4/6 inhibitors) and expand into new settings (earlier lines, combinations, biomarker-driven subsets).

Asset	Mechanism / Indication	Stage	Rationale
Atirmociclib (PF-07220060)	Selective CDK4 inhibitor	Phase 2	Next-generation cell-cycle agent aiming to improve safety and overcome resistance to first-gen CDK4/6 inhibitors.
Tegtociclib (PF-07104091)	CDK2 inhibitor	Phase 1/2	Addresses CDK2-dependent resistance pathways that emerge after CDK4/6 blockade.
PF-07248144	KAT6A/B epigenetic inhibitor	Phase 2 / 3	First-in-class epigenetic therapy for endocrine-resistant $HR^+/HER2^-$ breast cancer; potential new pillar post-CDK4/6 therapy.
Disitamab vedotin (PF-08046051)	HER2-directed antibody–drug conjugate	Early clinical	Expanding ADC franchise into HER2-low and HER2-expressing breast cancers; complements Seagen ADC portfolio.

KAT6A is a Promising Novel Target in ER+ Breast Cancer

The rationale for targeting KAT6A in breast cancer stems from its central role as an epigenetic activator of estrogen receptor (ER) signaling and cell proliferation pathways. KAT6A (also known as MYST3 or MOZ) is a histone acetyltransferase located on chromosome 8p11-12, a region amplified in approximately 10–15% of ER-positive breast cancers. Amplification or overexpression of KAT6A enhances chromatin accessibility at estrogen-responsive genes, promoting transcriptional activation of ER and its downstream targets—including MYC and cell-cycle regulators. This creates a hyper-transcriptional state that drives tumor growth and contributes to resistance to endocrine therapy and CDK4/6 inhibitors, two pillars of current $ER^+/HER2^-$ breast cancer treatment. Preclinical models show that inhibiting KAT6A/B reduces acetylation at these genomic loci, suppresses ER expression and induces durable tumor regression even in endocrine-resistant settings.

Pfizer is developing PF-7248144, a KAT6A/B inhibitor.
This molecule is currently in Phase 2 and Phase 3 testing for breast cancer.



Early Efficacy Signal for Pfizer KAT6 Quite Encouraging

	PF-07248144 5 mg q.d. Part 2A (*N*=35)	Combination PF-07248144 5 mg q.d. + fulvestrant 500 mg Parts 1B+2B (*N*=43)								
	N=35	Total *N*=43	2L *N*=23	3L+ *N*=20	Fulv treated *N*=5	Fulv naive *N*=38	*ESR1* MT *N*=24	*ESR1* WT *N*=18	*PIK3CA/AKT1/PTEN* MT *N*=19	*PIK3CA/AKT1/PTEN* WT *N*=23
Objective response (CR+PR), *n* (%)	4 (11.4)	13 (30.2)	5 (21.7)	8 (40.0)	3 (60.0)	10 (26.3)	8 (33.3)	5 (27.8)	5 (26.3)	8 (34.8)
95% CI[a]	3.2–26.7	17.2–46.1	7.5–43.7	19.1–63.9	14.7–94.7	13.4–43.1	14.5–52.2	7.1–48.5	6.5–46.1	15.3–54.2
Median duration of response (95% CI)[b]	12.0 (7.4–NE)	9.2 (7.2–NE)	NE (5.5–NE)	9.2 (7.2–NE)	N/A	N/A	9.2 (5.8–NE)	NE (NE–NE)	7.2 (5.5–NE)	NE (9.2–NE)
Disease control (CR+PR+SD+ non-CR/non-PD), *n* (%)	18 (51.4)	33 (76.7)	16 (69.6)	17 (85.0)	5 (100.0)	28 (73.7)	21 (87.5)	12 (66.7)	13 (68.4)	20 (87.0)
95% CI[a]	34.0–68.6	61.4–88.2	47.1– 86.8	62.1–96.8	47.8–100.0	56.9–86.6	67.6–97.3	41.0–86.7	43.4–87.4	66.4–97.2
CBR, *n* (%)	11 (31.4)	22 (51.2)	10 (43.5)	12 (60.0)	4 (80.0)	18 (47.4)	12 (50.0)	10 (55.5)	9 (47.4)	13 (56.5)
95% CI[a]	16.9–49.3	35.5–66.7	23.2– 65.5	36.1– 80.9	28.4–99.5	31.0–64.2	29.1–70.9	30.8–78.5	24.4–71.1	34.5–76.8
mPFS, 95% CI[b]	3.3 (2.0–5.8)	10.7 (5.3–NE)	NE (3.5–NE)	10.7 (5.5–NE)	N/A	N/A	10.7 (5.5–NE)	NE (3.5–NE)	7.2 (2.8–NE)	10.8 (5.6–NE)

[a]Clopper–Pearson method used. [b]Brookmeyer and Crowley method used. 2L, with at least one prior line of treatment; 3L+, as third line and above; Fulv, fulvestrant; N/A, not available; NE, not evaluable.

Source: Mukohara Tom, et. al, "Inhibition of lysine acetyltransferase KAT6 in ER$^+$HER2$^-$ metastatic breast cancer: a phase 1 trial,: *Nat Med.* 2024 Aug;30(8):2242-2250.

KAT6 Inhibitor Competitive Landscape

Compound (Company)	Stage	Strategy summary	Positioning
PF-07248144 (Pfizer)	Phase 3	Lead KAT6A/B inhibitor; moving into pivotal Phase 3 in $ER^+/HER2^-$ metastatic breast cancer post-CDK4/6 inhibitor + endocrine therapy.	Target: high-unmet need population (after CDK4/6 + endocrine). Combination with fulvestrant to extend endocrine therapies. First-in-class; aims for registration. Data show ~30% ORR in combo.
OP-3136 (Olema Oncology)	Phase 1	Oral KAT6A/B inhibitor designed specifically for women's cancers. Strategy emphasises combinations with endocrine therapy (e.g., CERAN/SERD) and CDK4/6 inhibitors.	Positioning: adding to existing endocrine backbone (palazestrant, CDK4/6) and broadening to other solid tumours (ovarian, lung, prostate) for volume. Emphasis on synergy rather than only monotherapy. clinicaltrialvanguard.
MEN2312 (developed at Insilico)	Phase 1	AI-designed KAT6A inhibitor (licensed from Insilico) for $ER^+/HER2^-$ breast cancer and other cancers. Strategy focuses on transcriptional repression of ER via epigenetic mechanism to overcome endocrine resistance.	Positioning: differentiation via AI-discovered chemistry, oral small molecule; potentially broad applications beyond breast cancer; early clinical. Also signals premium deal structure (~$500 M) indicating commercial confidence.
IDE251 (IDEAYA Biosciences)	Preclnical	Dual KAT6/KAT7 inhibitor; strategy focuses on tumours with 8p11 amplification (including subset of breast cancers) and other solid tumours. Biomarker-driven niche rather than broad endocrine refractory.	Positioning: more selective niche (8p11 amplified) ⇢ potentially higher margin, smaller market but clearer biomarker. Preclinical/IND-enabling stage. Less direct endocrine-therapy backbone focus so far.

Source: Stifel Investment Banking

#10. Quantum Leap

We attended a series of sessions held at ASCO this year led by Laura Esserman of UCSF.

After walking through the benefit of Bayesian adaptive clinical trials in breast cancer, Dr. Esserman introduced a speaker on the topic of improving surrogate endpoints in breast cancer trials.

Today, the most commonly used surrogate biomarker in studies of early breast cancer is pCR, particularly in HER2-positive and triple-negative breast cancer (TNBC).

High pCR rates often predict better EFS (event-free survival) and OS.

Today, for metastatic breast cancer, PFS is the most frequent primary endpoint in Phase II and III trials.

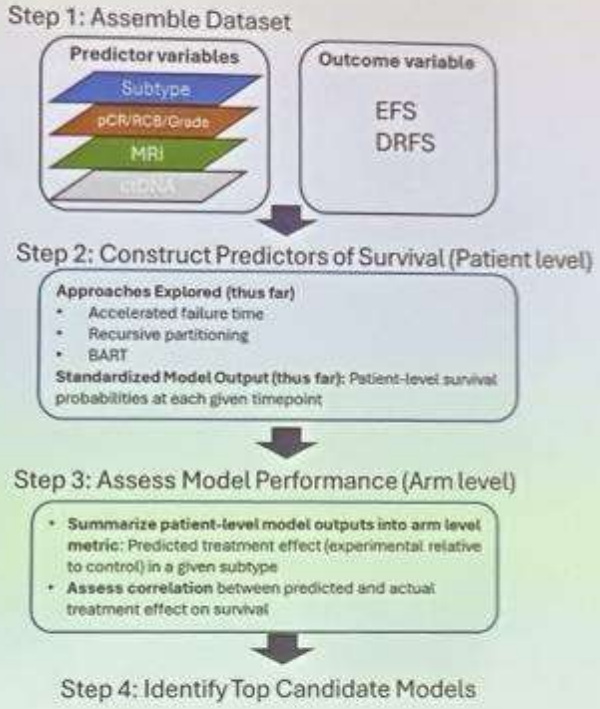
The main issue is that both pCR and PFS are not particularly good at predicting OS.

In contrast, MRD has been a great advance in the analysis of liquid tumors. MRD is highly predictive of OS in those diseases but, in contrast, in most other areas of oncology, we have not seen good predictors emerge for OS.

I-SPY Team Created a Multivariable Testing Framework

Process for Efficient Endpoint Development

- Goal: Develop a surrogate for survival outcome that strongly correlates with survival at the patient *and* trial arm levels
- I-SPY 2 dataset is assembled and split into training and test sets balancing for key variables
- Data hosted on OneSourceAI platform
  - Enables multiple analysts to work on common data
  - Facilitates new model development and code sharing
- Thus far, >30000 models constructed with different combinations of input variables and assessed for performance



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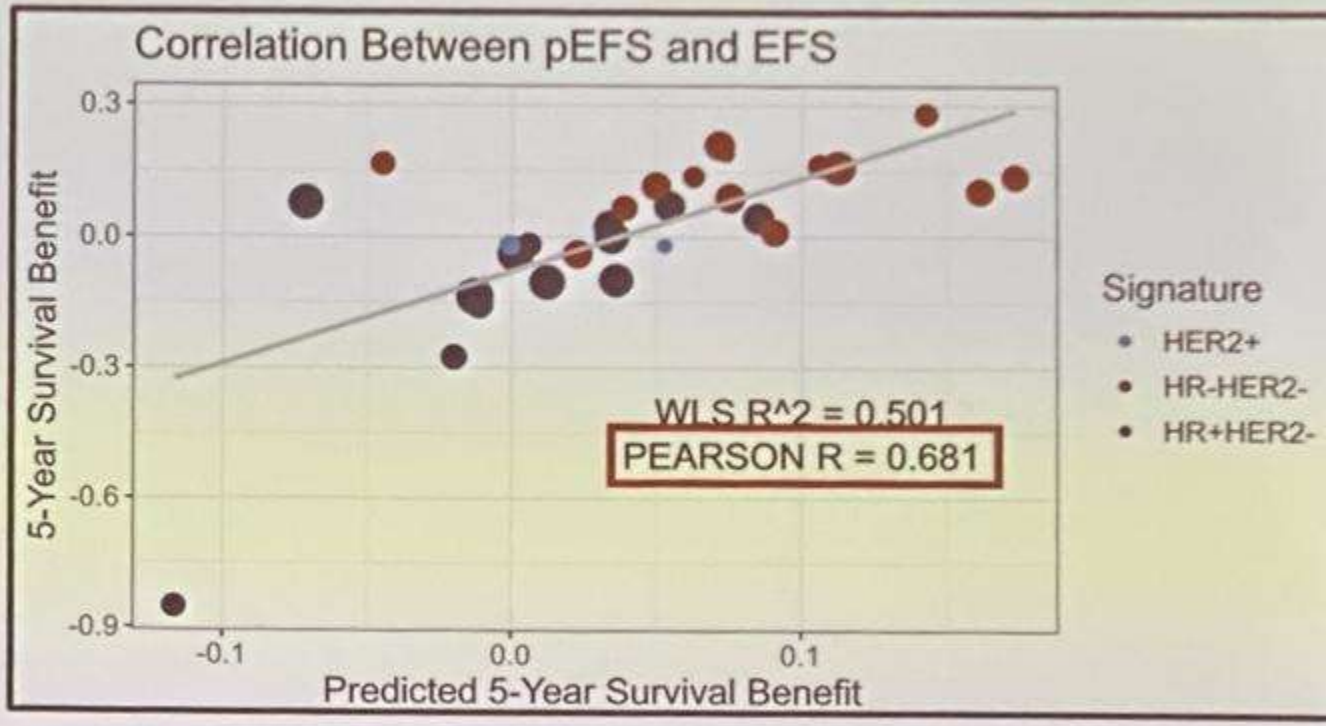
I-SPY Team Successful in Improving Breast Cancer Surrogate Endpoint

Multivariable Advanced Failure Time Models

One promising candidate is a multivariable AFT model incorporating:

- Tumor Biology: HR/HER2 subtype
- Extent of Disease at Baseline: Clinical T
- Extent of Disease at Surgery: Residual Cancer Burden (RCB)
- Post-treatment Aggressiveness: Post-surgical grade



Trial level correlation is within range of what was observed for MRD-CR in multiple myeloma

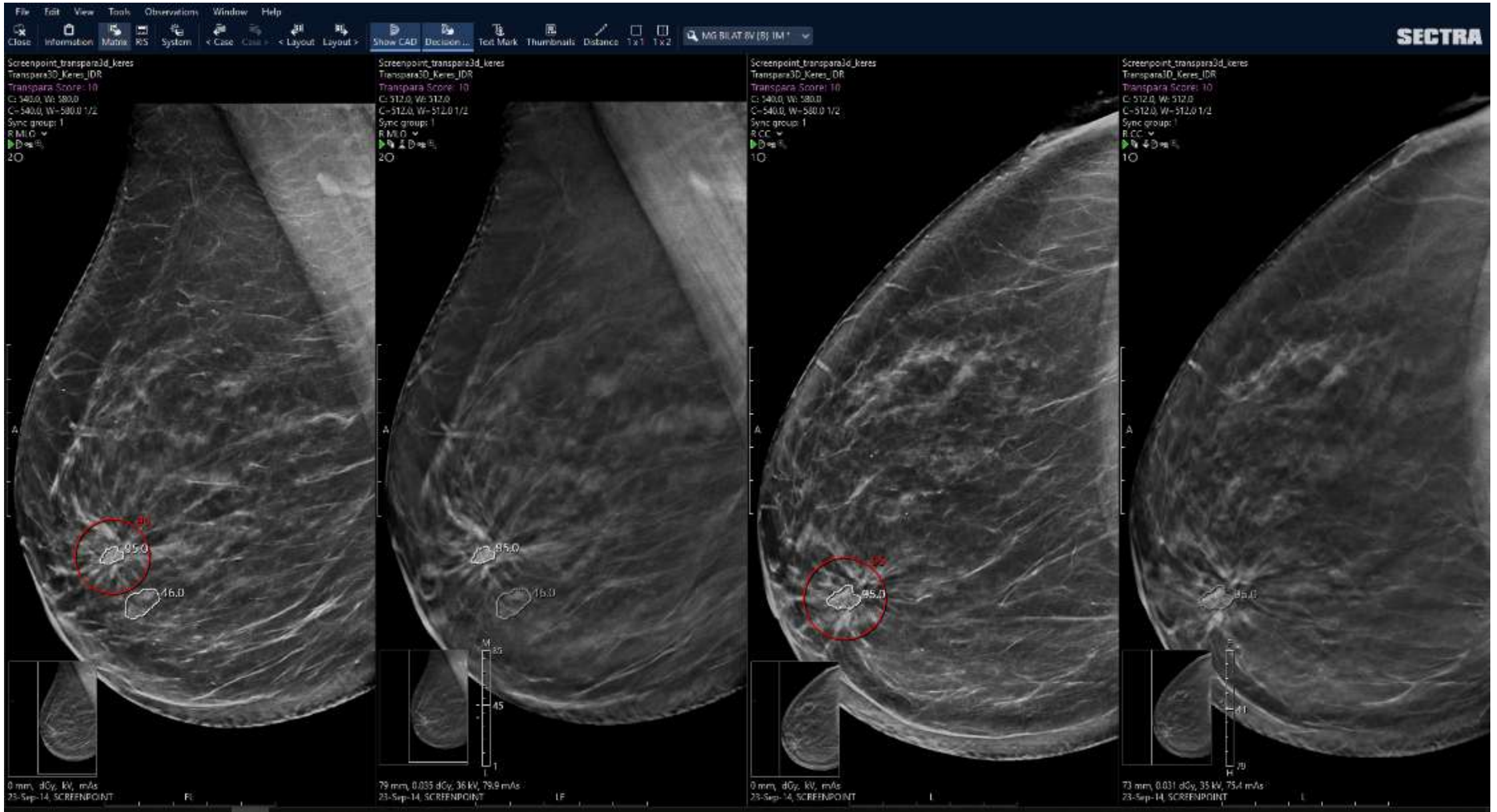
#11. Screenpoint Medical

ScreenPoint Medical is a Netherlands-based medical technology company founded in 2014 as a spin-off from Radboud University Medical Center in Nijmegen. It was established by Professor Nico Karssemeijer and Sir Michael Brady, two pioneers in computer-aided detection and medical image analysis. The company focuses on the use of deep learning and advanced image-analysis algorithms to improve the accuracy, speed and consistency of breast-cancer screening. Its flagship platform, Transpara, is an artificial-intelligence system designed to assist radiologists in interpreting both 2D mammography and 3D digital breast tomosynthesis (DBT) images. Transpara assigns a cancer-likelihood score and highlights suspicious regions, allowing radiologists to triage exams, prioritize high-risk cases and reduce workload while maintaining or improving detection rates.

Transpara is both FDA-cleared and CE-marked, making it one of the few breast-AI tools approved for clinical use in major global markets. The system is deployed in hospitals and screening programs across Europe, the United States and Asia, where it has demonstrated significant benefits such as faster reading times, higher sensitivity in dense-breast populations and improved overall workflow efficiency. ScreenPoint has also published multiple independent clinical studies showing that AI-assisted readings can achieve accuracy comparable to that of expert radiologists. In 2025, the company expanded its capabilities through the acquisition of Biomediq A/S, a Danish firm specializing in imaging biomarkers and risk assessment, with the goal of integrating personalized risk profiling into screening workflows.

SCREENPOINT
Medical

Screenpoint's AI Able to Identify Occult Breast Tumors



Appendix 1:

Detail on Historical Publications on Breast Cancer

(1700 B.C.E. to 1950)

The Edwin Smith Papyrus Identifies Breast Cancer in the 17th Century B.C.E.

The Edwin Smith Papryus, dated to around 1600 B.C.E. but likely derived from much older Old Kingdom sources (ca. 2500 B.C.E.), is the earliest known surgical treatise and includes the first recognizable reference to breast cancer. Written in hieratic script and attributed to the physician-priest Imhotep, it presents 48 clinical case histories arranged systematically from head to torso injuries. Among these, Case 45 describes “bulging tumors of the breast” — hard, cold, immovable swellings that cause no suppuration and are likened to masses of hematite. The text notes that such a lesion should be treated with no intervention: “There is no treatment.” This statement is striking because it represents not only a clinical observation of malignant disease but also an early recognition of its incurability within the therapeutic means of the time.

Unlike other entries that recommend splints, dressings, or cauterization, the papyrus’ description of breast tumors reflects a sober, empirical approach — distinguishing malignant from inflammatory conditions through observation and prognosis rather than mysticism. It demonstrates that Egyptian medicine, while intertwined with religion, had evolved a form of rational medical reasoning centuries before Hippocrates.

References: Ades (2017), Freeman et al. (2018), Hajdu (2011a), Lakhtakia (2014), Lukong (2017), Mukherjee (2002).

Plates vi & vii from the Edwin Smith Papyrus. From the New York Academy of Medicine.

400 B.C.E.: Hippocrates

Linked breast cancer to the four humors and black bile. Saw breast cancer as a "systemic disease".

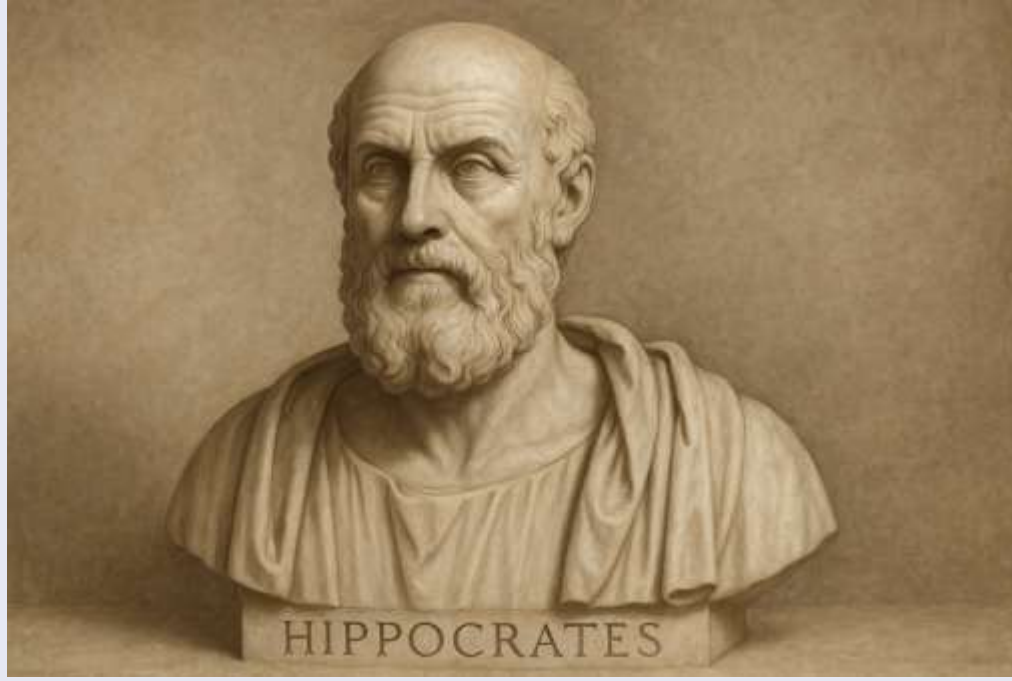
Hippocrates of Kos (c. 460–370 B.C.E.), often called the "Father of Western Medicine," was a Greek physician whose ideas transformed medicine from a mystical art into a rational discipline grounded in natural observation. He founded what later came to be known as the Hippocratic School, which emphasized that disease was not a punishment from the gods but arose from imbalances within the body and its environment.

His Corpus Hippocraticum introduced systematic case descriptions, prognoses and the notion that health depended on harmony among the four bodily humors—blood, phlegm, yellow bile and black bile. This framework became the dominant explanatory model of disease for nearly two millennia.

In the context of cancer, Hippocrates viewed malignant disease as a humoral disorder caused by an excess of black bile, the most noxious of the four humors. He described breast cancer as a particularly striking example: dark, hard, painful tumors that, when neglected, "burst forth" to release a black fluid. He coined the term karkinos ("crab") to describe these tumors, observing that their radiating veins resembled a crab's legs.

Hippocrates believed such cancers were incurable once advanced, advising against surgical intervention because disturbing them often hastened death. His interpretation—linking cancer to systemic imbalance rather than local injury—shaped medical thought for centuries, influencing Galen and persisting well into the early modern era.

References: Ades (2017), Ben-Dror (2022), Du Moulin (1993, p. 10), Ekmektzoglou (2009), Freeman (2018), Hajdu (2011a), Lukong (2017), Mukherjee (2002), Yan (2013), Yarris and Hunter (2003)



Hippocrates, 1546, *Medicorum Amnium,* Hieronymus Froben & Nicolaus Episcopius: Basel. From the author's medical library.

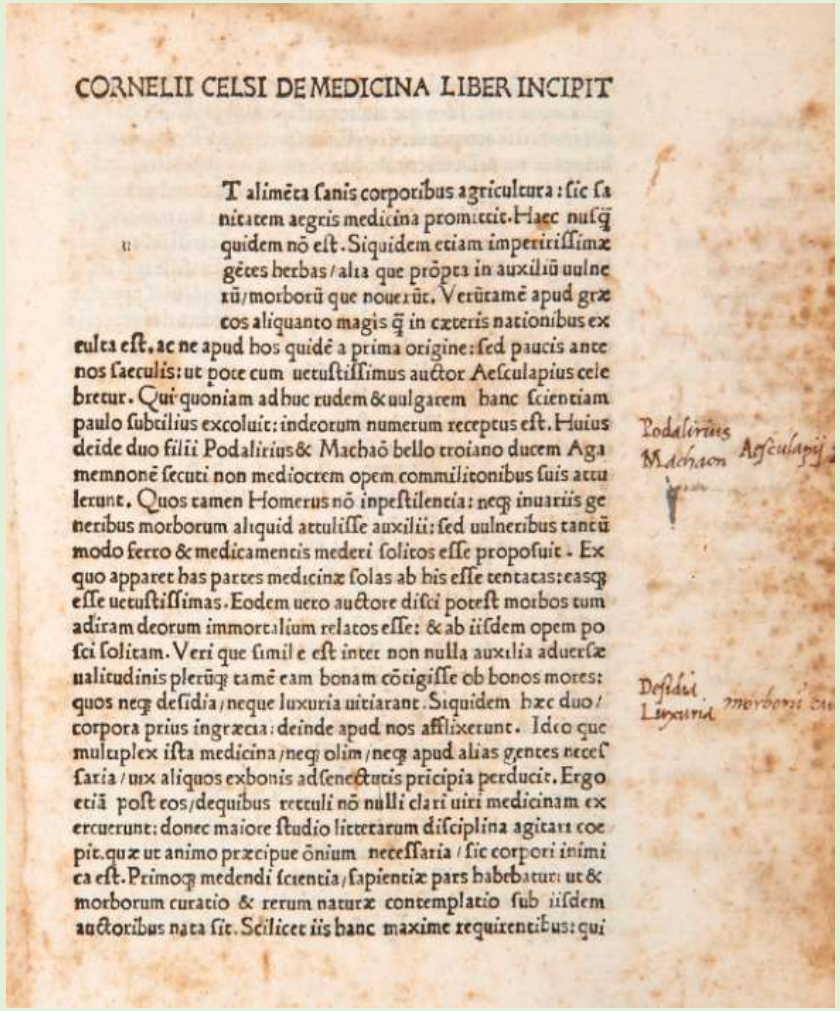
50 C.E.: Aurelius Cornelius Celsus

Counseled conservatism on surgery noting those who are cut “die quickly”.

Aulus Cornelius Celsus (c. 25 B.C.E.–50 C.E.), a Roman encyclopedist best known for his work De Medicina, gave one of the earliest systematic Latin descriptions of cancer and its treatment. He regarded cancer (carcinoma) as a disease arising from the body’s own tissues—especially from “black bile,” echoing Hippocratic humoral theory—but offered more precise clinical distinctions between early and advanced cases. Celsus observed that breast tumors could appear as hard, immobile masses with surrounding veins like a crab’s legs, hence the term cancer (Latin for crab). He distinguished between ulcerated and non-ulcerated cancers, warning that once ulceration or systemic symptoms appeared, the disease was incurable.

In terms of treatment, Celsus recommended surgical excision only for small, localized and non-ulcerated breast cancers and even then only with extreme caution. He advised that the entire tumor and surrounding tissue be removed to prevent recurrence but also warned that “those who are cut die quickly, those not cut die slowly.” For advanced cases, he counseled palliative measures such as soothing ointments and diet rather than aggressive intervention. His writings thus occupy a transitional place between Hippocratic humoral fatalism and the later surgical empiricism of Galen and Paul of Aegina—reflecting an early understanding that radical intervention could prolong life in select cases, but that the balance between benefit and harm was precarious.

References: Dibner 119, Du Moulin (1993, p. 12), Ekmektzoglou (2009), Freeman (2018), GMN 20; Hajdu (2011a), Norman 424, Osler 147, Waller 44, Wellcome 1392, Yan (2013).


CORNELII CELSI DE MEDICINA LIBER INCIPIT

T alimẽta ſanis corporibus agricultura: ſic ſa
nitatem aegris medicina promittit. Haec nuſq̃
quidem nõ eſt. Siquidem etiam imperitiſſimæ
gẽtes herbas/alia que prõpta in auxiliũ uulne
rũ/morborũ que nouerũt. Verũtamẽ apud græ
cos aliquanto magis q̃ in cæteris nationibus ex
culta eſt, ac ne apud hos quidẽ a prima origine: ſed paucis ante
nos ſæculis: ut pote cum uetuſtiſſimus auctor Aeſculapius cele
bretur. Qui quoniam adhuc rudem & uulgarem hanc ſcientiam
paulo ſubtilius excoluit: indeorum numerum receptus eſt. Huius
deide duo filii Podalirius & Machaõ bello troiano ducem Aga
memnonẽ ſecuti non mediocrem opem commilitonibus ſuis attu
lerunt. Quos tamen Homerus nõ inpeſtilentia: neq̃ inuariis ge
neribus morborum aliquid attuliſſe auxilii: ſed uulneribus tantũ
modo ferro & medicamentis mederi ſolitos eſſe propoſuit. Ex
quo apparet has partes medicinæ ſolas ab his eſſe tentatas: easq̃
eſſe uetuſtiſſimas. Eodem uero auctore diſci poteſt morbos tum
adiram deorum immortalium relatos eſſe: & ab iiſdem opem po
ſci ſolitam. Veri que ſimile eſt inter non nulla auxilia aduerſæ
ualitudinis plerũq̃ tamẽ eam bonam cõtigiſſe ob bonos mores:
quos neq̃ deſidia/neque luxuria uitiarant. Siquidem hæc duo/
corpora prius ingræcia: deinde apud nos afflixerunt. Ideo que
multiplex iſta medicina/neq̃ olim/neq̃ apud alias gentes neceſ
ſaria/uix aliquos exbonis adſenectutis principia perducit. Ergo
etiã poſt eos/dequibus retuli nõ nulli clari uiri medicinam ex
ercuerunt: donec maiore ſtudio litterarum diſciplina agitari coe
pit. quæ ut animo præcipue õnium neceſſaria/ſic corpori inimi
ca eſt. Primoq̃ medendi ſcientia/ſapientiæ pars habebatur: ut &
morborum curatio & rerum naturæ contemplatio ſub iiſdem
auctoribus nata ſit. Scilicet iis hanc maxime requirentibus: qui

Podalirius
Machaon
Aſculapij
Deſidi
Luxuria
morbori

Aurelius Cornelius Celsus (25 BC-50 AD). *De medicina*. Florence: Niccolò di Lorenzo della Magna, 1478. From the Medical Library of the author.

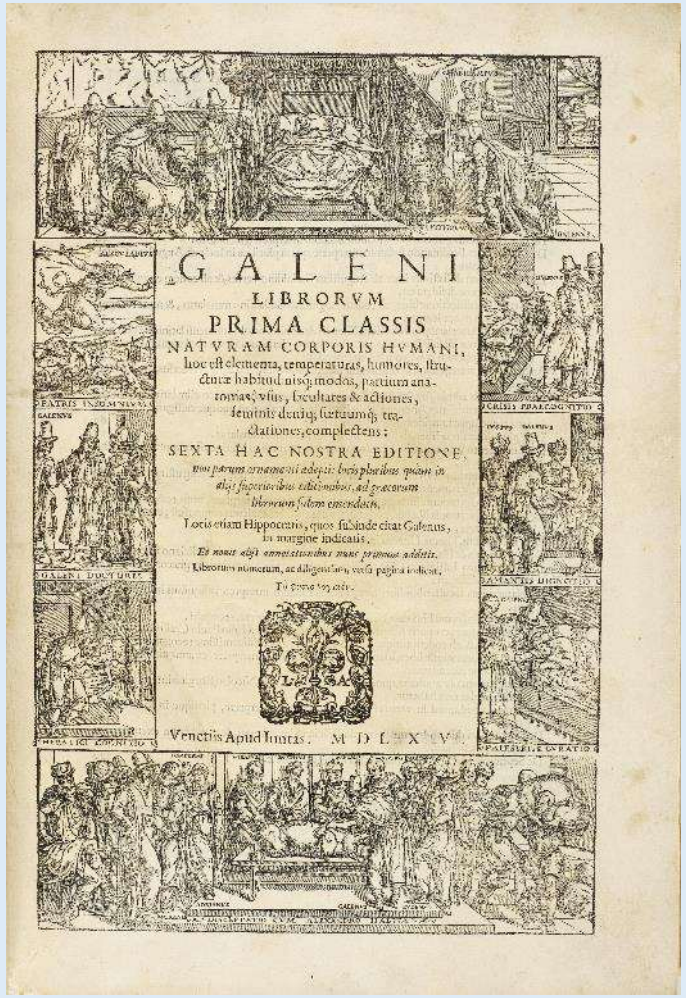
170 AD: Galen Breast Cancer View Based on Humors

Saw breast cancer caused by an imbalance of humors and counseled conservatism.

Galen of Pergamon (c. 129–216 A.D.), one of the most influential physicians of antiquity, synthesized and expanded the Hippocratic tradition into a comprehensive medical system that dominated medicine for over 1,400 years. In his vast writings—including *De Tumoribus praeter Naturam* and *De Locis Affectis*—he classified cancers as "cold and dry" diseases caused by an excess or coagulation of black bile. This humoral imbalance, he argued, corrupted the blood and tissues, producing hard, immovable and painful growths. Like Hippocrates, Galen believed the breast was particularly vulnerable to such accumulation because of its rich venous network and its role in menstruation and lactation, processes linked to the movement of humors in women's bodies. He described breast cancer as a paradigmatic example of a systemic disorder that manifested locally, with veins spreading from the tumor like the legs of a crab.

Galen's approach to treatment combined humoral correction with cautious surgical and medical management. He advised that early, "incipient" cancers might be treated by purging the body of black bile—using dietary regimens, purgatives (especially hellebore) and bloodletting—along with topical soothing agents. However, once the disease advanced, forming hard, fixed tumors or ulcerations, he considered it largely incurable. In such cases, surgery was discouraged because removing the tumor could "awaken" the underlying humoral imbalance, causing rapid recurrence or death. Thus, Galen's influence perpetuated a conservative, anti-operative stance toward advanced breast cancer that shaped medical attitudes well into the Renaissance. His authority on the subject was so immense that for centuries, physicians approached cancer not as a local lesion to be excised, but as a systemic imbalance to be moderated—a view only overturned in the modern surgical and pathological revolutions of the 18th and 19th centuries.

References: Ades (2017), Du Moulin (1993, p. 10), Ekmektzoglou (2009), Freeman (2018), Hajdu (2011a), Krivatsy 4493, Lakhtakia (2014), Lukong (2017), Mukherjee (2002), Olson (2002, p. 13), Yarris and Hunter (2003).



Claudius Galenus *Librorum prima clasis naturam corporis humani*.... Venice: Guinta, *1565-1597*.

250 AD: Leonidas and Aetius of Amida

The first written human description of a mastectomy for breast cancer.

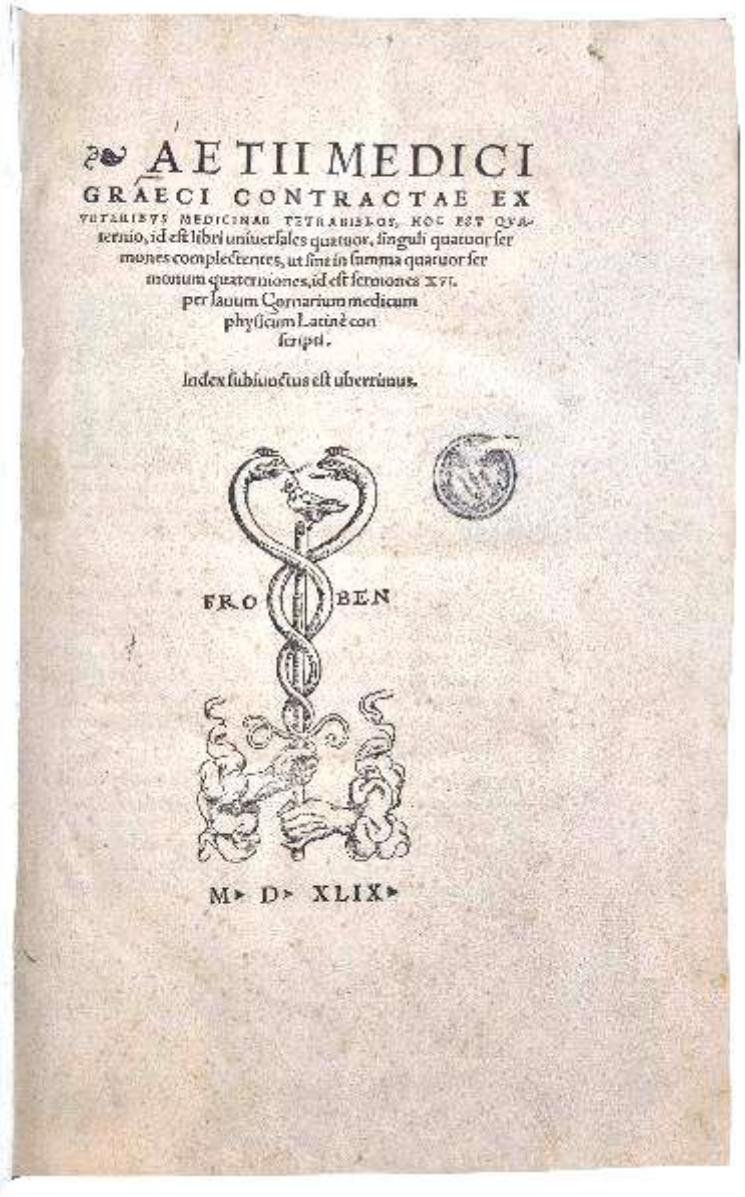
Leonidas, a doctor working probably in the 2nd or 3rd century AD, says that his operation of a breast cancer patient went as follows. First, the patient was positioned lying down on her back on the operating table. Then, when the appropriate preparations had been made, he made an incision into the breast directly above the cancer and immediately cauterised the wound.

When the bleeding from this incision stopped and a scab appeared, Leonidas then made a new, deep incision into the breast and proceeded slowly, cutting and cauterising, each time waiting for the bleeding to stop before making a fresh incision. This slow method of surgery was designed to avoid hemorrhaging. Once the relevant part of the breast had been cut off, Leonidas then burned the whole area until it was dry.

There is no surviving work written by Leonidas. However, Aetius of Amida, reproduced his experience in treating breast cancer (see Aëtius, *Libri medicinales* 16.45).

Aëtius of Amida, the 6th-century Byzantine physician, based his work on breast cancer on earlier physicians like Archigenes and Leonidas. He described it as the most common cancer, likely occurring after menopause and noted it was most frequent in large, fleshy female breasts. His work included differentiating between ulcerated and non-ulcerated tumors and acknowledging that breast cancer was rare in men. He also described a cancer localized to the nipple with a better prognosis and provided detailed surgical methods, often combining excision with cauterization, for treatment.

References: Du Moulin (1993, p. 13), Durling 48, Ekmektzoglou (2009), Freeman (2018), Heirs of Hippocrates, 49, Hajdu (2011a), Lakhtakia (2014), Olson (2002, p. 11).


AETII MEDICI
GRAECI CONTRACTAE EX
VETERIBVS MEDICINAE TETRABIBLOS, HOC EST QVA-
ternio, id est libri universales quatuor, singuli quatuor ser
mones complectentes, ut sint in summa quatuor ser
monum quaterniones, id est sermones XVI.
per Iauum Cornarium medicum
physicum Latinè con
scripti.
Index subiunctus est uberrimus.
FRO BEN
M▸ D▸ XLIX▸

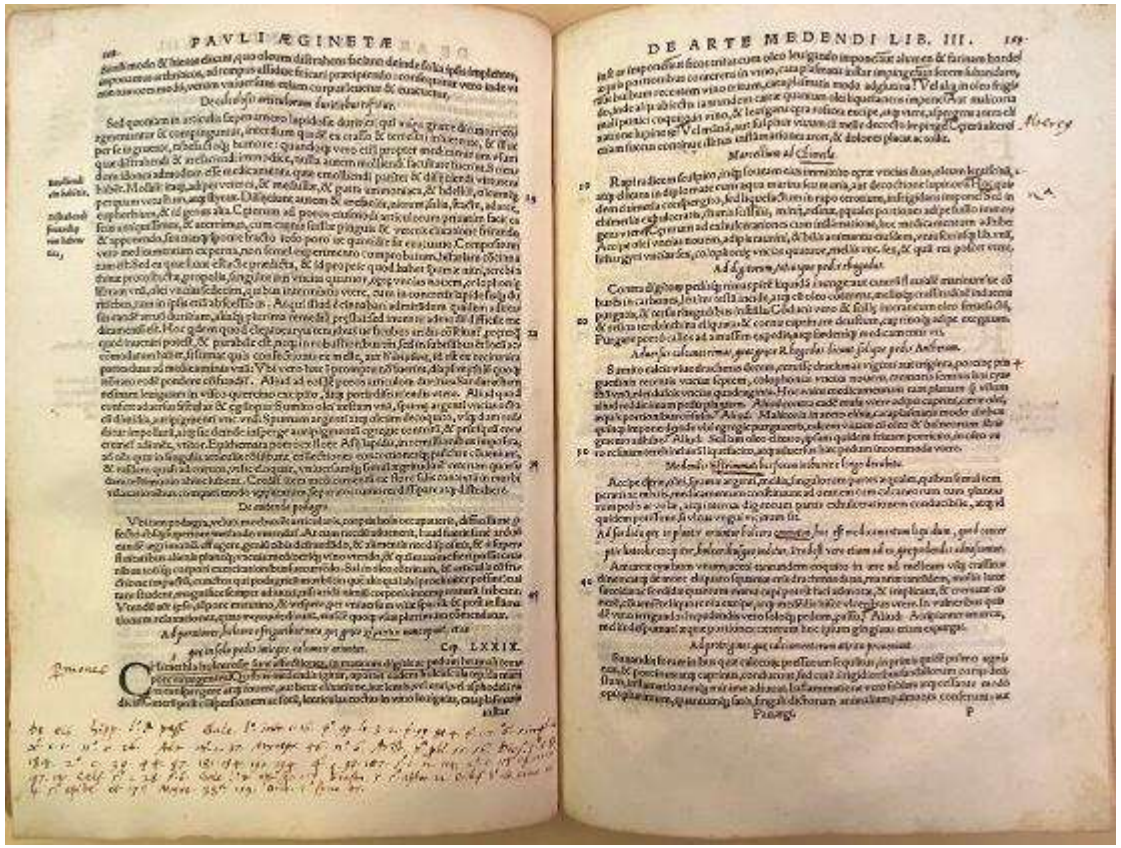
Aetius of Amida, 1549, Contractae ex veteribus medicinae tetrabiblos, hoc est quaternio, id est libri universales quatuor, singuli quatuor sermones complectentes, Basel: Froben. From the author's medical library.

660 AD: Paul of Aegina

Gave a detailed description of mastectomy for breast cancer.

"The extreme practicality of the text and its consequent use doubtless accounts for its rarity today. Its section on surgery, Book VI, has been called the principal medical work of the Byzantine era" (Stillwell, The awakening interest in science, 473).

Garrison-Morton-Norman (2025, #5549): Paul of Aegiina was the most famous physician and surgeon in the Byzantine Empire during the seventh century and probably thereafter. According to Eugene F. Rice, "Paulus Aegineta", Catalogus translationum et commentariorum IV (1980) p. 146, more codices of his works prior to the 13th century survived than any other Greek texts except the Bible and some patristic works, indicating that Paul's writings continued to be recopied and widely read. Paul gave original descriptions of lithotomy, trephining, tonsillectomy, paracentesis and amputation of the breast. The first clear description of the effects of lead poisoning also comes from him, indicating that lead poisoning was known in antiquity.



Aetius of Amida, 1549, Contractae ex veteribus medicinae tetrabiblos, hoc est quaternio, id est libri universales quatuor, singuli quatuor sermones complectentes, Basel: Froben. From the author's medical library.

References: Du Moulin (1993, p. 12), Ekmektzoglou (2009), GMN 5549, Olson (2002, p. 13), Ricci p. 196, Stillwell 473, Yan (2013).

990 AD: Abu al-Qasim al-Zahrawi (Albucasis)

Albucasis (Abu al-Qasim al-Zahrawi), born in Al-Andalus (Spain) in the 10th century, was a towering figure in the history of surgery and one of the earliest to describe operative management of breast cancer.

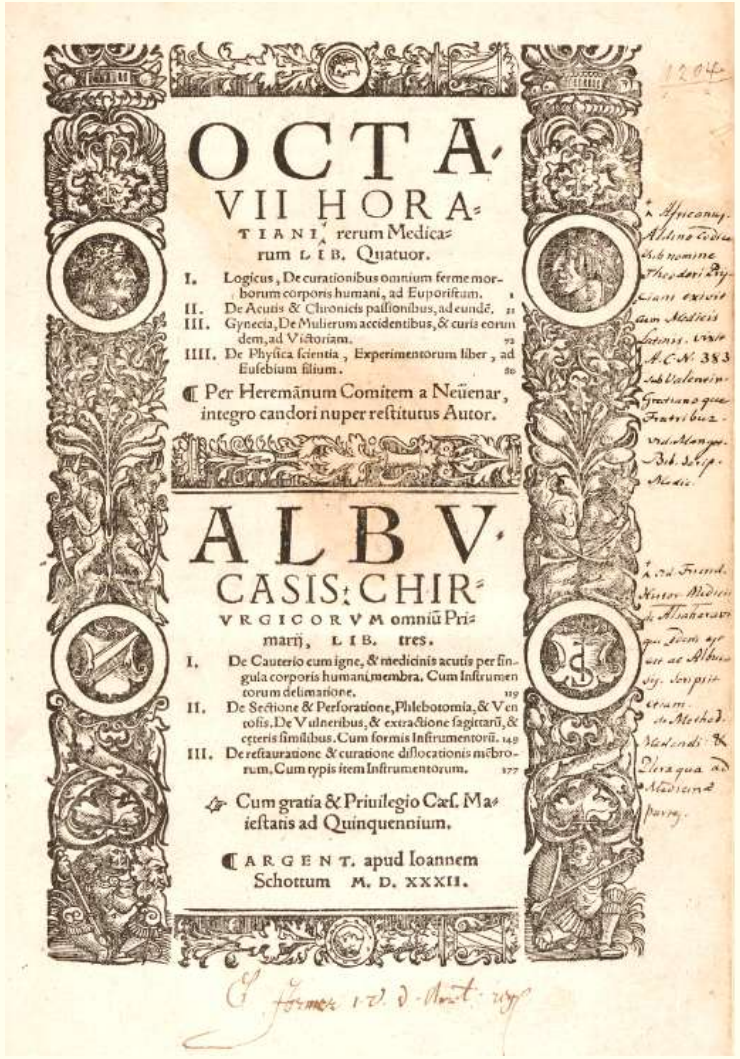
In his monumental work *Al-Tasrif*—known in Latin as *Cyrurgia*—he provided detailed observations on surgical techniques and principles that reflected a remarkable combination of practical skill and clinical prudence.

He recommended surgical removal of cancers of the breast and other organs but emphasized selectivity, advocating intervention only for small, superficial tumors that were amenable to complete excision. For larger or deep-seated cancers, he wisely counseled restraint, recognizing the limitations of contemporary surgery and the high risk of mortality.

Albucasis also provided one of the earliest systematic accounts of operative technique and hemostasis, recommending bloodletting before surgery to prepare the body and allowing blood to flow freely during the operation to cleanse the wound—resorting to cauterization only for severe hemorrhage. His reflections on surgical outcomes—distinguishing between operations that cure and those that kill—illustrate his deep awareness of surgical risk and ethical responsibility.

Through *Cyrurgia*, Albucasis laid the intellectual and procedural foundations of medieval surgery, influencing generations of European physicians from the 12th to the 17th century and marking an important milestone in the early understanding and treatment of breast cancer.

References: Ades (2017), Durling 3764, Ekmektzoglou (2009), Hajdu (2011a), Lakhtakia (2014), Stillwell 532.


OCTA-
VII HORA-
TIANI rerum Medica-
rum LIB. Quatuor.
I. Logicus, De curationibus omnium ferme mor-
borum corporis humani, ad Euporistum.
II. De Acutis & Chronicis passionibus, ad eundē.
III. Gynecia, De Mulierum accidentibus, & curis eorun
dem, ad Victoriam.
IIII. De Physica scientia, Experimentorum liber, ad
Eusebium filium.
Per Heremānum Comitem a Neüenar,
integro candori nuper restitutus Autor.
ALBV-
CASIS CHIR-
VRGICORVM omniū Pri-
marij, LIB. tres.
I. De Cauterio cum igne, & medicinis acutis per sin-
gula corporis humani membra. Cum Instrumen
torum delineatione.
II. De Sectione & Perforatione, Phlebotomia, & Ven
tosis, De Vulneribus, & extractione sagittarū, &
cęteris simílibus. Cum formis Instrumentorū.
III. De restauratione & curatione dislocationis mēbro-
rum. Cum typis item Instrumentorum.
Cum gratia & Priuilegio Cæs. Ma-
iestatis ad Quinquennium.
ARGENT. apud Ioannem
Schottum M. D. XXXII.

Theodorus Priscianus, 1532, Octavii Horatiani rerum medicarum libri quatuor . . . Albucasis chirurgicorum omnium primarii Strasbourg: Joannus Scotus.

1296 AD: Lanfranc of Milan

The first to describe how to distinguish benign enlargement of the breast and malignant cancer.

Lanfranc, originally named Guido Lanfranchi, was an Italian physician and surgeon from Milan who played a pivotal role in shaping the foundations of medieval surgical science. After being exiled from Italy for political reasons, he relocated first to Lyon and later to Paris in 1295, where he became one of the most influential medical teachers of his time.

He gained renown for his pioneering work on diseases of the breast, being the first to clearly describe how to differentiate benign enlargement from malignant cancer, a diagnostic insight far ahead of his era. He also cautioned surgeons against performing operations in anatomically complex regions such as the neck, anus and other areas dense with arteries, veins and nerves, recognizing the dangers of uncontrolled bleeding and nerve injury.

Lanfranc was a passionate advocate for the unity of medicine and surgery, insisting that no one could be a competent physician without knowledge of surgical practice, nor a skilled surgeon without understanding medical theory. His two major works, *Chirurgia Parva* (1290) and *Chirurgia Magna* (1296), were models of clarity and organization, reflecting his belief that surgery should be grounded in both theory and experience. The latter, *Chirurgia Magna*, became a standard reference for centuries, helping to elevate surgery from a manual craft to an academic discipline. Through his teaching and writings, Lanfranc established the intellectual framework that would define French surgery for generations to come, bridging the gap between the empirical and the scholarly traditions of medieval medicine.

References: De Moulin (1993), Durling 2725; GMN 5553 (1490 ed), Hajdu (2004), Hajdu (2011a), Sakofaras and Safioleas (2009), VD 16 L 250,

Lanfranc of Milan, 1525, *Kleyne Wundartznei, aus fürbit des wolerfarnen M. Gregorii Flüguß, durch Orthonem Brunfelß verteutscht.* Strassburg: Christian Egenolph. From the author's medical library.

1363 AD: Guy de Chauliac Introduced Surgical Realism

Guy de Chauliac (c. 1300–1368), often called the “Father of Medieval Surgery,” was a French physician whose monumental work *Chirurgia Magna* (completed around 1363) synthesized classical, Arabic and scholastic medical knowledge into a surgical manual that dominated Europe for centuries.

Deeply influenced by Hippocrates, Galen, Avicenna and Albucasis (Abulcasis), Guy de Chauliac understood breast cancer within the long humoral tradition—as a cold, dense and melancholy tumor arising from an excess of black bile in the blood. He described cancer mammae as a hard, painful swelling, often livid or dark in color, with projecting veins resembling the legs of a crab. He distinguished between occult (hidden) cancers, which had not yet ulcerated and ulcerated cancers, which were more dangerous and generally incurable.

In treatment, Chauliac advocated a cautious, stepwise approach that reflected the balance between Galenic theory and surgical realism. For early or “occult” cancers, he recommended dietary regulation and purgatives designed to reduce the melancholic humor, along with topical remedies such as cooling or emollient plasters (for example, made with lead, henbane, or camphor). For ulcerated or advanced cancers, he generally advised against surgery, believing that radical excision often hastened death—a direct echo of Celsus and Galen.

Nevertheless, when the tumor was small and well circumscribed, he permitted surgical removal “with the root,” followed by cauterization to prevent recurrence. Though rooted in humoral causation, Guy de Chaulliac combined theoretical restraint with practical surgical insight, bridging the gap between ancient doctrine and the empirical approaches that would emerge during the Renaissance.

References: Ades (2017), Du Moulin (1993, p. 25), Durling 2243, Häfner & Häfner (2019), Hajdu (2004), Hajdu (2011a), Hirsch-H. I, 894.

Key Reference: Chauliac, Guy de, 1598, *La grande chirurgie* (Laurent Joubert editor), Tournon: Claude Michel. From the author’s medical library.

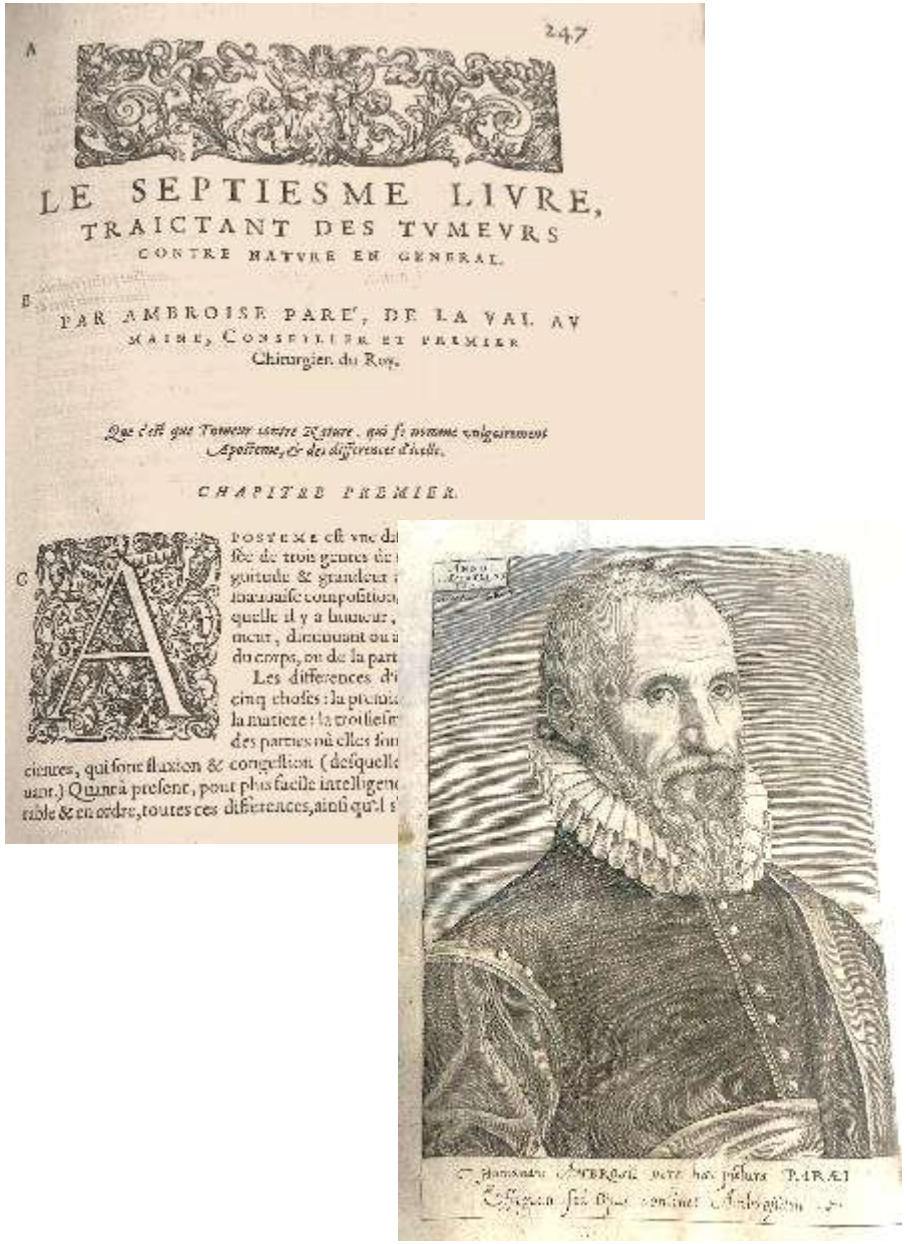
1575: Ambroise Paré

A Galenist, Pare saw breast tumors as “sluggish” and “cold”. He adopted topical treatments and superstitious ideas like putting animals on tumors.

Ambroise Paré (1510–1590), one of the most influential Renaissance surgeons, treated breast cancer within the traditional Galenic framework of humoral pathology. In his *Oeuvres complètes* (1575), under the section “Tumeurs contre nature,” Paré classified cancers among unnatural swellings caused by the corruption and thickening of humors—particularly black bile. Like earlier authorities such as Aëtius and Galen, he viewed scirrhous and cancerous growths as the result of sluggish, cold humors and prescribed conservative measures such as purging and topical treatments to balance these fluids. Paré adopted the use of mercury ointments for external cancers and, in severe ulcerated cases, even bizarre poultices such as freshly split young animals applied warm to the breast—a practice reflecting both Galenic “heat” theory and early modern superstition rather than empirical oncology. Malgaigne calls this “the first real surgical treatise since Guy de Chauliac; the latter was still writing under Arabian influence, while Paré brought in the new experimental spirit of the Renaissance“

Paré’s case histories reveal his humane temperament and restraint. In his account of Madame de Montigny, a lady-in-waiting who presented with a walnut-sized lump in her breast, Paré correctly diagnosed cancer but chose not to alarm her, treating instead with mild purgatives and local lead and mercury applications. When the patient turned to a quack promising a cure through irritant therapies, the tumor rapidly worsened and she died, prompting Paré’s ironic reflection that the physician had “cured her of all the ailments of this world.” Through such examples, Paré demonstrated both the limitations of sixteenth-century cancer medicine and an early sense of clinical ethics, tempering intervention with compassion and skepticism toward false cures.

References: Du Moulin (1993, p. 26), Durling 3520, Ekmektzoglou (2009), Garrison-Morton-Norman 5565, Olson (2002, p. 18), Sakofras and Safioleas (2010), Skuse (2015), Waller 7171; Wellcome I, 4819


247

LE SEPTIESME LIVRE,
TRAICTANT DES TVMEVRS
CONTRE NATVRE EN GENERAL.

PAR AMBROISE PARE', DE LA VAL AV
MAINE, CONSEILLER ET PREMIER
Chirurgien du Roy.

Que c'eſt que Tumeur contre Nature, qui ſe nomme vulgairement Apoſteme, & des differences d'icelle.

CHAPITRE PREMIER.

Ambroise Paré, 1575, *Les oeuvres…avec les figures & portraicts tant de l'anatomie que des instruments de chirurgie, & de plusieurs monstres*. Paris: Gabriel Buon. From the author’s medical library.

1600: Gabriele Falloppio

A Galenist, Falloppio attributed breast cancer to black bile and was cautious on surgical removal.

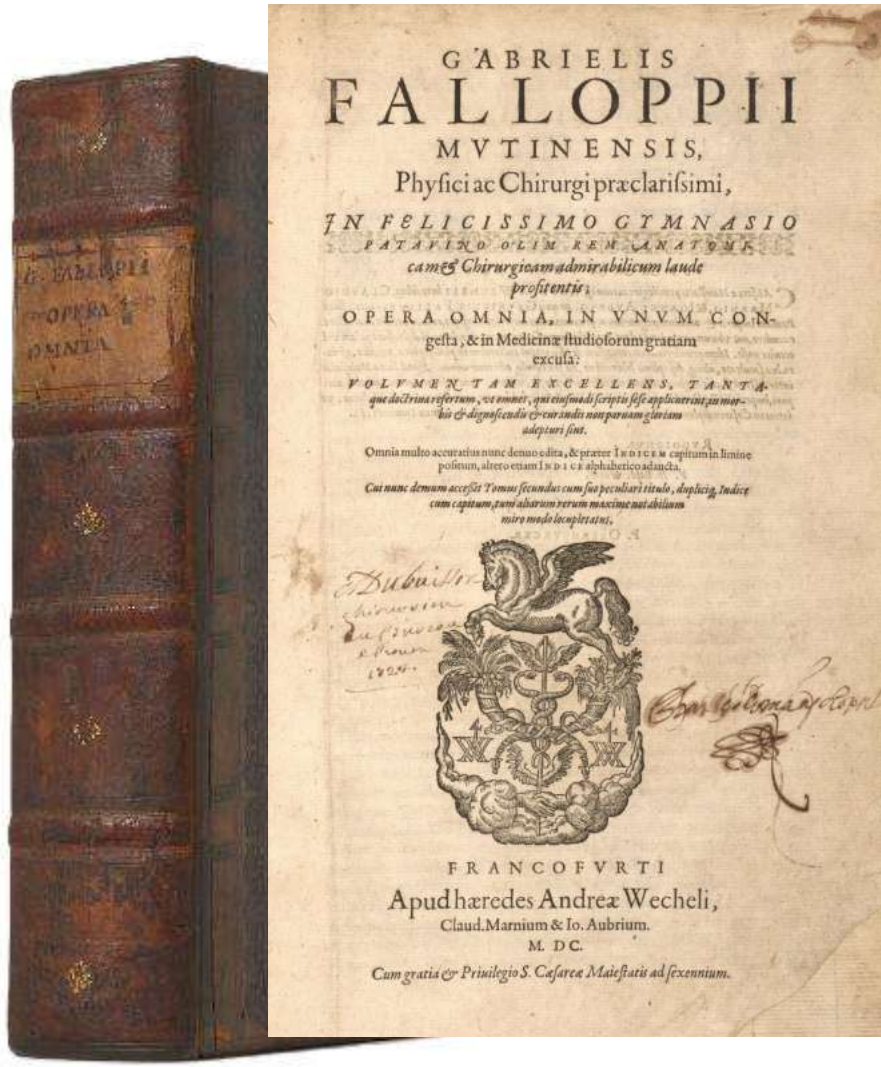
Gabriele Falloppio (1523-1562) is best known for his contributions to anatomy including the identification of the Fallopian Tubes.

He described tumors in the breast (then typically called “scirrhus” or hardened tumors) in his surgical treatises, though he did not develop a fully articulated pathological theory of breast cancer in the way modern medicine does.

His surgical tracts appeared only after his death. Edited by former students, they clearly bear the character of lectures. In his humoristic views on the genesis of malignant growths, Falloppio was a confirmed Galenist. He did accept the existence of two kinds of black bile, however, a natural and a non-natural species.

Non-natural bile did not originate in the liver as did the natural variety, but was a ‘combustion product’ of other humours as was already explained by Henri de Mondeville some three centuries earlier. In spite of the considerable lapse of time that separated them, Falloppio counted Henri de Mondeville among the ‘iuruores’, together with Guglielmo, Bruno, Teodorico, Guy and the like. These mediaeval surgeons probably owed their age-old juniority to the fact that after them no important new theories were proposed in the field of oncology.

References: Du Moulin (1993, p. 27.), Durling 1427 and 1428; Ekmektzoglou (2009), Waller 2939; Wellcome I, 2167


G. ABRIELIS
FALLOPPII
MVTINENSIS,
Phyſici ac Chirurgi præclariſſimi,
IN FELICISSIMO GYMNASIO
PATAVINO OLIM REM ANATOMI-
cam & Chirurgicam admirabilicum laude
profitentis,
OPERA OMNIA, IN VNVM CON-
geſta, & in Medicinæ ſtudioſorum gratiam
excuſa:
VOLVMEN TAM EXCELLENS, TANTA-
que doctrina refertum, vt omnes, qui eiuſmodi ſcriptis ſeſe applicuerint, ea mor-
bis & dignoſcendis & curandis non paruam gloriam
adepturi ſint.
Omnia multo accuratius nunc denuo edita, & præter INDICEM capitum in limine
poſitum, altero etiam INDICE alphabetico adiuncta.
Cui nunc demum acceſſit Tomus ſecundus cum ſua peculiari titulo, duplici, Indice
cum capitum, tum aliarum rerum maxime nec abſimum
miro modo locupletatus.
FRANCOFVRTI
Apud hæredes Andreæ Wecheli,
Claud. Marnium & Io. Aubrium.
M. DC.
Cum gratia & Priuilegio S. Cæſareæ Maieſtatis ad ſexennium.

Gabriele Falloppio, 1600-1606, *Opera Omni,* Frankfurt: Andreas Wechelus, C. Marnius & J. Aubrius, Two earlier single-volume collections of the author's works were published in 1584, but these two volumes with the appendix from a more complete edition. From the author’s medical library.

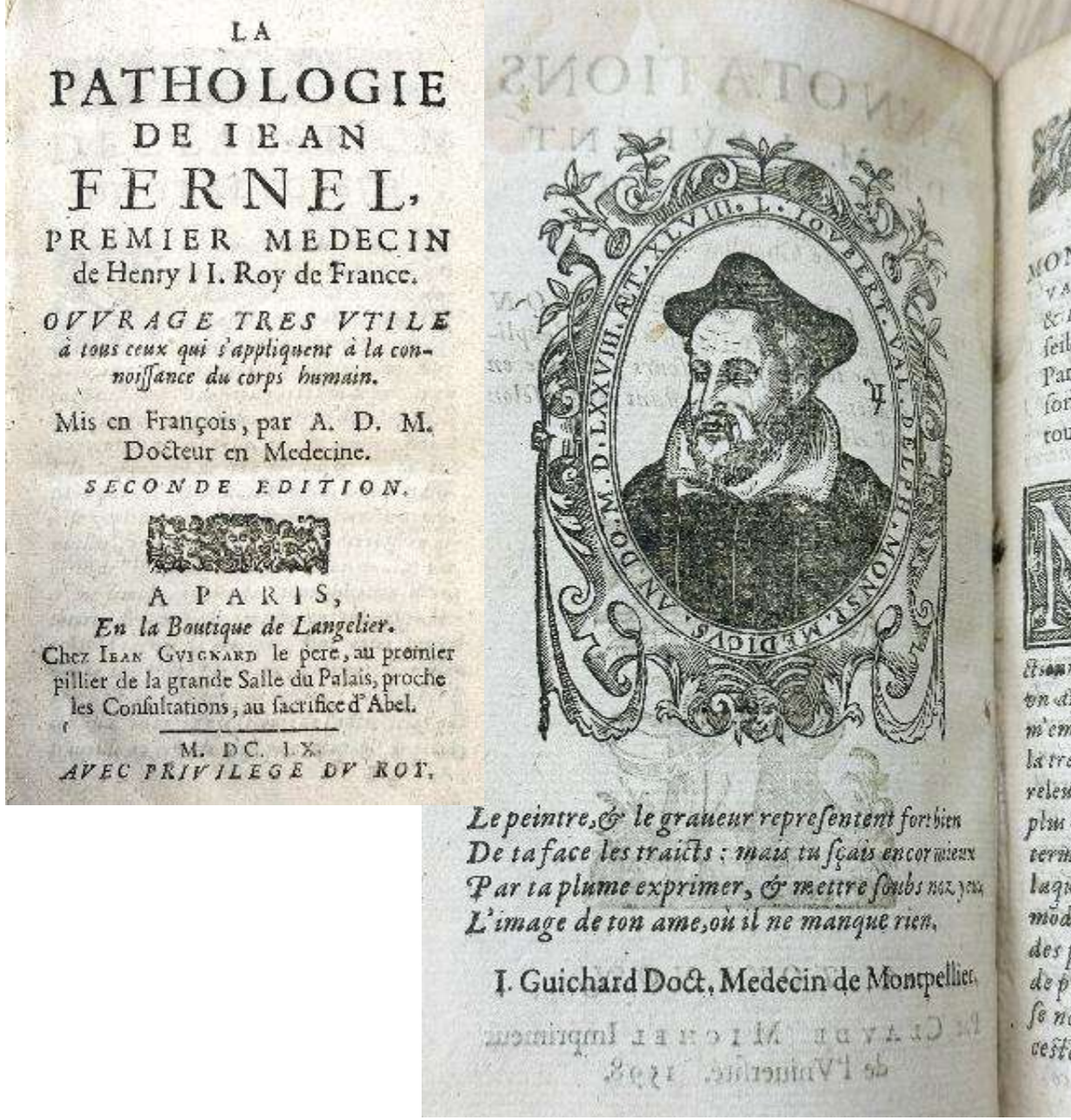
1609: Jean Fernel

Discusses carcinoma of the breast in detail.

Jean Fernel (1497–1558) was a towering figure of Renaissance medicine whose work profoundly shaped early modern understandings of disease, including breast cancer. In his seminal treatise *De Pathologia libri septem* Fernel sought to create a systematic science of disease that integrated classical Galenic theory with his own clinical observations. Within this framework, he described cancer of the breast (cancer mammae) as a chronic, hard and progressively painful swelling rooted in the accumulation and corruption of black bile (melancholia) within the tissues of the breast. He observed that the disease often began as a small, knot-like induration that eventually became ulcerated and destructive, spreading through neighboring structures.

Fernel's *Pathologia* also helped distinguish benign from malignant breast lesions, marking one of the earliest recognitions of differing biological behaviors within breast diseases. His writings described the "occult" (non-ulcerated) and "open" (ulcerated) forms of cancer, noting their incurability once the disease invaded deeply or spread systemically. While treatment recommendations remained grounded in humoral evacuation—dietary regulation, purgatives and occasionally surgical extirpation—Fernel emphasized caution, warning that surgery often accelerated death by "stirring" the malignant humor. His influence extended throughout the 16th and 17th centuries, shaping the conceptual vocabulary of cancer in physicians such as Riolan, Zacchia and later Boerhaave.

References: Borgen (2000), Brown (2022), Collins (2016), GMN 4457, Goodall (1951), Robinson (2016), Sakofras and Safioleas (2010).


LA
PATHOLOGIE
DE IEAN
FERNEL,
PREMIER MEDECIN
de Henry II. Roy de France.
OVVRAGE TRES VTILE
à tous ceux qui s'appliquent à la connoissance du corps humain.
Mis en François, par A. D. M.
Docteur en Medecine.
SECONDE EDITION.
A PARIS,
En la Boutique de Langelier.
Chez Iean Guignard le pere, au premier pillier de la grande Salle du Palais, proche les Consultations, au sacrifice d'Abel.
M. DC. IX.
AVEC PRIVILEGE DV ROY.
Le peintre, & le graueur repreſentent fort bien
De ta face les traicts : mais tu ſçais encor mieux
Par ta plume exprimer, & mettre ſoubs nos yeux
L'image de ton ame, où il ne manque rien.
I. Guichard Doct. Medecin de Montpellier.

Jean Fernel, 1609, *La Pathologie de Jean Fernel Premier Medicine de Henry II. Roy de France,* Paris: Boutique de Langlier, First edition. From the author's medical library.

1655: Johannes Scultetus

Advocated palpation and visual inspection for breast cancer diagnosis.

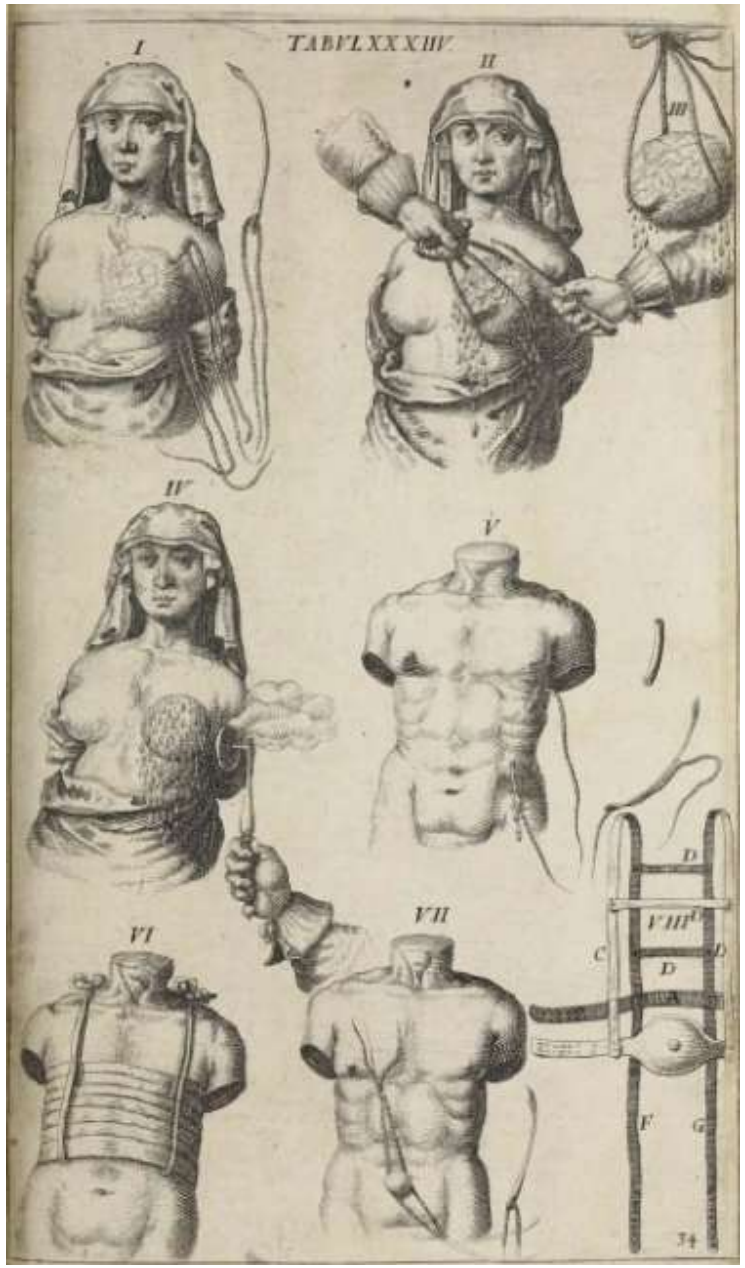
Johannes Scultetus (1595–1645), a German surgeon best known for his landmark work *Armamentarium Chirurgicum* (first published posthumously in 1655), made important early contributions to the understanding and surgical treatment of breast cancer.

A meticulous observer and gifted illustrator, Scultetus compiled one of the most comprehensive surgical manuals of the seventeenth century, richly illustrated with detailed woodcuts of instruments and operative techniques. In his sections on cancer mammae, he described the disease as a hard, painful tumor of the breast that often became ulcerated and emitted a foul odor—characteristics consistent with malignant progression. He stressed careful palpation and visual examination for diagnosis and noted the disease's tendency to recur after surgery, anticipating the later recognition of cancer's infiltrative nature.

His operative recommendations included complete excision of the affected breast, cauterization of the wound margins and the use of ligatures to control hemorrhage—practices that made his surgical methods safer than those of his contemporaries.

Beyond his surgical innovations, Scultetus' Armamentarium provided an anatomically precise and visually accessible foundation for subsequent generations of surgeons. While still working within a humoral framework—attributing breast cancer to corrupted black bile—Scultetus advanced the practical treatment of the disease by emphasizing early excision, cleanliness and wound management rather than speculative remedies.

References: De Moulin (1993, p. 27), Norman 1912; Heirs of Hippocrates 466; Garrison-Morton 5571; Krivatsy 10746; Mukherjee (2002), Skuse (2015), Waller 8792; VD 17, 39:153208L.



Johannes Sculetus, 1655, *Armamentarium Chirgicum*: Ulm: Balthasar Kühnen First edition.

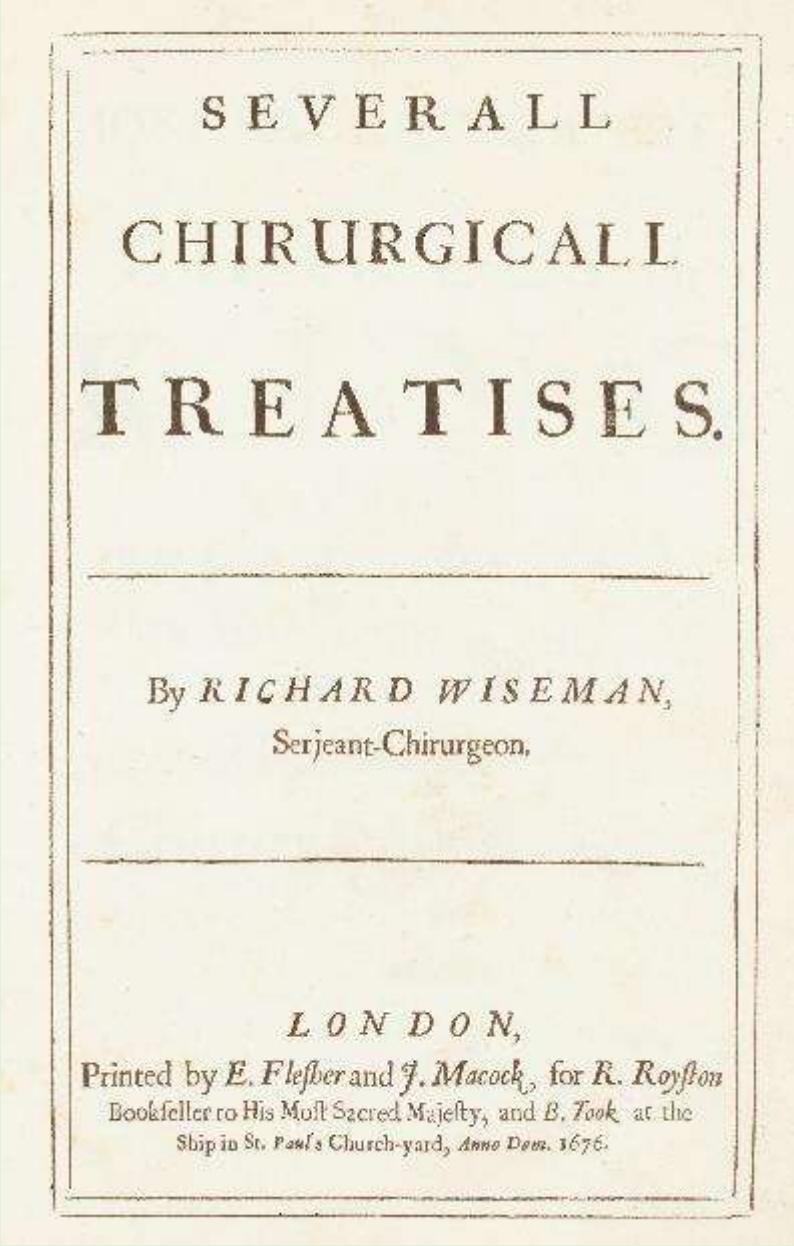
1676: Richard Wiseman

Practiced mastectomy and preferred only to operate on early breast cancers as his survival outcomes were not encouraging.

Daniel de Moulin, *A Short History of Breast Cancer* (p. 38): "The patient was usually considered cured as soon as her wound had healed. Very few surgeons reported on their late results. Richard Wiseman (1622–76), surgeon to King Charges II and the author of a very popular textbook, remarked that only two patients out of a series of twelve breast cancer cases were definitely cured by mastectomy. One of them was only 20 years old. Two others died after the operation, the eight others expired under conservative treatment."

Hayes Martin (Sep 1951, *Cancer*): "In surgery he cautions the operator "that the Patient be of a strong Constitution and of a tolerable good Habit of body and not in a declining age, when the Menstrua are ceased. Secondly, that the Cancer be loose and the Axilla free from painfull Glands." (Here he is obviously thinking of cancer as mainly a disease of the breast.) He advises that the operation be performed in the spring or autumn and not in the heat of summer or in the extreme cold of winter. He speaks of the preparation of the instruments and "compresses, restrictive Powders and Desensatives." Hemostasis was accomplished mainly by compress or button cautery. In discussing surgery of the breast, he describes how the operator places a "ligature about the basis [sic] of the cancerous Tumour" and then "pulls it to him with one hand while he cuts it off with the other." One cannot but be impressed by the courage of such surgeons and with the fortitude of the patients. In cancer of the breast, he employed mainly the scalpel after applying ligatures or sutures to pull the breast toward him (Fig. 4). The cautery was used to control hemorrhage. He must have been persuasive, for, so far as his records are concerned, only two patients refused operation in cancer of the breast after he had advised it."

References: De Moulin (1993, p. 38), Ekmektzoglou (2009), Skuse (2015).


SEVERALL

CHIRURGICALL

TREATISES.

By *RICHARD WISEMAN*,
Serjeant-Chirurgeon.

LONDON,
Printed by *E. Flesher* and *J. Macock*, for *R. Royston*
Bookseller to His Most Sacred Majesty, and *B. Took* at the
Ship in St. *Paul's* Church-yard, *Anno Dom.* 1676.

Richard Wiseman, 1676, *Severall Chichurgicall Treatises*, London: E. Fleber and J. Macock, First edition. From the author's medical library.

1685: Nicholas Tulp

Discusses scirrhus and carcinoma of the breast in detail. Incorrectly saw breast cancer as contagious.

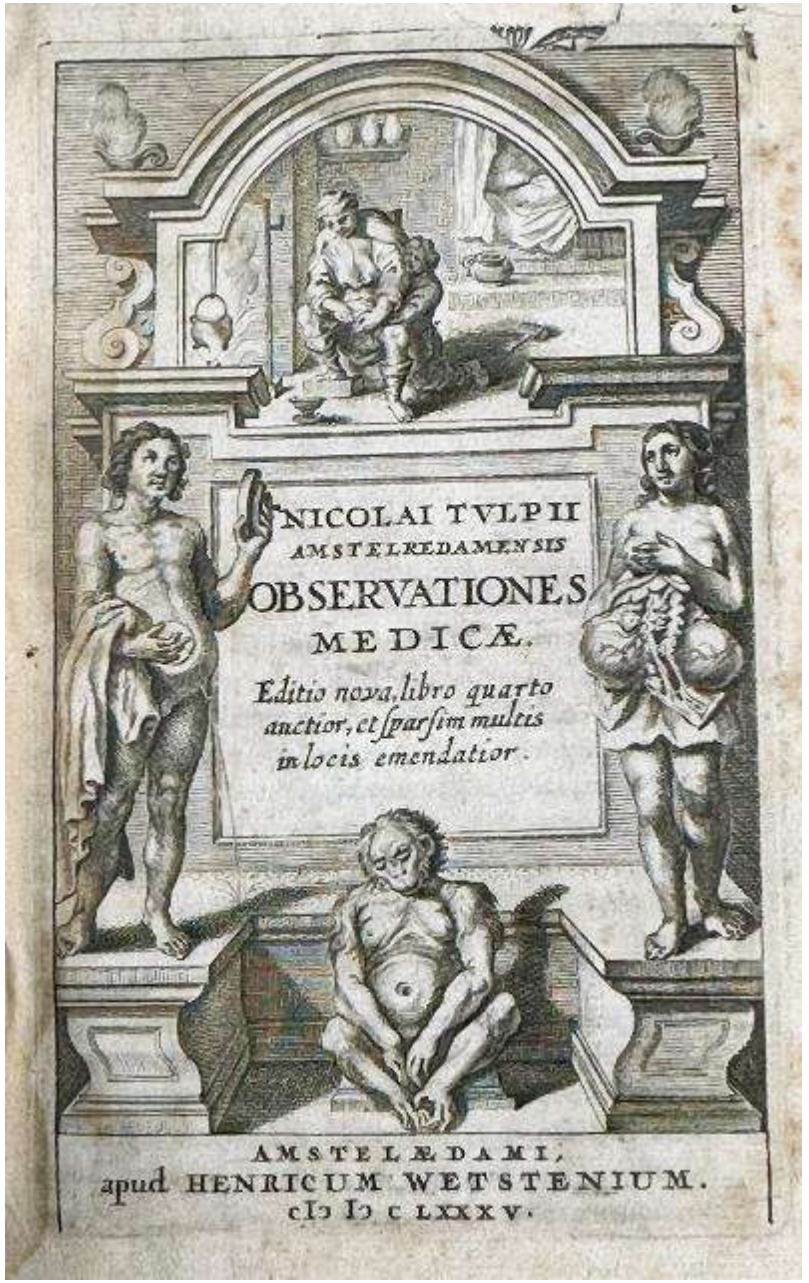
A question that would remain unsettled for quite some time to come concerned the possible contagiousness of cancer, of the ulcerating type in particular. Amongst those who considered the disease to be infectious was the Amsterdam physician and anatomist Nicholas Tulp (1593–1674), who was immortalized by Rembrandt in his famous 'Anatomical Lesson'.

In support of his view, Tulp cited the case of his patient Adriana Lamberta, an elderly lady suffering from open breast cancer, who was thought to have conveyed the disease to her housemaid.

Since scientific communications were mostly written in Latin at the time and medical books were slow to become obsolete, the misfortune of the two Amsterdam women served for a long time as a positive proof all over Europe. This illustrates how, even in the seventeenth and eighteenth centuries, a single observation could be accepted as conclusive evidence.

The history of scientific medicine is to no small extent a history of the handling of evidence. The belief in the contagiousness of cancer persisted until well into the nineteenth century in medical and legislative minds and even today traces of the old anxiety seem to linger amongst patients and their relatives. In the seventeenth and eighteenth centuries, cancer patients were not, in some places, admitted to public hospitals.

References: DuMoulin (1993, p. 33), Ekmektzoglou (2009), Sakofras and Safioleas (2010).



Nicholas Tulp, 1685, *Observationes medicae,* Amsterdam: H. Westenium, First edition. From the author's medical library.

1697: Jean-Adrien Helvetius

An early practitioner of breast cancer surgery and had some successes despite a lack of anesthesia and antisepsis.

Adrian Helvetius was a Dutch surgeon from the 17th century who performed lumpectomies and mastectomies for breast cancer, claiming surgery was a cure. He is associated with the "tenaculum helvetianum," a surgical instrument used in these operations and his work is documented in historical engravings and texts. See image at lower right.

While his surgeries were radical and risky, with a lack of anesthesia and antiseptics, some patients experienced a normal recovery and lived long lives after the procedure.

Daniel de Moulin (*A Short History of Breast Cancer*, p. 32): “Helvetius held the view that cancer begins with a drop of fluid coagulating within a gland. A ‘ferment’ would be influential in the further expansion of the process. The cause of the primordial coagulation he held to be in most cases some form of external trauma: a blow, a fall and the like.

In an early stage, the lesion could be made to dissolve by means of caustic chemicals; once the tumour had set hard it was better not to ‘irritate’ it with such remedies since the effect might be quite the opposite. He gave, however, no definition of the early stage. Helvetius was in favour of operative therapy: by excision when the lesion was still small, by amputation when the growth was extensive and in a state of ulceration.”

References: Androutsos (2011), De Moulin (1993, p. 32).

Jean-Adrien Helvetius, 1697, *Lettre sur la nature et la guérison du cancer. (in:) Traité des pertes de sang de quelque espéce qu'elles soient,* Paris: Laurent d'Houry, First edition.

1707: Pierre Dionis

Attributed breast cancer to stagnation of the lymphs and souring.

Pierre Dionis (1643–1718) was an outstanding Paris surgeon, whose anatomical and surgical lectures and demonstrations in the Jardin des Plantes attracted numerous attendants from all over Europe. He referred to three different authorities in explaining breast cancer. First, Jean-Baptiste Alliot, physician to the Bastille prison in Paris, held that scirrhus developed from black bile, but could contain some acid as well. Should this acid get the upper hand of the salt in the blood, scirrhus would turn into carcinoma.

Second, Claude-Deshais Gendron, personal physician to royalty, described malignant growth as 'nerve-like and gland-like parts' which had turned, together with lymph vessels, into an even, cold, homogenous mass in which the original elements are no longer recognizable. It spreads along 'filamens durs', which it sends into the adjoining parts. These solid protrusions are the real 'cancer roots', not the dilated veins of the ancients. Third, Adrian Helvetius (1661–1741) argued that cancer begins with a drop of fluid coagulating within a gland. A 'ferment' would be influential in the further expansion of the process.

Dionis was a follower of both Hoffman and Sylvius in attributing the origin of cancer to the stagnation of lymph in the breast, followed by inspissation and souring. Dionis accepted the ancient view of some sort of relation existing between the uterus and the breast, since most patients are between forty and sixty years old when they contract the disease.

References: DuMoulin (1993, p. 32), Ekmektzoglou (2009), Olson (2002, p. 159).


444 DES OPE'RATIONS DE CHIRURGIE,

FIG. XXVII. POUR LE MAMMELON.

DES OPERA-TIONS QU'ON

LEs mammelles qui font un des principaux or-nements de la femme, & qui ſont ſi néceſſai-s pour la nourriture de l'enfant, ne ſont pas plus emptes de maladies & ne ſont pas moins ſon-iſes à la main du Chirurgien que les autres par-s du corps, & il eſt ſouvent obligé d'y faire s opérations très-cruelles.

On diſtingue les maladies qui y arrivent & les érations qu'elles demandent, en deux; ſçavoir, celles du mammelon, & en celles de la mam-elle.

Le mammelon eſt cette éminence qui ſort du lieu de la mammelle, où abouriſſent tous les nduits lactez qui verſent le lait dans la bouche l'enfant. Quand le mammelon eſt trop petit, nfant a de la peine à le prendre & ne fait que hifoner; & s'il eſt trop gros, il emplit trop la iche de l'enfant qui ne peut point le ſucer: is pour le choiſir d'un volume médiocre & pro-tionné, il doit être de la groſſeur d'une noi-e & un peu plus long, afin que l'enfant le te-

Pierre Dionis, 1707, *Cours d'opérations de chirurgie, de démontrées au Jardin Royal,* Paris: Laurent d'Houry, First edition. From the author's medical library.

1720: Guillaume Houppeville

Wrote the first monograph solely on the topic of breast cancer that we are aware of.

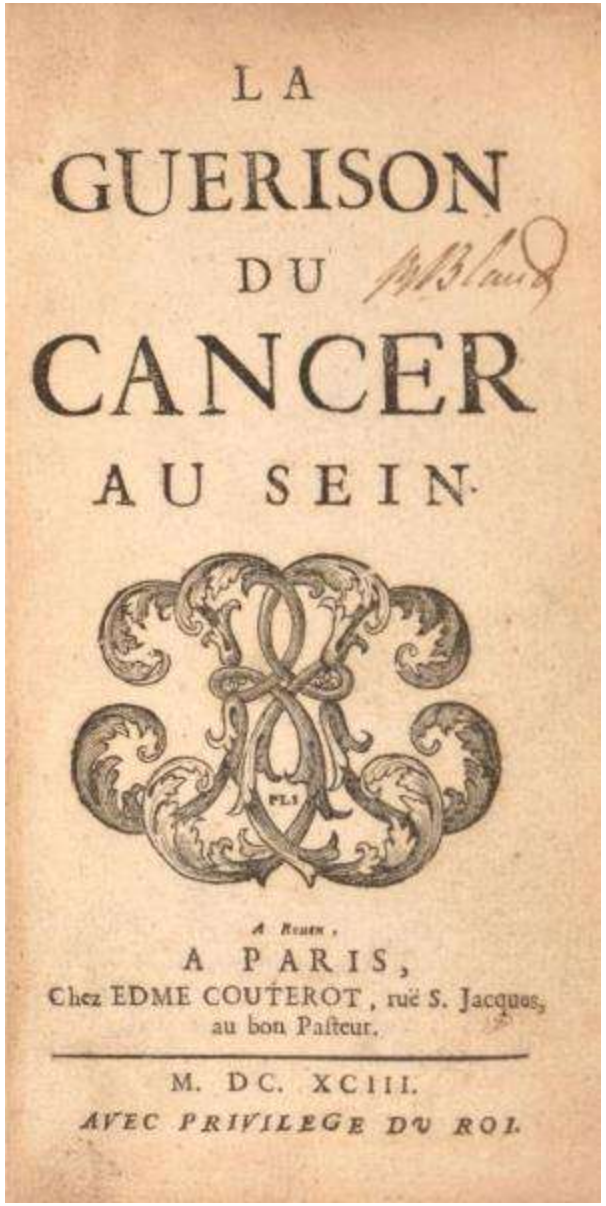
Guillaume Houppeville's *La Guérison du Cancer au Sein* (The Cure of Breast Cancer), published in Paris in 1720, is the earliest monograph devoted entirely to breast cancer that we can find.

Houppeville, a surgeon of Rouen, sought to bring clinical observation and practical treatment to what had long been considered an incurable and mysterious disease. His treatise discusses the visible and palpable signs of breast cancer, its progression and the characteristic hardness and pain that distinguished malignant tumors from benign swellings.

He also explored the emotional and physiological origins of the disease—often attributing it to "black bile" and melancholy—but combined this with firsthand surgical experience and an early appreciation of the disease's local invasiveness.

Houppeville outlined a therapeutic approach that included topical applications, cauterization and cautious surgical excision—methods reflecting both the limited tools of his era and a strikingly realistic understanding of cancer's tendency to recur. He emphasized the importance of early intervention before ulceration and metastasis and his tone was both compassionate and pragmatic.

References: Krivatsy 6078, Robinson (1986), Sakofras and Safioleas (2010).


LA
GUERISON
DU
CANCER
AU SEIN.
A Rouen,
A PARIS,
Chez EDME COUTEROT, ruë S. Jacques,
au bon Pasteur.
M. DC. XCIII.
AVEC PRIVILEGE DU ROI.

Guillaume Houppeville, 1720, *La Guerison du Cancer de Sein,* Paris: Edme Couterot, First edition. From the author's medical library.

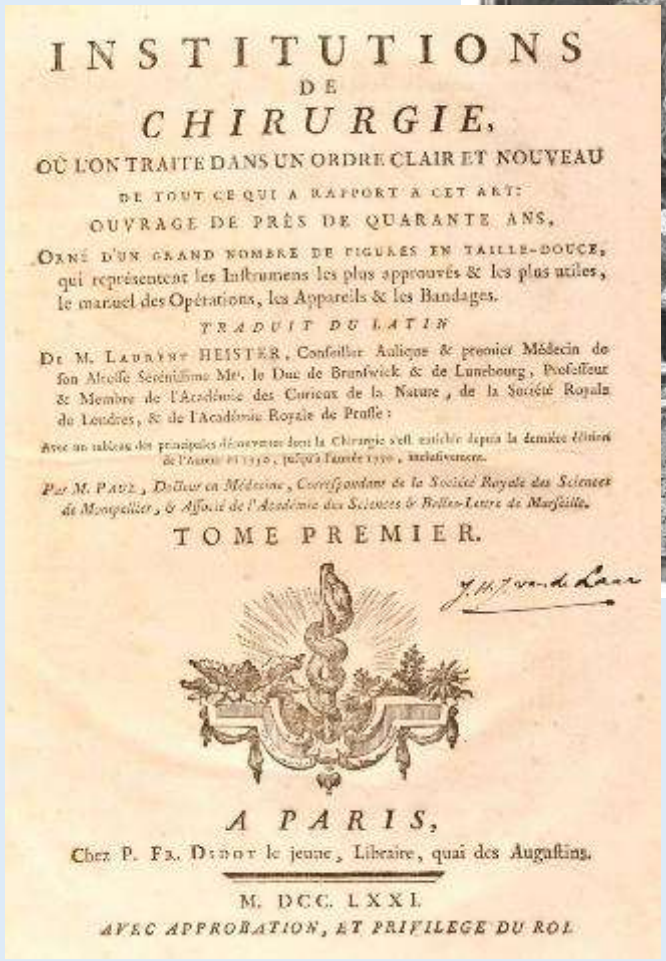
1739: Lorenz Heister

Practiced mastectomy with abysmally bad results.

Lorenz Heister (1683–1758), the eminent German anatomist and surgeon, addressed breast cancer extensively in his influential surgical texts, particularly in his Chirurgie (first published 1718, with later editions throughout the 18th century). Heister viewed breast cancer—cancer mammae—as one of the most formidable diseases known to surgeons. In line with the late Galenic and early Enlightenment medical thought, he described it as arising from the degeneration or coagulation of the melancholic humor, often beginning as a “scirrhus” (a hard, painful swelling) that might evolve into ulcerated cancer. He attributed the disease to depression and childlessness. He emphasized the typical clinical features of hardness, fixation, burning pain, dark discoloration and retraction of the nipple—symptoms that remained diagnostic hallmarks well into the nineteenth century. Heister was also one of the first modern authors to systematize breast cancer’s natural history, recognizing both “occult” (hidden, unbroken skin) and “ulcerated” forms.

Heister adopted a cautious yet surgical stance. While acknowledging that palliative measures—such as mild purgatives, topical emollients and narcotics—might ease pain, he maintained that radical excision offered the only hope of cure if the cancer were detected early and well-circumscribed. However, he warned that surgery performed too late, when glands or the axilla were involved, could hasten death. He insisted on removing not only the visible tumor but also surrounding tissue to minimize recurrence—a principle that foreshadowed later radical mastectomy.

References: de Moulin (1993, p. 41), Ekmektzoglou (2009), Lukong (2017), Olson (2002, p. 33).


INSTITUTIONS
DE
CHIRURGIE,
OÙ L'ON TRAITE DANS UN ORDRE CLAIR ET NOUVEAU
DE TOUT CE QUI A RAPPORT À CET ART:
OUVRAGE DE PRÈS DE QUARANTE ANS,
ORNÉ D'UN GRAND NOMBRE DE FIGURES EN TAILLE-DOUCE,
qui représentent les Instrumens les plus approuvés & les plus utiles,
le manuel des Opérations, les Appareils & les Bandages.
TRADUIT DU LATIN
DE M. LAURENT HEISTER, Conseiller Aulique & premier Médecin de
son Altesse Sérénissime Mr. le Duc de Brunswick & de Lunebourg, Professeur
& Membre de l'Académie des Curieux de la Nature, de la Société Royale
de Londres, & de l'Académie Royale de Prusse:
Avec un tableau des principales découvertes dont la Chirurgie s'est enrichie depuis la dernière édition
de l'Auteur, en 1750, jusqu'à l'année 1770, inclusivement.
Par M. PAUL, Docteur en Médecine, Correspondant de la Société Royale des Sciences
de Montpellier, & Associé de l'Académie des Sciences & Belles-Lettres de Marseille.
TOME PREMIER.
A PARIS,
Chez P. Fr. DIDOT le jeune, Libraire, quai des Augustins.
M. DCC. LXXI.
AVEC APPROBATION, ET PRIVILEGE DU ROI.

Lorenz Heister, 1739, *Institutions de Chirurgie (2 volumes),* Didot: Paris, First edition. From the author’s medical library.

1742: Henri-François Le Dran

Argued that breast cancer was local and not systemic, giving a rationale for the performance of radical mastectomy operations. He was the first to discard Galenic / humoral descriptions of the disease.

Henri François Le Dran (1685–1770) was one of the most influential 18th-century surgeons to challenge the long-standing Hippocratic and Galenic notion that breast cancer was a systemic or humoral disease caused by an imbalance of the bodily fluids.

Le Dran argued instead that cancer was initially a local organic disease, beginning in a specific part of the breast and only later spreading through the lymphatic system to adjacent structures such as the axillary glands. This concept—local origin followed by lymphatic dissemination—was revolutionary because it provided a rational surgical framework: if the tumor and the affected lymph nodes could be removed before dissemination, the disease might be cured. Le Dran therefore recommended early excision of the breast tumor together with the axillary nodes, laying the theoretical groundwork for modern oncologic surgery.

Le Dran's localist view directly contradicted the prevailing humoral doctrines and anticipated later 19th-century developments by William Halsted, whose radical mastectomy extended Le Dran's logic to include removal of the pectoral muscles and complete axillary clearance. While Le Dran lacked the histologic tools to confirm his theories, his staged model of cancer progression—from local lesion to nodal and then systemic spread—marked a decisive intellectual shift in cancer theory. His influence persisted for over a century, bridging pre-modern surgical empiricism and the scientific oncology of the modern era and his writings are among the earliest to justify lymphatic dissection as an essential part of breast cancer treatment.

References: Ben-Dror (2022), de Moulin (1993), Ekmektzoglou (2009), GMN 2607, Lukong (2017), Magnoni (2022), Olson (2022, p. 34).


MÉMOIRES
DE
L'ACADÉMIE ROYALE
DE CHIRURGIE.
MÉMOIRE
AVEC UN PRÉCIS
DE PLUSIEURS OBSERVATIONS
SUR LE CANCER.

Le Dran, Henri François , 1757, *Mémoire avec un précis de plusieurs observations sur le cancer. Mém. Acad. roy. Chir. (Paris), 3, 1-54,*. From the author's medical library.

1771: Guillaume Mauquest de la Motte

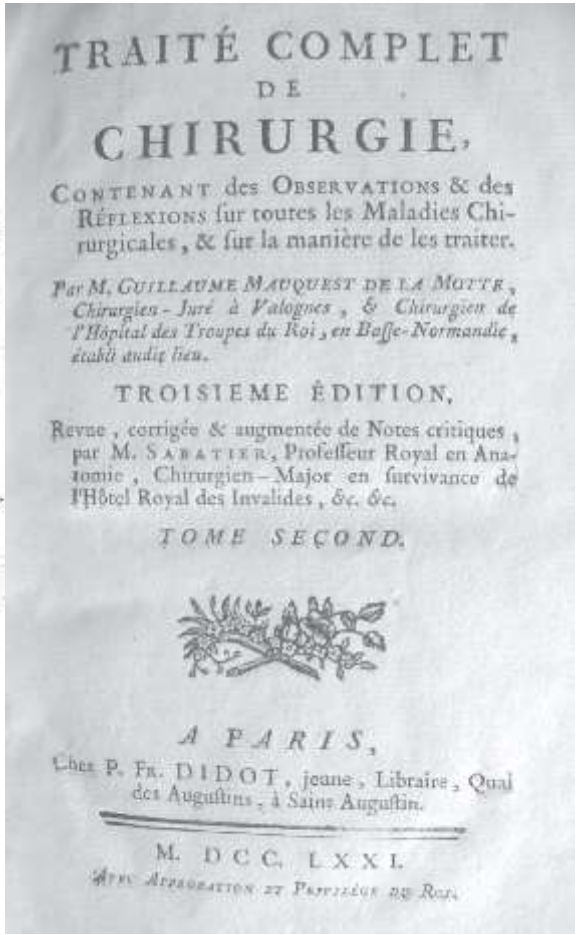
Gave a very detailed description of breast cancer in an era before pathological anatomy took hold. Recognized that breast cancer surgery was unlikely to succeed.

Guillaume Mauquest de La Motte (1655–1737) was one of the most respected French surgeons of the late seventeenth and early eighteenth centuries, whose *Traité complet de chirurgie* ("Complete Treatise on Surgery") was widely read across Europe.

La Motte devoted several chapters to diseases of the breast, especially cancer du sein (breast cancer), abcès du sein (breast abscess) and disorders associated with lactation. He offered one of the most clinically detailed and empirically grounded discussions of breast cancer before the rise of pathological anatomy. La Motte described breast cancer as a hard, irregular and often immovable tumor that gradually ulcerated and emitted a fetid discharge. He distinguished it from benign "scirrhous" swellings and mastitis, noting its tendency to recur even after surgical removal. While recognizing that surgery—usually radical excision of the breast—was sometimes necessary, he cautioned that such operations often led to swift relapse or death.

His writing influenced later figures such as Henri-François Le Dran and Jean-Louis Petit, who further developed the idea of cancer's local spread through lymphatics. Through his detailed case histories and pragmatic approach, La Motte helped move breast cancer surgery from speculative theory toward a more evidence-based and humane clinical practice.

References: De Moulin (1993), Hajdu (2012),


TRAITÉ COMPLET
DE
CHIRURGIE,
CONTENANT des OBSERVATIONS & des RÉFLEXIONS sur toutes les Maladies Chirurgicales, & sur la manière de les traiter.
Par M. GUILLAUME MAUQUEST DE LA MOTTE, Chirurgien-Juré à Valognes, & Chirurgien de l'Hôpital des Troupes du Roi, en Basse-Normandie, établi audit lieu.
TROISIEME ÉDITION,
Revue, corrigée & augmentée de Notes critiques, par M. SABATIER, Professeur Royal en Anatomie, Chirurgien-Major en survivance de l'Hôtel Royal des Invalides, &c. &c.
TOME SECOND.
A PARIS,
Chez P. Fr. DIDOT, jeune, Libraire, Quai des Augustins, à Saint Augustin.
M. DCC. LXXI.
AVEC APPROBATION ET PRIVILÈGE DU ROI.

Guillaume Mauquest de la Motte, 1771, *Traite Complet de chirurgerie,* Paris: Didot Jeune. From the author's medical library.

1784: Jean-Louis Petit

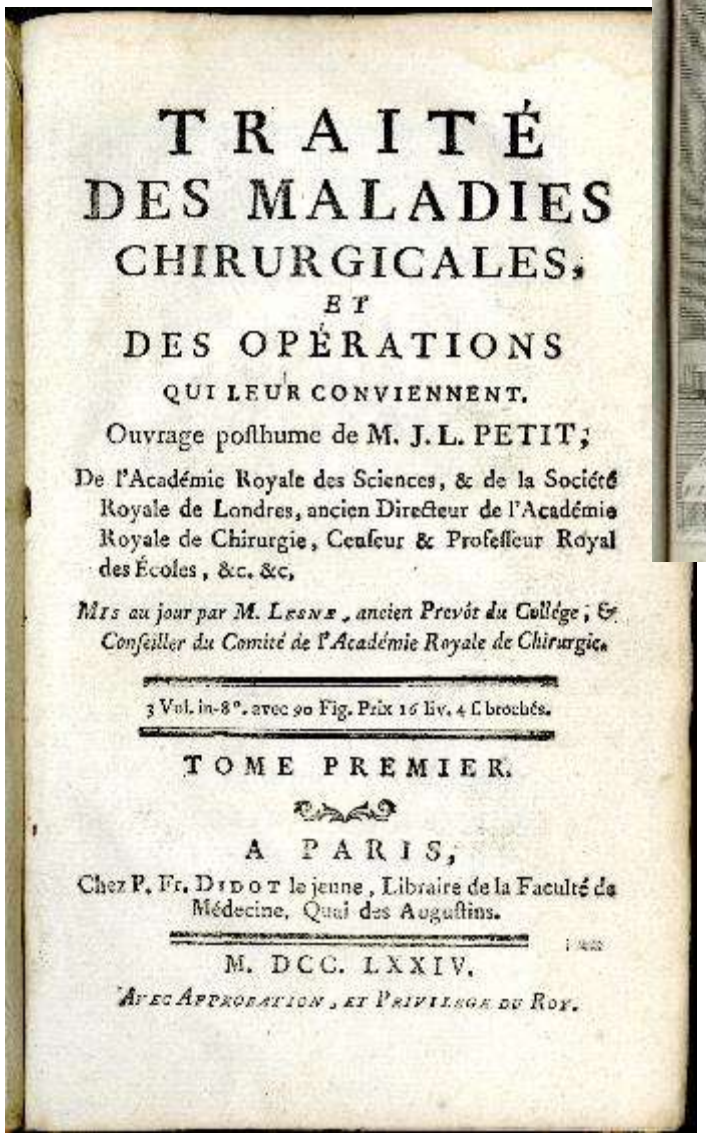
Highly conservative about operating on breast cancers.

Jean-Louis Petit (1674–1750), one of the most influential French surgeons of the eighteenth century, made foundational contributions to the surgical understanding and management of breast cancer through his posthumously published work Traité des Maladies Chirurgicales et des Opérations qui leur Conviennent (“Treatise on Surgical Diseases and the Operations Appropriate to Them”).

This text distilled Petit’s lifetime of clinical and anatomical experience, combining precise surgical reasoning with a deep concern for physiology and patient outcomes. In his chapters on cancer du sein, Petit offered one of the earliest scientifically reasoned analyses of breast cancer’s local spread, describing how the disease extended through the lymphatic vessels into regional nodes—a conceptual breakthrough that prefigured the lymphatic theory later articulated by Henri-François Le Dran.

Petit’s treatise also set new standards for surgical technique and operative caution. He advocated for complete excision of the tumor and surrounding tissues, including the axillary lymph nodes when involved, but insisted that surgery should be performed only when the cancer was localized and the patient strong enough to endure the procedure. His observations on recurrence led him to conclude that cancer was not merely a local lesion but a systemic disorder that surgery alone could not always cure. At the same time, Petit’s writings emphasized meticulous hemostasis—he invented the modern screw tourniquet—and gentle handling of tissues, innovations that made breast operations safer and more controlled.

References: De Moulin (1993), Ekmektzoglou (2009), Olson (2002).


TRAITÉ
DES MALADIES
CHIRURGICALES,
ET
DES OPÉRATIONS
QUI LEUR CONVIENNENT.
Ouvrage posthume de M. J. L. PETIT;
De l'Académie Royale des Sciences, & de la Société Royale de Londres, ancien Directeur de l'Académie Royale de Chirurgie, Censeur & Professeur Royal des Écoles, &c. &c.
Mis au jour par M. Lesne, ancien Prevôt du Collége; & Conseiller du Comité de l'Académie Royale de Chirurgie.
3 Vol. in-8°. avec 90 Fig. Prix 16 liv. 4 s. brochés.
TOME PREMIER.
A PARIS,
Chez P. Fr. Didot le jeune, Libraire de la Faculté de Médecine, Quai des Augustins.
M. DCC. LXXIV.
Avec Approbation, et Privilege du Roy.

Jean-Louis Petit, 1784, *Traité des Maladies Chirurgicales et des Opérations* Paris: P. Fr. Didot, First edition. From the author’s medical library.

1787: Paolo Mascagni

His studies of the lymph nodes helped to stimulate interest in lymph nodes as a mechanism of spread of breast cancer.

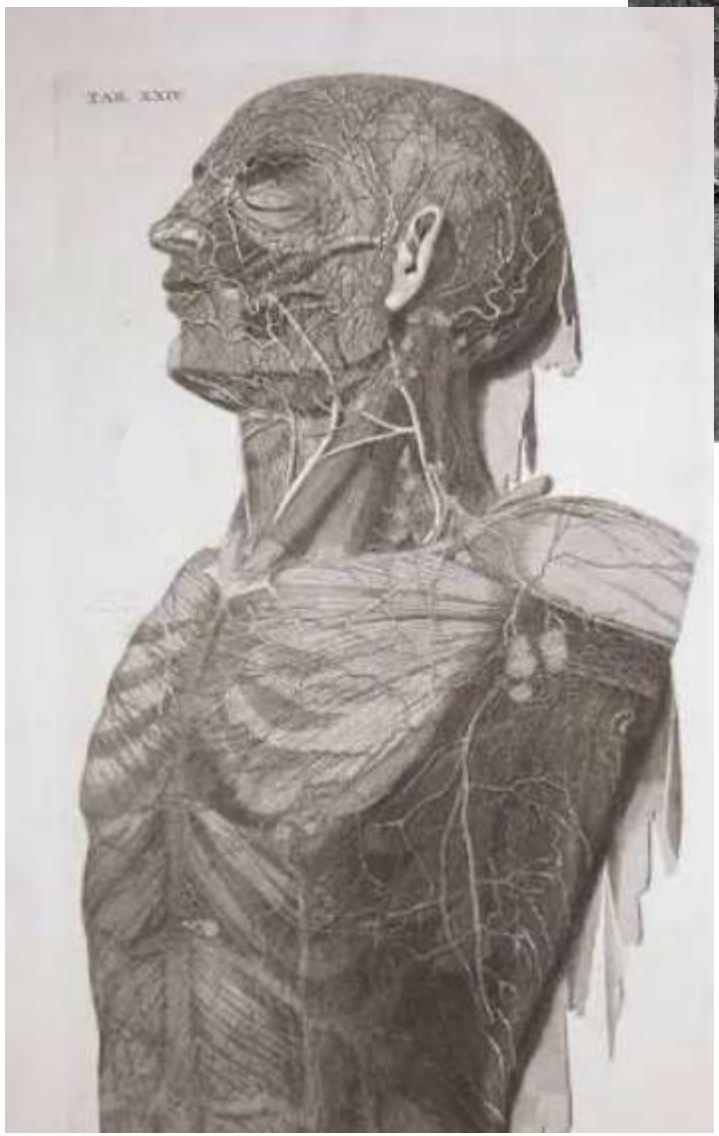
Mascagni was appointed professor of anatomy at the University of Siena at the age of 22; in 1787 he submitted to the *Academie des Sciences in Paris his Vasorum lymphaticorum corporis humani historia et ichnographia*.

This was a magnificent production, which gained him lasting fame and paved the way for progress in anatomy, physiology and clinical medicine, since half of the lymphatic vessels now known were discovered by him.

His extremely detailed discoveries of naked-eye anatomical distribution of the lymphatics could only be described through illustrations.

For this purpose Mascagni hired Ciro Santi, a painter and engraver from Bologna who lived in Sienna until about 1780. Santi prepared 27 drawings and engraved 27 spectacular copperplates and 16 key plates. These depict vessels in some of the finest detail present in anatomical illustration before the advent of photography.

Daniel de Moulin (A Short History of Breast Cancer p. 47): Mascagni's studies "probably incited by the current interest in lymph as a fluid matrix of cancer, did much to elucidate the lymph drainage system of the breast. This, in turn, promoted the theory of lymphatic dissemination."



Paulo Mascagni, 1787, *Vasorum lymphaticorum corporis humani historia et ichnographia,* Sienna: Pazzini Carli. First edition. From the author's medical library.

References: De Moulin (1993), Hajdu (2012),

1809: Samuel Cooper

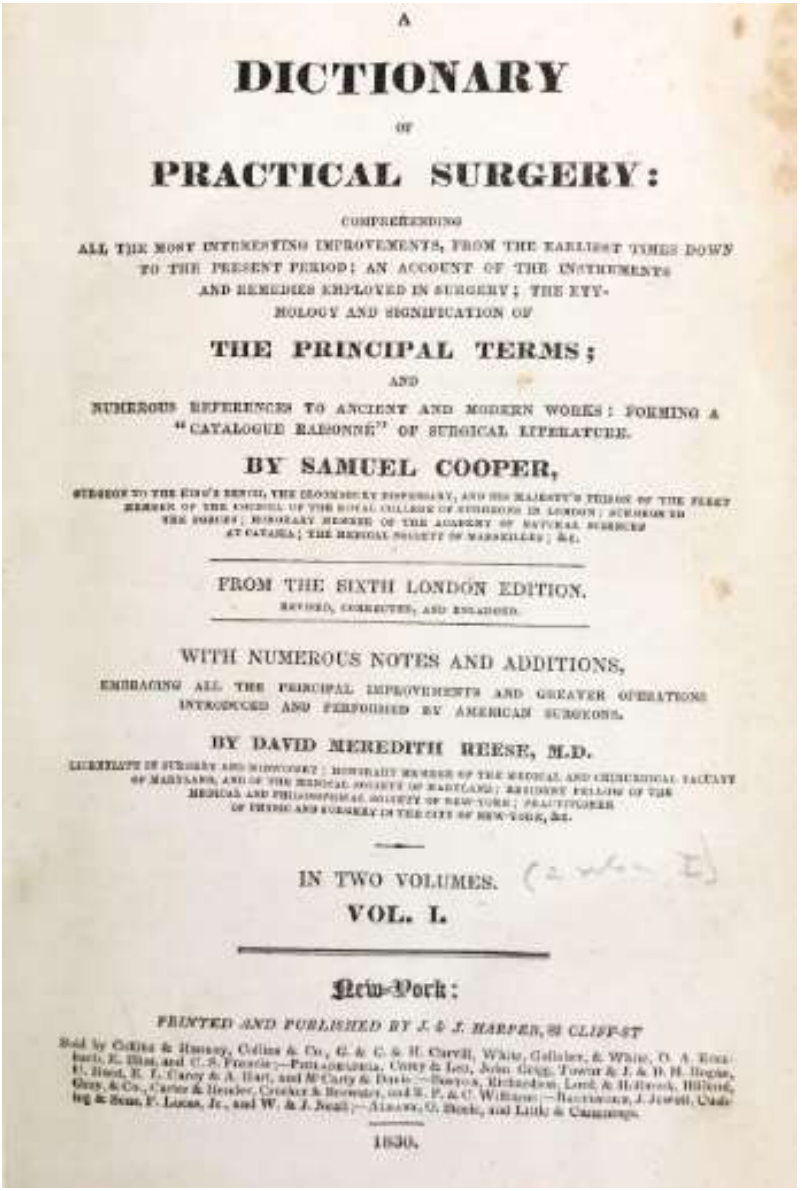
Standard surgical encyclopedia of early 19th century with good coverage on breast cancer surgery.

Samuel Cooper (1780–1848) was a British surgeon and medical writer whose A Dictionary of Practical Surgery (first published in 1809 and revised through multiple editions) became one of the most widely read and influential surgical reference works of the nineteenth century. He provided one of the clearest and most practical accounts of breast cancer ("cancer of the breast") then available.

Drawing on earlier authorities such as Le Dran, Petit and Heister as well as his own clinical observations, Cooper described breast cancer as a hard, painful and progressively ulcerating tumor, often beginning as a small nodule near the nipple and characterized by a tendency to invade surrounding tissues and regional lymph nodes. He carefully distinguished it from benign scirrhous tumors and chronic glandular swellings, helping general surgeons and students to make more accurate diagnoses at a time when pathology was still in its infancy.

He emphasized that extirpation (surgical removal) was the only potentially curative measure when performed early and completely, yet he warned that recurrence was common and that advanced cases should not be operated upon, as surgery might hasten death by aggravating the systemic nature of the disease. He provided instructions for mastectomy using ligature to avoid hemorrhage. He discussed palliative approaches—dietary modification, opiates, topical applications—and presented the disease in humane, unvarnished language that reflected his concern for the patient's suffering as much as for technical success.

References: De Moulin (1993).



A

DICTIONARY

OF

PRACTICAL SURGERY:

COMPREHENDING

ALL THE MOST INTERESTING IMPROVEMENTS, FROM THE EARLIEST TIMES DOWN TO THE PRESENT PERIOD; AN ACCOUNT OF THE INSTRUMENTS AND REMEDIES EMPLOYED IN SURGERY; THE ETYMOLOGY AND SIGNIFICATION OF

THE PRINCIPAL TERMS;

AND

NUMEROUS REFERENCES TO ANCIENT AND MODERN WORKS: FORMING A "CATALOGUE RAISONNÉ" OF SURGICAL LITERATURE.

BY SAMUEL COOPER,

FROM THE SIXTH LONDON EDITION.

REVISED, CORRECTED, AND ENLARGED.

WITH NUMEROUS NOTES AND ADDITIONS,

EMBRACING ALL THE PRINCIPAL IMPROVEMENTS AND GREATER OPERATIONS INTRODUCED AND PERFORMED BY AMERICAN SURGEONS.

BY DAVID MEREDITH REESE, M.D.

IN TWO VOLUMES.

VOL. I.

New-York:

PRINTED AND PUBLISHED BY J. & J. HARPER, 82 CLIFF-ST

1830.

Samuel Cooper, 1809-,A Dictionary of Practical Surgery: London, First edition. From the author's medical library.

1829: Joseph Claude Anthelme Récamier

Récamier was the first to recognize the process of metastasis. He also described for the first time invasion of veins by cancer.

Joseph Claude Anthelme Récamier (1774–1852) was a pioneering French physician and surgeon. His 1829 treatise, *Recherches sur le Traitement du Cancer*, represents one of the first systematic clinical investigations into cancer as a chronic and local disease rather than merely a fatal systemic affliction. Récamier carefully described the pathology, natural course and prognosis of cancers, introducing a tone of empirical precision and humane experimentation that helped redefine oncology as a clinical discipline.

Récamier's contribution lay in his advocacy of "méthode compressive"—the methodical use of graduated compression to treat tumors, especially those of the breast and lymphatic regions. He believed that sustained, uniform pressure could slow the vascular supply to cancerous tissue, leading to its atrophy or stabilization. This was an original attempt to manage cancer conservatively at a time when radical mastectomy was still crude and dangerous.

Récamier is perhaps most known for coining the term "métastase" to describe the spread of cancer from one organ to another, marking a turning point in medical understanding of cancer's systemic behavior. His insistence that metastasis occurred through the lymphatic and vascular systems anticipated the microscopic and pathological discoveries of Virchow and others later in the 19th century. In breast cancer, Récamier distinguished between scirrhous, encephaloid and ulcerated forms, correlating clinical features with stages of progression. He stressed early diagnosis, palliation and the moral care of the patient.

References: Androutsos (2011), De Moulin (1993), Ekmektzoglou (2009), Hajdu (2012), Garrison-Morton-Norman 2610

Joseph Claude Anthelme Récamier, 1829, *Recherches sur le traitement du cancer par la compression méthodique. 2 vols. Paris: Gabon, 1829.* First edition. From the author's medical library.

1831: James Syme

First to associate involved axillary nodes with a poor prognosis in breast cancer.

James Syme (1799-1870) was a prominent Scottish surgeon. In his System of Surgery (1831), the Scottish surgeon James Syme provides one of the most detailed early-nineteenth-century accounts of breast cancer—then called carcinoma or scirrhus of the mamma—and its management before anesthesia and antisepsis transformed operative practice.

Syme admits that the cause is often obscure. He considers the suppression of menstruation, emotional distress and systemic disturbances as predisposing or aggravating factors—reflecting the humoral and constitutional theories still current in early Victorian medicine.

Borgen (2000) wrote: “Syme's experience led him to believe that surgery should not be attempted for breast cancer because the result was almost uniformly unfavorable. Dr. John Brown, Syme's third surgical apprentice, published a moving description of the horrors of a mastectomy performed in the pre-anesthesia, pre-sterile technique era. His account, Rab and His Friends, provides insight into why virtually all patients died after surgery: sepsis. This is not surprising since, by Brown's account, the surgeon allowed the patient's beloved mastiff to remain in the operating theater during the surgery. Syme was opposed in his view by Dr. Joseph Lister (1827–1912) who believed that surgical extirpation of the disease represented the best hope of a cure. Moreover, he recognized that infection rather than breast cancer was responsible for the majority of surgical deaths. Syme and Lister argued about many issues in surgery and held each other in considerable contempt (it is worth noting that Syme's daughter Agnes, at the age of 24, married Joseph Lister).”

References: Borgen (2000), Brown (2022), Collins (2016), GMN 4457, Goodall (1951), Olson (2002, p. 47), Robinson (2016), Sakofras and Safioleas (2010).

James Syme, 1831, *The Principles of Surgery,* Longman: London, First edition. From the author’s medical library.

Syme: One of The First Practitioners of Mastectomy

While far from the first to describe mastectomy, Syme was one of the first to describe mastectomy in detail and routinely but reluctantly practice the operation in the early 1800s – well before Halsted.

Because internal or external medicines had "confessedly" failed, Syme declares surgery the only possible remedy. Palliative measures—leeches, hemlock poultices, soothing lotions and chloride of lime washes—could relieve pain or fetor but not cure. The knife, though controversial, offered the only chance of permanent relief. He stresses that success depends on careful case selection:

- No operation if the disease invades muscle, skin, or distant organs.
- A guarded prognosis if glands are already diseased or the cancer rapidly progressive.
- A more hopeful outlook if the tumor is circumscribed, slow-growing and confined to the breast of a relatively healthy patient, especially under forty or above sixty.

Syme gives a remarkably practical description of mastectomy, writing:

> "The operation is performed by making two semilunar incisions, one above and the other below the tumour, so as to include the nipple and the whole morbid mass, together with any portion of skin that may appear diseased, or be drawn inwards by the contraction of the tumour. "

He then describes removing any diseased skin or pectoral muscle and examining the axilla for affected glands. He advises clean dissection, careful hemostasis and closure with adhesive plaster. Recovery could be rapid if no relapse occurred. Though acknowledging that recurrence was common, he insists it is not universal and argues that "permanent recovery is not so hopeless as it has been represented." Even when secondary disease later appeared, this did not invalidate the attempt to remove the primary tumor; it merely showed the persistence of a constitutional predisposition. Thus, in Syme's view, surgery offered the only rational and sometimes successful path, provided it was done early, thoroughly and in suitable cases.

James Syme, Portrait from the Wellcome Collection. Reproduced in 1932 from a glass-plate negative.

1831: Jean-Baptiste Bourgery

A spectacular anatomical treatise that provided an idealized view of breast cancer surgery.

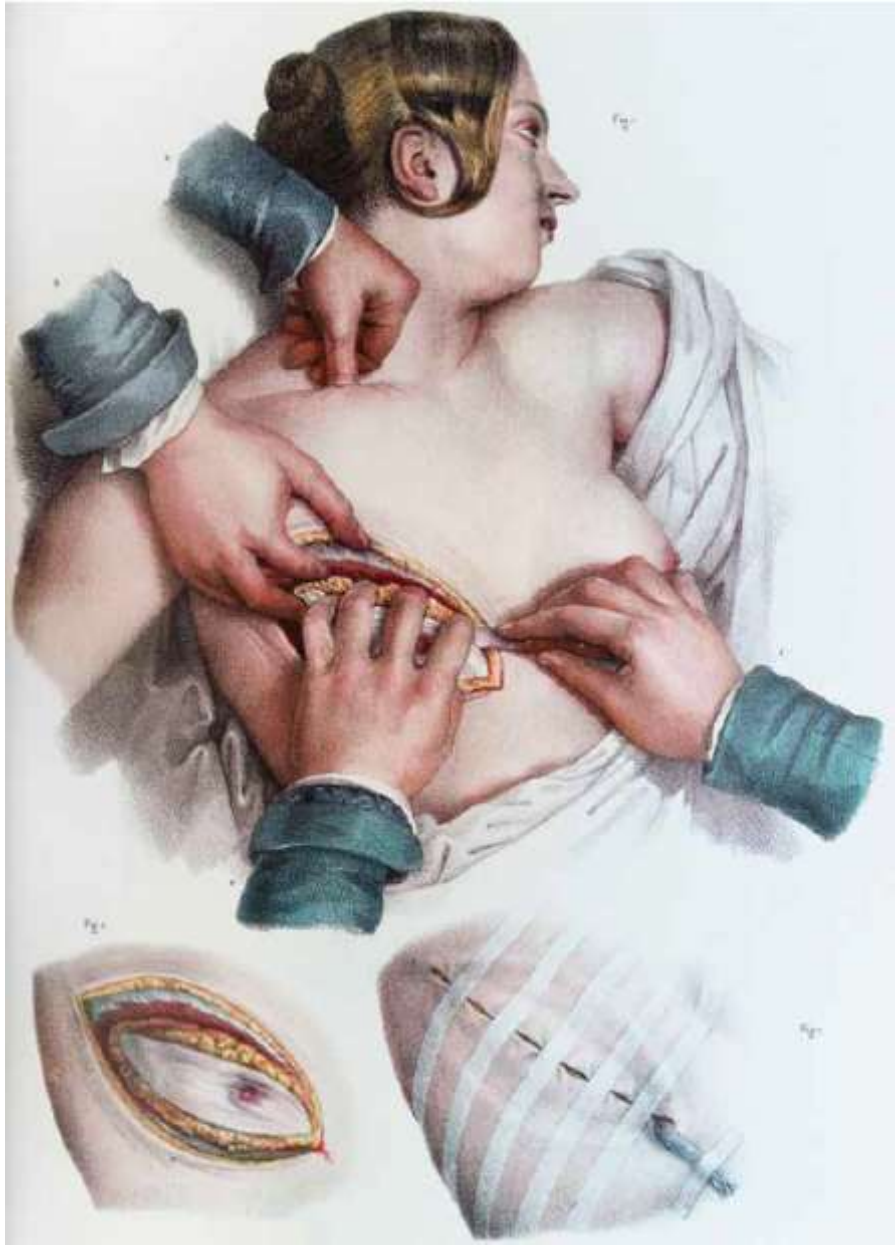
Jean-Baptiste-Marc Bourgery (1797–1849), the celebrated French anatomist and surgeon whose monumental work, Traité complet de l'anatomie de l'homme ("Complete Treatise on Human Anatomy"), first published in 1831, stands among the greatest achievements in medical illustration and anatomical science.

Bourgery's *Traité complet de l'anatomie de l'homme* was revolutionary for its integration of visual art, surgical precision and pathological relevance. His detailed plates of the female breast and thoracic region depicted the glandular structure, vascular supply and lymphatic drainage pathways with unprecedented clarity—crucial knowledge for surgeons attempting to perform mastectomies or manage axillary node disease.

By illustrating how the mammary lymphatics connected to the axillary and internal mammary nodes, Bourgery provided the anatomical foundation for the lymphatic theory of cancer spread, which underpinned 19th-century surgical oncology from Le Dran and Velpeau through to Halsted.

This work has been criticized in modern times for providing an overly idealized view of this difficult disease.

References: De Moulin (1993).



Jean-Baptiste Bourgery, 1831, *ATraite Complet de l'anatomie de l'homme comprenant la medicine operatoire, 1831-1854,* Paris: Delaunay, First edition. From the author's medical library.

1838: Johannes Peter Müller

Müller realized the necessity of the cell theory for the comprehension of the nature of cancer. He recognized cells, their nuclei and nucleoli and could distinguish various types of tumors microscopically.

Daniel de Moulin, *A Short History of Breast Cancer* (1993, p. 68): "Johannes Müller (1801–58) (Fig. 23), professor of anatomy and physiology in Berlin, may well be looked upon as the founder of cancer histology.

Müller was an exceptionally versatile scientist who introduced modern experimental physiology in Germany. Microscopic anatomy was receiving much attention in his department and it was probably no coincidence that, in the same year (1838), Theodor Schwann, who was working in Müller's department, described the animal cell and Müller himself published his treatise *Über den feinern Bau and die Formen der krankhaften Geschwülste*, which was to become a classic in the history of cancerology. He established that pathologic growth consists of cells, just like any other tissue. In contrast to normal structures, however, the natural proportions had disappeared. The elements of form of cancerous growths are analogous to those of the normal elements of form of the body itself, or correspond with 'embryonic formations', as he called them, i.e. parts of tissue which are in a state of development. Most prominent amongst the cellular constituents of malignant growths were 'kugelartige Zellen', vesicular cells, containing granules or a single somewhat bigger nucleus, or even entire young cells. These he looked upon as the actual 'seminium morbi'.

A second type of cellular elements consisted of 'tailed bodies', which Müller regarded as connective tissue cells in an early stage of maturation."

References: de Moulin (1993), GMN 2612, Lukong (2017), Olson (2002, p. 57).

Johannes Peter Müller, 1838, *Ueber den feinern Bau und die Formen der krankhaften Geschwülste. Lief. 1. Berlin: G. Reimer,*. First edition.

1845: Jean Carpentier-Méricourt

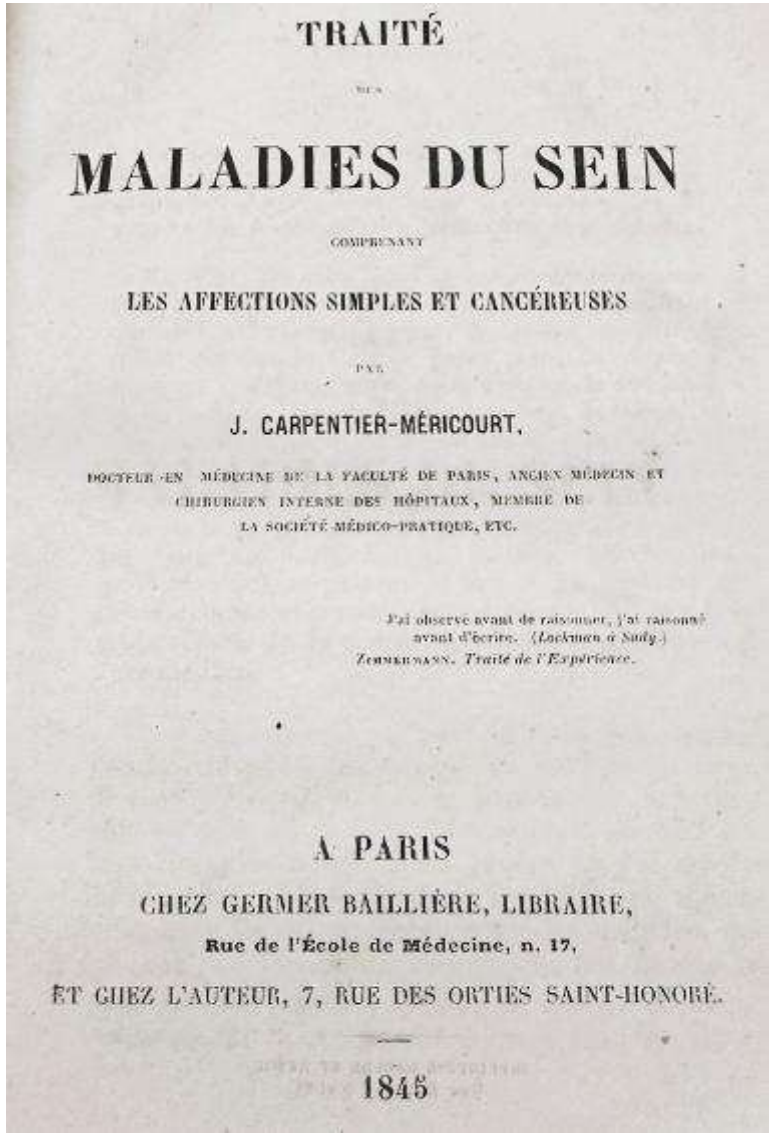
Advanced breast cancer surgery by describing how to manage hemorrhage and wound infection.

Jean Carpentier-Méricourt was a French physician and surgeon whose 1845 work, Traité des Maladies du Sein (“Treatise on the Diseases of the Breast”), represented one of the most detailed and methodical studies of breast pathology in the pre-microscopic era. Writing in Paris during a period when breast disease was still poorly differentiated clinically and pathologically, Carpentier-Méricourt sought to bring order and precision to the confusing terminology that surrounded tumors, abscesses and chronic inflammations of the breast.

His treatise systematically classified benign and malignant breast lesions, described their clinical evolution, texture and surgical appearance and analyzed their relation to age, reproductive history and trauma. He emphasized the importance of early recognition of carcinoma, distinguishing it from chronic mastitis and scirrhous induration and described in careful anatomical detail the involvement of the skin, nipple and axillary nodes.

Carpentier-Méricourt’s Traité also offered a comprehensive survey of surgical management and postoperative care before the antiseptic revolution. He discussed various forms of mastectomy then in use—partial, total and regional—arguing that the extent of excision should match the perceived spread of disease and recommending careful management of hemorrhage and wound infection. Carpentier-Méricourt’s 1845 treatise marks an important transitional text—bridging the descriptive empiricism of the 18th century with the emerging pathological and surgical rationalism that would define 19th-century breast cancer science.

References:


TRAITÉ

DES

MALADIES DU SEIN

COMPRENANT

LES AFFECTIONS SIMPLES ET CANCÉREUSES

PAR

J. CARPENTIER-MÉRICOURT,

DOCTEUR EN MÉDECINE DE LA FACULTÉ DE PARIS, ANCIEN MÉDECIN ET CHIRURGIEN INTERNE DES HÔPITAUX, MEMBRE DE LA SOCIÉTÉ MÉDICO-PRATIQUE, ETC.

J'ai observé avant de raisonner, j'ai raisonné avant d'écrire. (Lockmann à Sully.)
ZIMMERMANN. *Traité de l'Expérience.*

A PARIS

CHEZ GERMER BAILLIÈRE, LIBRAIRE,

Rue de l'École de Médecine, n. 17.

ET CHEZ L'AUTEUR, 7, RUE DES ORTIES SAINT-HONORÉ.

1845

Jean Carpentier-Méricourt, 1845-, *Tradte de Maldies du Sein,* Paris: Bailliere. First edition. From the author’s medical library.

1850: Alexandre Esquirou

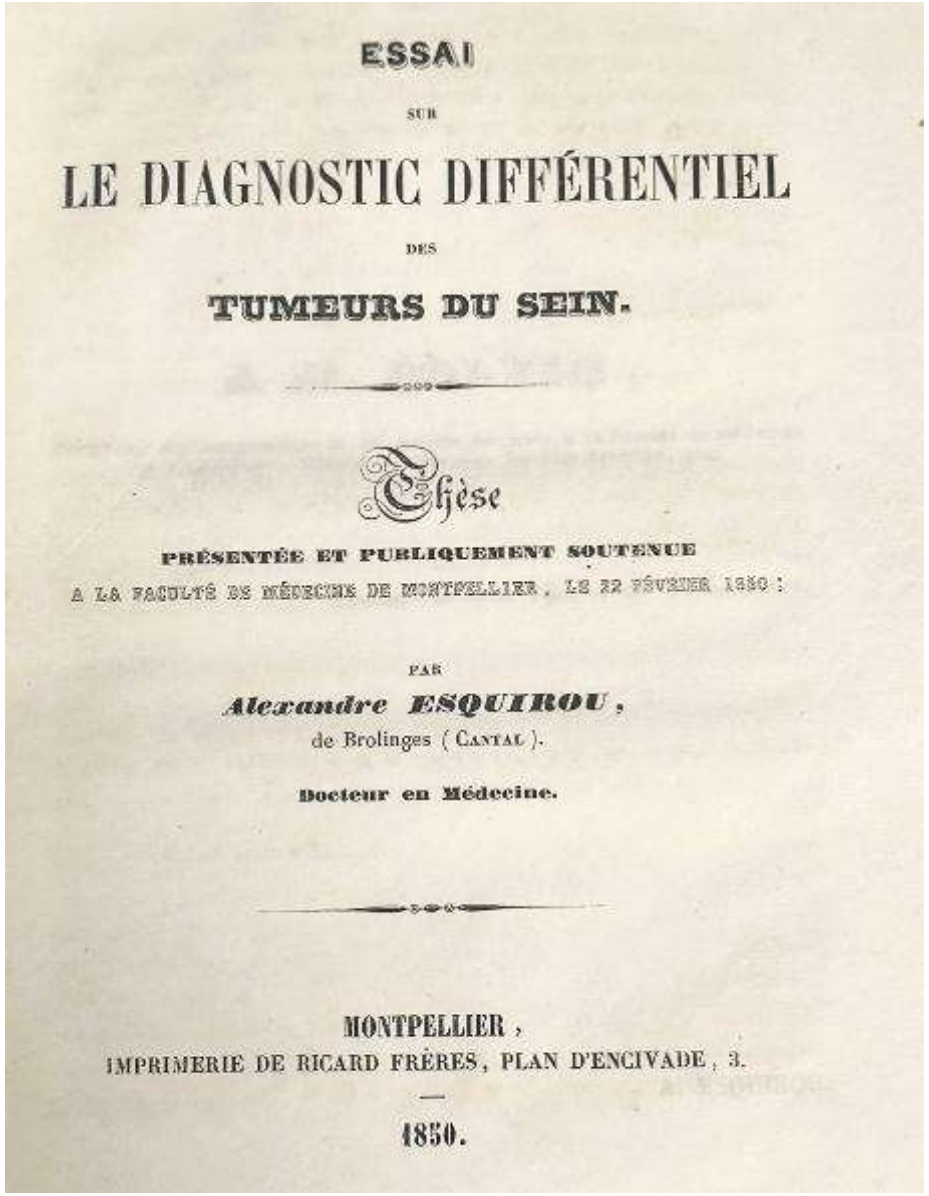
The most important work on diagnosis of malignant breast cancer of the mid-19th Century.

Alexandre Esquiou's 1850 Montpellier thesis, "Essai sur le Diagnostic Différentiel des Tumeurs du Sein" ("Essay on the Differential Diagnosis of Breast Tumors"), represents a mid-19th-century attempt to bring clinical precision to the understanding and classification of breast diseases at a time when pathology was rapidly evolving.

Writing in the intellectual tradition of the French medical schools, Esquiou focused on distinguishing malignant breast tumors—particularly scirrhous and encephaloid carcinomas—from benign conditions such as cysts, lipomas, glandular hypertrophy, chronic mastitis and fibrous indurations. Drawing on both physical examination and emerging pathological observations, he emphasized palpation, tumor consistency, adhesion to skin or muscle, nipple retraction and lymphatic involvement as key diagnostic clues.

Esquiou's thesis stressed that misdiagnosis often led to either unnecessary mutilating surgery or dangerous therapeutic delay. He advocated a rational diagnostic framework grounded in clinical observation, early recognition of malignant signs and careful correlation with autopsy findings. While written before the advent of histopathology and radiologic imaging, the work anticipated later diagnostic refinements by delineating a systematic clinical approach to differentiating breast tumors, thus bridging the empirical bedside tradition and the emerging scientific medicine of the later 19th century.

References:


ESSAI

SUR

LE DIAGNOSTIC DIFFÉRENTIEL

DES

TUMEURS DU SEIN.

Thèse

PRÉSENTÉE ET PUBLIQUEMENT SOUTENUE

A LA FACULTÉ DE MÉDECINE DE MONTPELLIER, LE 22 FÉVRIER 1850 ;

PAR

Alexandre ESQUIROU,

de Brolinges (Cantal).

Docteur en Médecine.

MONTPELLIER,

IMPRIMERIE DE RICARD FRÈRES, PLAN D'ENCIVADE, 3.

1850.

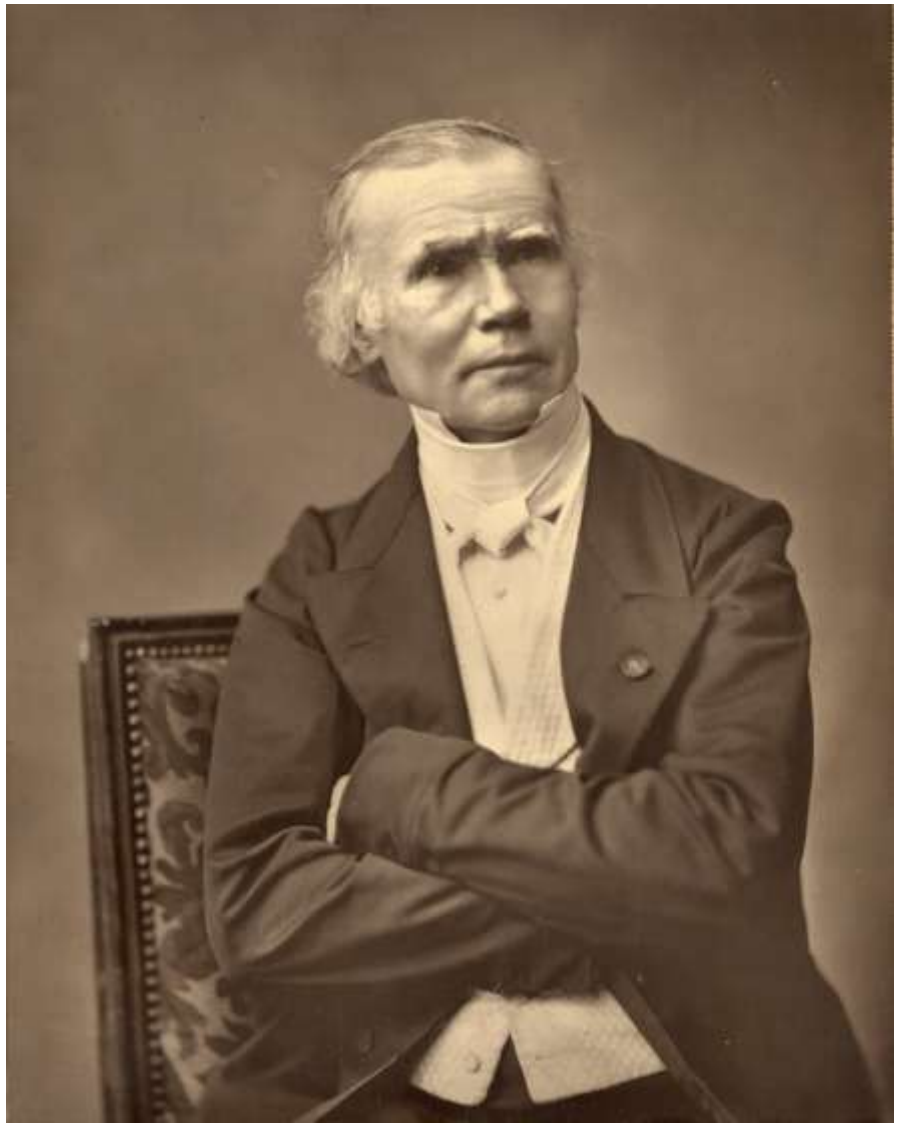
Alexandre Esquiou, 1850, Essai sur le Diagnostic Differentiel des Tumeurs de Sein.; These presentee ... a la faculte de Montpellier, le 22 Fevrier, Montpellier: Ricard Freres. From the author's medical book collection.

1854: Alfred Armand Louis Marie Velpeau

"His great treatise on tumours of the breast, his best work, was the most important of its time on the subject. It includes a good account of hyperplastic disease of the breast." (Garrison-Morton).

Daniel de Moulin, (1994, pp. 69-71): Velpeau was one of the greatest authorities on mammary carcinoma of the middle of the last century. In his voluminous *Traité des maladies du sein*, gave an excellent survey of the contemporary state of affairs. Velpeau distinguished three main groups of breast cancer on the basis of external features: scirrhus, encephaloid and a fibroplastic form.[175] Many varieties existed particularly in the scirrhus: 'scirrhus ligneux, lardacé, disséminé, en plaques', etc., as well as a number of subvarieties, all of this he amply specified and described. The type of cancer which was named 'cancer encéphaloïde' or 'cancer fongueux' by Laennec, was also known as medullary cancer and was first described by William Hey (1736–1819), a surgeon in Leeds and a former student of John Hunter. He had given it the name of 'fungus hæmatodes'. This is, in contrast to scirrhus, a soft type of growth and particularly malignant. Hey had compared the tumour mass to brain marrow and thought that it was formed by extravasated blood and lymph, which afterwards became organized.[176] The separation of fungus from cancer in a proper sense and the great numbers of different designations given to the former tumour by all sorts of researchers, created the utmost confusion. It was also a matter of dispute whether fungus could be considered a cancer. Velpeau apparently regarded it as a species of cancer: in the 250 cases of cancer he had witnessed, there were sixty of the encephaloid type. The differential diagnosis between this tumour and scirrhus – which was also a cancer, in Velpeau's opinion – was relatively easy in the case of the breast. When scirrhus involves the skin, the affected part is drawn backward, whereas encephaloid pushes it forward. Among the fibroplastic cancers Velpeau included chondroid and colloid cancers."

References: de Moulin (1993), Ekmektzoglou (2009), GMN 5771, Hajdu (2012), Olson (2002).



Alfred Velpeau, 1854, *Traité des maladies du sein et de la région mammaire.* Paris: V. Masson, From the author's medical library.

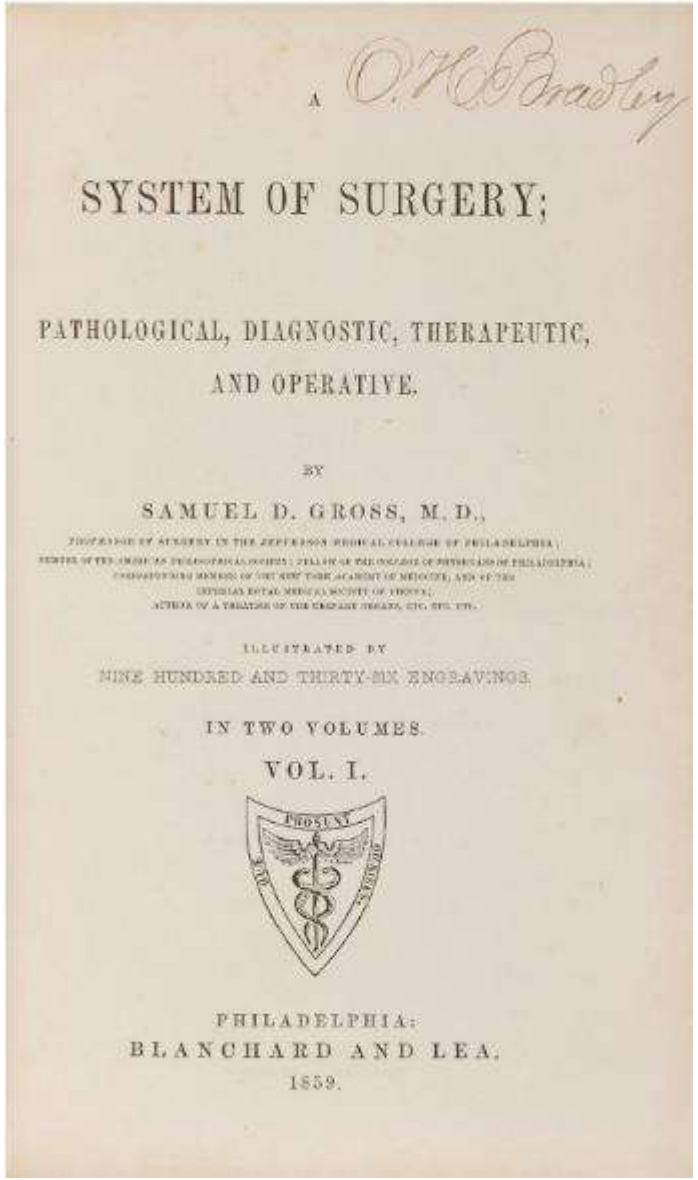
1859: Samuel D. Gross

Advocate of conservatism in breast cancer surgery.

Samuel D. Gross described a conservative resection with axillary dissection only when the lymph nodes were obviously involved. Samuel D. Gross's monumental 1859 treatise, *A System of Surgery: Pathological, Diagnostic, Therapeutic and Operative*, includes an influential discussion of breast cancer that reflected—and shaped—American surgical thought on the disease prior to the Halstedian era. Gross devoted extensive sections to tumors of the mammary gland, describing their anatomy, pathology, clinical presentation and surgical management in extraordinary detail. Drawing on his experience at Jefferson Medical College and his earlier publications, he characterized carcinoma of the breast as a progressive, locally invasive and systemically fatal disease. He recognized the importance of early diagnosis and complete surgical removal, yet his understanding of cancer's biology was rooted in the local-contagion theory, dominant before the acceptance of metastasis as a systemic process.

From a therapeutic standpoint, Gross was one of the strongest advocates for radical surgical excision of breast tumors, including removal of surrounding tissues and lymph nodes when visibly involved—anticipating, in part, Halsted's principles. He emphasized complete extirpation as the only potentially curative measure, warning that incomplete operations almost always led to recurrence. Gross also discussed palliative care for inoperable cases, including pain control, caustic applications and dietary measures, but he regarded such approaches as secondary to surgery. Although limited by the absence of anesthesia beyond ether and the lack of antisepsis (introduced by Lister only a few years later), Gross's 1859 text stands as a pivotal synthesis of pre-modern breast cancer surgery, bridging the empirical surgical tradition of the early 19th century with the methodical, evidence-oriented practice that would follow.

References: De Moulin (1993), Hajdu (2012).


A

SYSTEM OF SURGERY;

PATHOLOGICAL, DIAGNOSTIC, THERAPEUTIC,

AND OPERATIVE.

BY

SAMUEL D. GROSS, M. D.,

ILLUSTRATED BY

NINE HUNDRED AND THIRTY-SIX ENGRAVINGS.

IN TWO VOLUMES.

VOL. I.

PHILADELPHIA:

BLANCHARD AND LEA.

1859.

Samuel D. Gross, 1859-, *A System of Surgery: Pathological, Diagnostic, Therapeutic and Operative*: Philadelphia: Blanchard and Lea, First edition. From the author's medical library.

1863: Rudolph Virchow

Foundational work on the cellular origins of cancer.

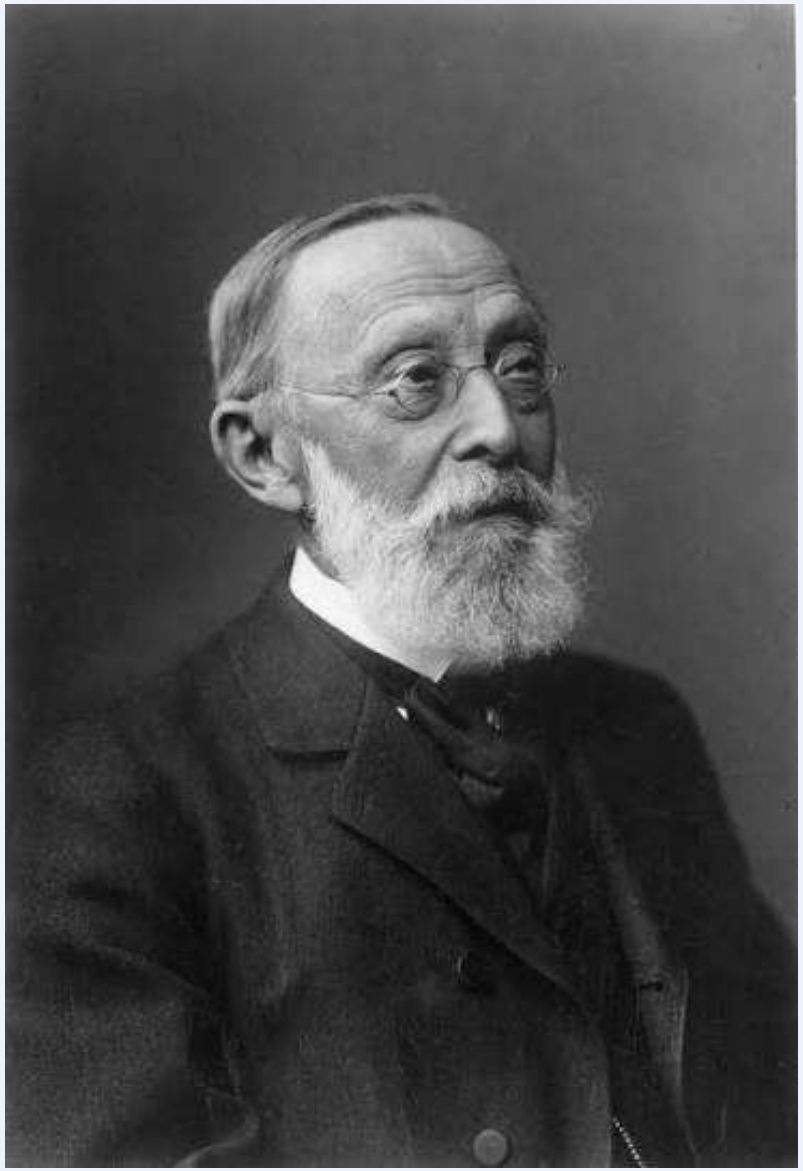
This monumental treatise—The Pathological Tumors—is Virchow's most extensive and influential writing on cancer. It systematically classifies tumors based on cellular origin and structure, inaugurating the modern histological approach to oncology.

In Volume I and II, Virchow elaborates his famous dictum "Omnis cellula e cellula" ("Every cell from a cell") and develops the theory of neoplasia—that cancers arise from the abnormal proliferation of normal tissue elements, not from exudation as earlier theorists claimed.

He devotes detailed sections to "Carcinoma der Mamma" (carcinoma of the breast) and "Carcinoma der Gebärmutter" (of the uterus), describing their microscopic architecture, modes of invasion and metastasis. He distinguishes scirrhous (hard) carcinoma of the breast, rich in fibrous stroma, from medullary (soft) carcinoma and he correlates their gross texture with the density of the connective tissue and cell content.

Virchow also linked chronic irritation and inflammation to tumor development, positing that persistent tissue injury and reparative cell proliferation could predispose to cancer formation. This insight anticipated modern ideas about the role of inflammation, infection and immune response in oncogenesis. His work on lymphatic and epithelial cancers provided early morphological descriptions of breast carcinoma, guiding later surgical and pathological classifications. Moreover, his emphasis on systematic tissue examination shaped the diagnostic approach to breast cancer for more than a century, influencing figures like Halsted and Handley in their pathological and surgical models of local spread.

References: DeVita and Rosenberg (2012), Ekmektzoglou (2009), Hajdu (2012), Lukong (2017), Mukherjee (2002), Olson (2002, p. 57).



Rudolph Virchow, 1857, *Die krankhaften Geschwuelste*: Berlin: August Hirschwald, First edition.

1867: Charles Hewitt Moore

He showed that breast cancer recurrence was not due to the development of an entirely new tumor because of constitutional susceptibility, as was then generally theorized, but to incomplete removal of the original tumor

Charles Hewitt Moore (1821–1870) was a pioneering British surgeon and pathologist whose meticulous research helped redefine the understanding of cancer as a systemic and constitutional disease rather than a purely local one. Working at Middlesex Hospital in London, where he collaborated closely with the pathologist Sir James Paget, Moore carried out some of the earliest microscopic and clinical investigations of breast cancer recurrence and dissemination. In his influential writings—particularly his 1865 paper “On the Influence of Inadequate Operations on the Occurrence of Local Return of Cancer”—he challenged the prevailing surgical dogma that wider and more radical excisions would guarantee a cure.

Through careful pathological study of excised tissue and postmortem findings, Moore demonstrated that breast cancer cells could remain dormant or spread microscopically beyond the apparent tumor margins, explaining why recurrences often occurred even after apparently successful operations. This was a major conceptual leap, shifting the focus from the extent of surgery to the biological nature of the disease.

Modern surgical treatment of cancer is based upon principles laid down by Moore. For cancer of the breast he showed that recurrence was not due to the development of an entirely new tumor because of constitutional susceptibility, as was then generally theorized, but to incomplete removal of the original tumor. He insisted that the entire breast be carefully removed in every case of breast cancer.

References: Ades (2017), De Moulin (1993), Ekmektzoglou (2009), GMN 2619.

Charles Hewitt Moore, 1867-, *On the influence of inadequate operations on the theory of cancer. Med.-chir. Trans. 50, 245-80,*, London, First edition.

1874: James Paget

Showed that areolar cancer can precede breast cancer.

Defined clinicopathologic entities and the eponymous nipple/areolar lesion linked to underlying carcinoma. Showed that aureolar cancer can precede breast cancer. Paget's disease, described by Sir James Paget in 1874, is classified as mammary and extramammary. The mammary type is rare and often associated with intraductal cancer (93-100% of cases). It is more prevalent in postmenopausal women and it appears as an eczematoid, erythematous, moist or crusted lesion, with or without fine scaling, infiltration and inversion of the nipple. It must be distinguished from erosive adenomatosis of the nipple, cutaneous extension of breast carcinoma, psoriasis, atopic dermatitis, contact dermatitis, chronic eczema, lactiferous ducts ectasia, Bowen's disease, basal cell carcinoma, melanoma and intraductal papilloma.

Diagnosis is histological and prognosis and treatment depend on the type of underlying breast cancer. Extramammary Paget's disease is considered an adenocarcinoma originating from the skin or skin appendages in areas with apocrine glands. The primary location is the vulvar area, followed by the perianal region, scrotum, penis and axillae. It starts as an erythematous plaque of indolent growth, with well-defined edges, fine scaling, excoriations, exulcerations and lichenification. In most cases it is not associated with cancer, although there are publications linking it to tumors of the vulva, vagina, cervix and corpus uteri, bladder, ovary, gallbladder, liver, breast, colon and rectum. Differential diagnoses are candidiasis, psoriasis and chronic lichen simplex. Histopathology confirms the diagnosis. Before treatment begins, associated malignancies should be investigated. Surgical excision and micrographic surgery are the best treatment options, although recurrences are frequent.

References: De Moulin (1993), GMN 5772, Hajdu (2012).

James Paget, 1874, On disease of the mammary areola preceding cancer of the mammary gland. *St. Barth. Hosp. Rep.*, 10, 87-89., London.

1880: Theodor Billroth

A monograph on cancer and other diseases of the breast, including a discussion of cancer of the male breast in the final chapter.

Daniel de Moulin (1993, pp. 81-83):, Theodor Billroth (1829–94) was professor of surgery, first in Zürich (1860–67) and subsequently in Vienna. He belonged to that heroic generation of surgeons who, only a few decades after the introduction of antisepsis in 1864, raised surgery from a traditional craft to a scientific discipline. According to Billroth, the morphological diagnosis of cancer had lately gained so much in reliability, that it offered at least as much certainty as the clinical signs elaborated through the ages.

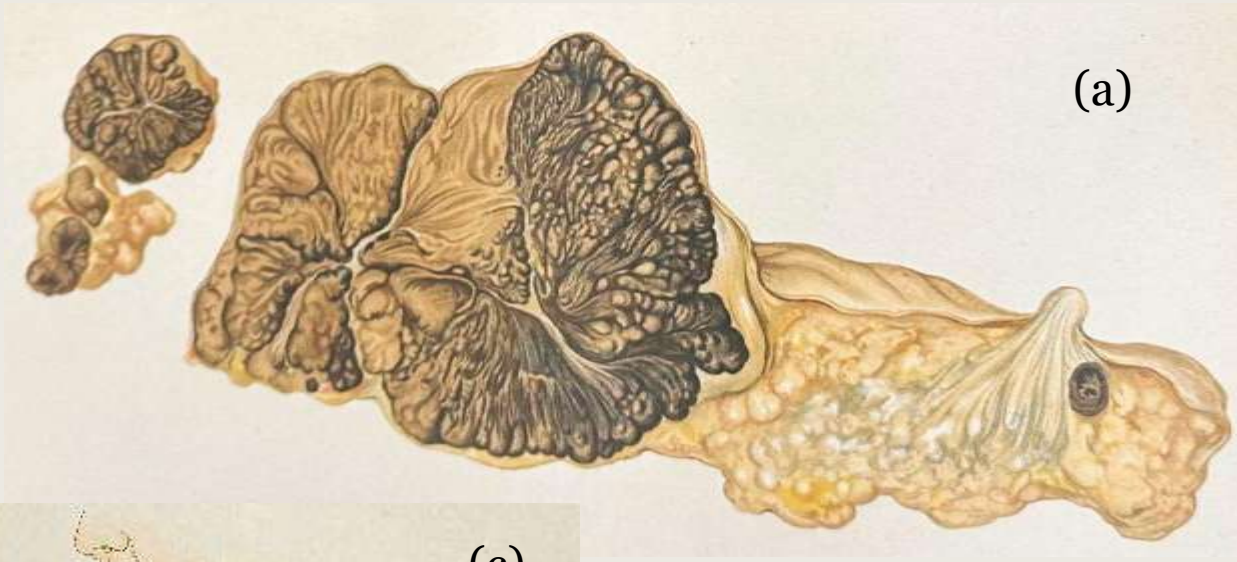
Billroth tried to put things in order [with classification] by accepting only four kinds of breast cancer. For survey purposes, he drew up a vocabulary in which he listed both his own nomenclature and the names in common use that had been given to the same type of tumour by others. Billroth's table is valuable even today for the student of historical oncology. I. Die theils weicheren, theils härteren Carcinomknoten: histologisch meist als acinöses Carcinom auftretend (Billroth), II. Die carcinomatöse Infiltration: histologisch meist als tubulöses Carcinom auftretend. Carcinoma simplex (Billroth). Usually spreading at an early stage to the skin, partly as an infiltration, partly as multiple nodules, III. Der atrophirende, vernarbende Brustkrebs: Scirrhus (Billroth). IV. Gallertkrebs: Gross: Glatiniform carcinoma. By means of fine woodcuts, Billroth gave a detailed description of the gross and microscopic features of each one of his four species.

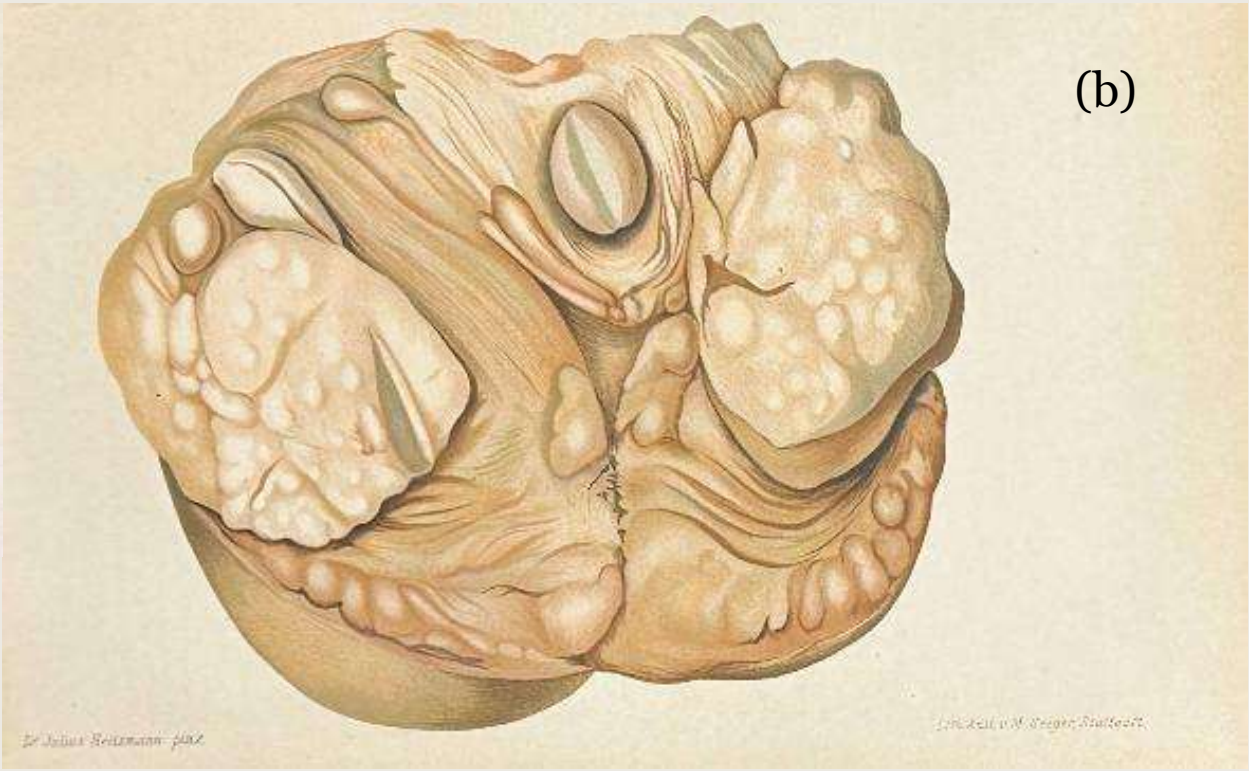
Typical of mammary cancer is the acinar appearance which, although it may also be observed in tumours elsewhere in the body, is particularly characteristic for neoplasms of the breast.

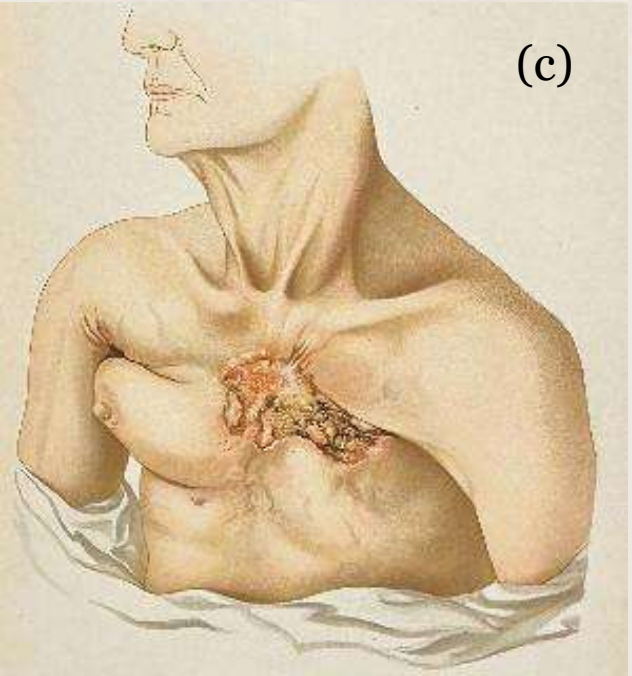
References: De Moulin (1993), GMN 5773, Olson (2002, p. 60).

Christian Albert Theodor Billroth, 1885, *Die Krankheiten der Brustdrüsen*. Stuttgart: Ferdinand Enke. From the author's medical library.

Billroth Provided Detailed Descriptive Imagery







Key: (a) chromolithograph of a sectioned carcinoma of the breast, depicting a scirrhous or medullary carcinoma (Large lobulated masses with dark brownish-grey cut surfaces (representing tumor tissue),Lighter yellow fatty areas at the periphery (normal adipose tissue); (b) cross-section of a breast with multiple firm, pale nodular tumors embedded in a fibrous stroma; (c) metastatic tumor of the left breast in locally advanced stage. From: Christian Albert Theodor Billroth, 1885, *Die Krankheiten der Brustdrüsen*. Stuttgart: Ferdinand Enke.

1880: Samuel W. Gross

Advocated the "dinner plate operation" with radical dissection of the breast, skin, paramammary fat, pectoral fascia and axillary contents.

Samuel Weissel Gross (1837-1889), an American surgeon, followed his illustrious father, Samuel D. Gross1(1805-1884) at the Jefferson Medical College in Philadelphia, Pennsylvania.

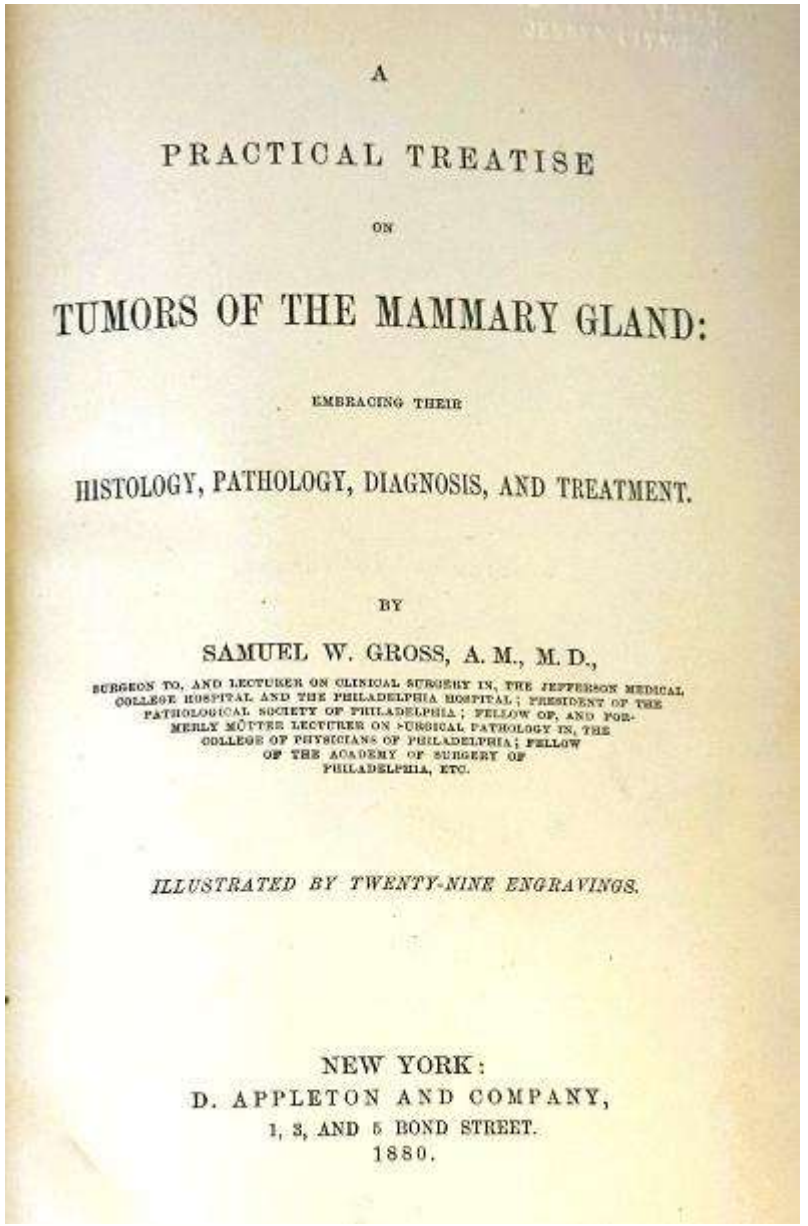
Samuel W. Gross synthesized a vast body of European and American surgical experience and provided the first data-driven assessment of operative outcomes in U.S. breast-cancer surgery. Having analyzed more than 200 cases, he drew a sharp distinction between "incomplete" and "complete" excision.

In his first 55 patients—treated by removing only the tumor or part of the breast—recurrence was universal and fatal within months. This convinced Gross that local recurrence stemmed from microscopic spread through the pectoral fascia and axillary lymphatics,

Gross thereafter insisted on total ablation of the mammary gland, the overlying skin, the pectoral fascia and the axillary contents in one en bloc operation. This "complete eradication," performed before the Halsted era, improved three-year survival to roughly 19 percent, a striking advance for the time. He rejected caustics, poultices and "resolvents," urging early, decisive surgery as the only rational therapy, yet acknowledged that constitutional factors often predetermined relapse.

This was the most comprehensive pre-Halsted work on breast surgery.

References: De Moulin (1993), Ekmektzoglou (2009), Hajdu (2012).



A

PRACTICAL TREATISE

ON

TUMORS OF THE MAMMARY GLAND:

EMBRACING THEIR

HISTOLOGY, PATHOLOGY, DIAGNOSIS, AND TREATMENT.

BY

SAMUEL W. GROSS, A. M., M. D.,

SURGEON TO, AND LECTURER ON CLINICAL SURGERY IN, THE JEFFERSON MEDICAL COLLEGE HOSPITAL AND THE PHILADELPHIA HOSPITAL; PRESIDENT OF THE PATHOLOGICAL SOCIETY OF PHILADELPHIA; FELLOW OF, AND FORMERLY MÜTTER LECTURER ON SURGICAL PATHOLOGY IN, THE COLLEGE OF PHYSICIANS OF PHILADELPHIA; FELLOW OF THE ACADEMY OF SURGERY OF PHILADELPHIA, ETC.

ILLUSTRATED BY TWENTY-NINE ENGRAVINGS.

NEW YORK:
D. APPLETON AND COMPANY,
1, 3, AND 5 BOND STREET.
1880.

Samuel W. Gross, 1880-, *A Practical Treatise on Tumors of the Mammary Gland*: New York: Appleton, First edition. From the author's medical library.

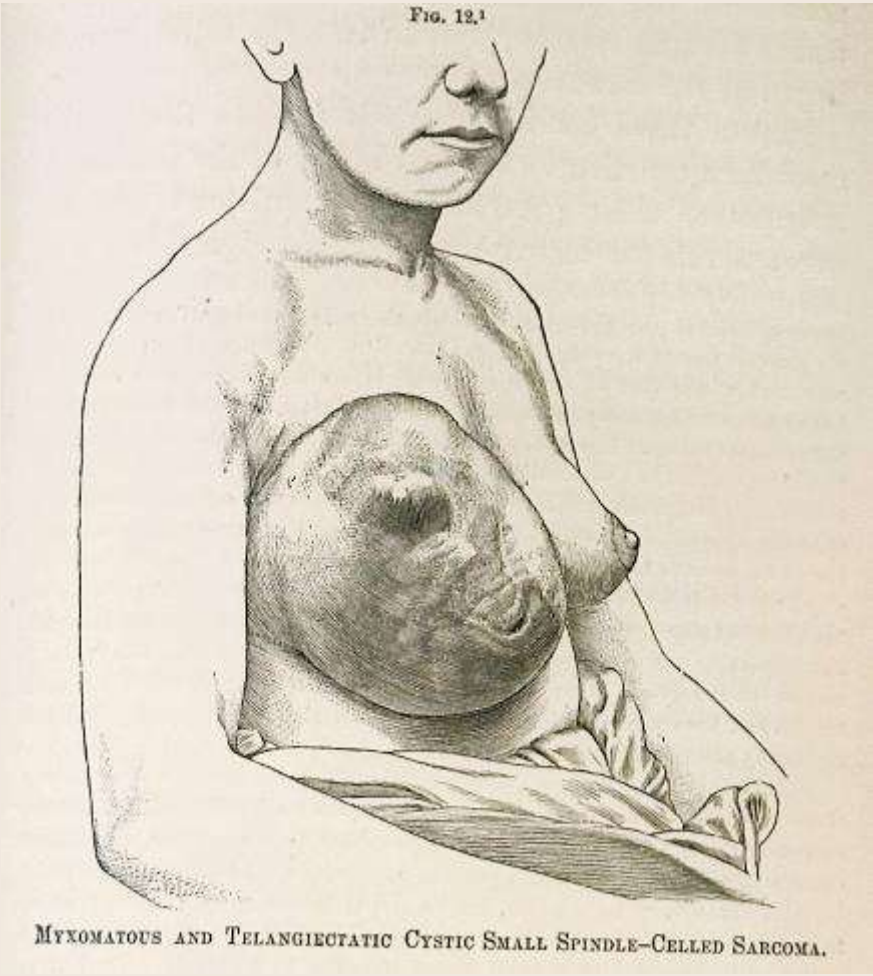
Gross' Work Marked a Turning Point in American Breast Surgery

Focused in building an evidence-based approach to surgical eradication of breast cancer in the late 1800s. His work ended up being the foundation that Halsted's contributions were built upon.

Gross's treatise represents a turning point in American surgical oncology. It linked meticulous pathologic observation—he classified scirrhous, encephaloid and colloid forms of carcinoma—with systematic operative technique and statistical follow-up. By integrating microscopic anatomy, clinical features (nipple retraction, stony hardness, glandular invasion) and quantified results, Gross transformed breast-cancer management from empirical art to an evidence-based discipline.

His doctrine of early, radical, anatomically complete extirpation directly anticipated William Stewart Halsted's radical mastectomy of the 1890s and his influence permeated American surgical teaching through The System of Surgery (1859–1882) and Jefferson Medical College. In bridging descriptive pathology and modern oncologic surgery, Gross laid the conceptual and technical groundwork for the surgical eradication principle that dominated breast-cancer treatment for the next century.

Daniel De Moulin (1993) described Gross' contributions in detail, writing: "Samuel Gross's contributions to the understanding and treatment of breast cancer mark one of the most significant milestones in 19th-century American surgical thought, bridging the era of descriptive pathology and the rise of modern oncologic surgery. Drawing deeply on European authorities such as Velpeau, Brodie and Lebert but adding his own vast clinical experience, Gross provided the first comprehensive American synthesis of mammary pathology and surgery, beginning with his *Elements of Pathological Anatomy* (1839, 1845, 1857) and culminating in his monumental *System of Surgery* (1859–1882). He systematically classified breast tumors into scirrhous, encephaloid and colloid forms, described their microscopic structures, patterns of infiltration and modes of metastasis and distinguished malignant from benign growths with a clarity unmatched in earlier American literature."



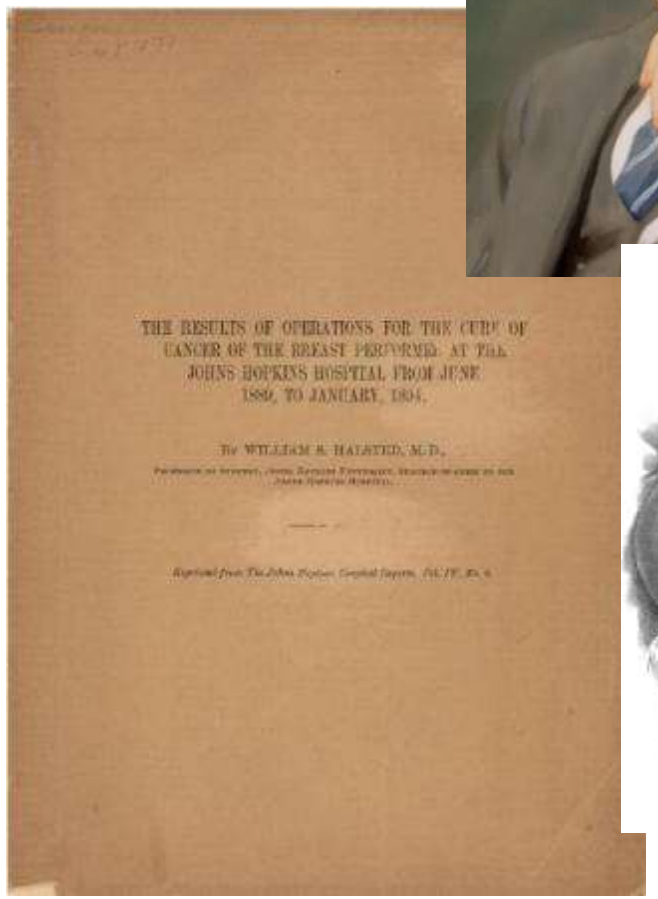
Illusrration from Samuel W. Gross, 1880-, *A Practical Treatise on Tumors of the Mammary Gland*: New York: Appleton.

1894: William Halsted

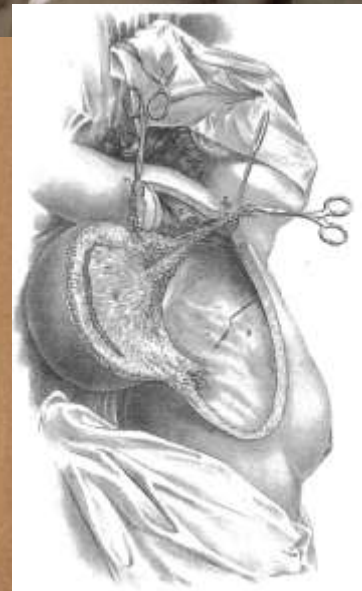
His method of radical mastectomy, with some modifications, remained the cornerstone of surgical treatment of carcinoma of the breast for many decades.

Published in *The Johns Hopkins Hospital Reports* (1894–1895), “The Results of Operations for the Cure of Cancer of the Breast Performed at the Johns Hopkins Hospital from June, 1889, to January, 1894” presented one of the earliest systematic surgical analyses of breast cancer outcomes in the United States. Compiled by surgeons under the leadership of William Stewart Halsted, the report documented the results of 50 consecutive breast cancer operations performed during the hospital’s first five years. Halsted described in detail his radical mastectomy technique, which involved *en bloc* removal of the breast, underlying pectoral muscles and axillary lymph nodes—a method designed to achieve complete local eradication of the disease. The study meticulously recorded recurrence rates, survival outcomes and postoperative complications, reflecting a new era of scientific rigor in surgical oncology through careful case documentation and long-term follow-up.

The report’s findings demonstrated that local recurrence rates were significantly reduced with the radical approach compared to earlier, more limited operations and that patients treated with complete resection experienced longer periods of disease-free survival. Halsted’s conclusions—that breast cancer spread in an orderly, regional fashion through contiguous tissue and lymphatic channels—formed the theoretical foundation of modern surgical oncology for decades. Though later challenged by systemic theories of cancer dissemination, the 1894–1895 Johns Hopkins report represented a pivotal milestone in the history of breast cancer surgery, marking the transition from empirical to evidence-based operative practice and establishing the Halsted radical mastectomy as the gold standard of treatment well into the twentieth century.


THE RESULTS OF OPERATIONS FOR THE CURE OF CANCER OF THE BREAST PERFORMED AT THE JOHNS HOPKINS HOSPITAL, FROM JUNE 1889, TO JANUARY, 1894.

By WILLIAM S. HALSTED, M.D.,



"The Results of Operations for the Cure of Cancer of the Breast Performed at the Johns Hopkins Hospital from June, 1889, to January, 1894." Reprint from: The Johns Hopkins Hospital Reports, Vol. IV, No. 6 (1894-1895). Baltimore, 1894-1895. First edition. From the author’s medical library. Previously in the collection of Haskell Norman.

References: Ades (2017), De Moulin (1993), Ekmektzoglou (2009), Garrison-Morton-Norman 5777, Hajdu (2012), Lukong (2017), Mukherjee (2002), Norman 983, Olson (2002, p. 45).

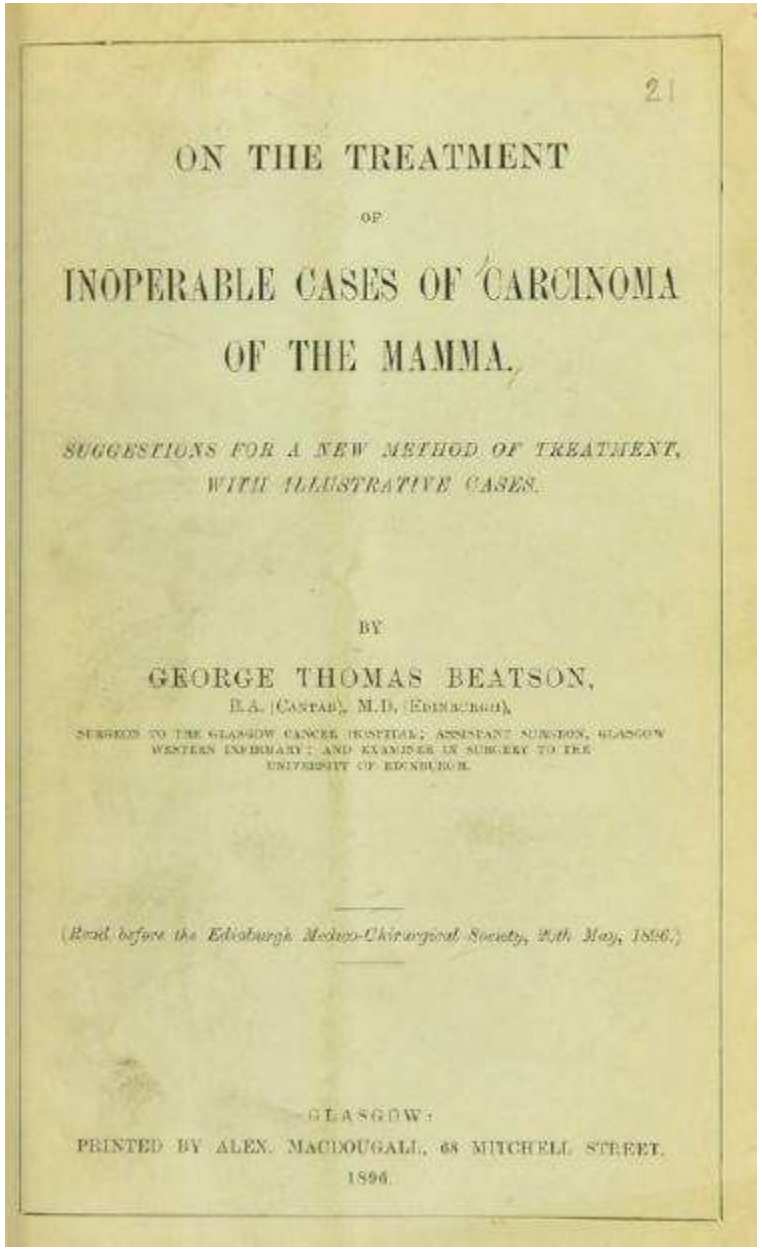
1896: George Beatson

First to find that some breast tumors are hormonally driven.

George Thomas Beatson's 1896 paper, "On the Treatment of Inoperable Cases of Carcinoma of the Mamma" represents one of the most profound breakthroughs in the history of breast cancer therapy. In this work, published in Glasgow by Alex MacDougall, Beatson described three cases of advanced, inoperable breast cancer treated by bilateral oophorectomy—the surgical removal of the ovaries. Drawing on his knowledge of animal physiology and the role of the ovaries in lactation, he hypothesized that suppressing ovarian function might also influence the growth of breast tumors. Remarkably, in one of his patients, he observed marked regression of the breast tumor and symptomatic improvement following the procedure, offering the first clinical evidence that hormonal manipulation could affect the course of cancer.

Beatson's paper effectively founded the field of endocrine therapy in oncology, decades before the discovery of hormones themselves. His bold and physiologically reasoned approach introduced the concept that breast cancer could be hormonally driven and that intervention in the body's internal milieu might control tumor progression. Although his technique—surgical castration—was later replaced by pharmacologic methods such as estrogen blockade and aromatase inhibition, the principles he established became the cornerstone of modern hormone-dependent breast cancer treatment. Beatson's 1896 paper, published in a modest Scottish pamphlet and based on a small clinical series, stands as one of the most visionary works in medical history, linking reproductive biology to cancer therapy for the first time.

References: Ades (2017), Benson (2008), De Moulin (1993), DeVita and Chu (2008), Ekmektzoglou (2009), Hadju (2012), Lo, Pritchard, Robinson, Albtain (2009), Love and Philips (2002), Lukong (2017), Olson (2002, p. 78), Stockwell (1983).



21

ON THE TREATMENT

OF

INOPERABLE CASES OF CARCINOMA

OF THE MAMMA,

SUGGESTIONS FOR A NEW METHOD OF TREATMENT, WITH ILLUSTRATIVE CASES.

BY

GEORGE THOMAS BEATSON,

(Read before the Edinburgh Medico-Chirurgical Society, 28th May, 1896.)

GLASGOW:

PRINTED BY ALEX. MACDOUGALL, 68 MITCHELL STREET.

1896.

George Beatson, 1896, *On the treatment of inoperable cases of carcinoma of the mamma : suggestions for a new method of treatment, with illustrative cases,* Glasgow: Alex MacDougall, First edition. From the author's medical library.

1896: Emil Grubbé

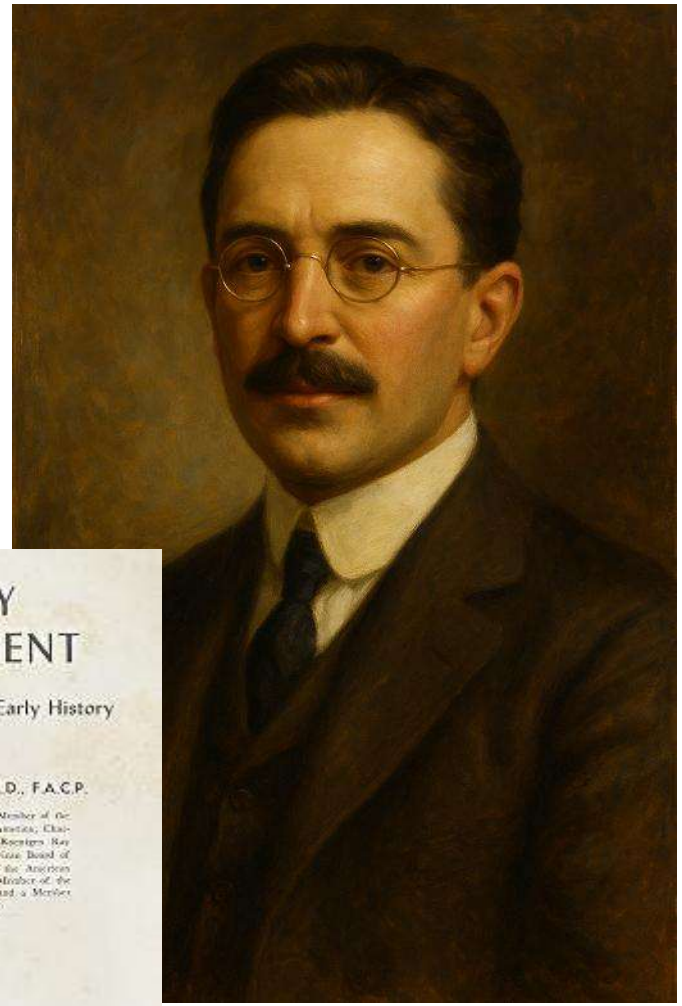
Conducted the first treatment of a breast cancer patient with radiation in 1896.

Emil H. Grubbé (1875–1960) was an American physician and one of the earliest pioneers of radiation therapy in cancer treatment, including breast cancer. In 1896—just months after Wilhelm Röntgen's discovery of X-rays—Grubbé, then a medical student in Chicago, built one of the first X-ray tubes in the United States and used it experimentally to treat a woman with recurrent breast carcinoma, marking what is widely considered the first therapeutic use of radiation in oncology. Although rudimentary and conducted without the safety knowledge later generations would develop, his early experiments demonstrated that X-rays could shrink malignant tumors.

"Dr. Grubbe was an extraordinary man, a creature of his time and place. He was colorful, flamboyant and occasionally saw himself in a somewhat better light than did his contemporaries. He was, however, a true American pioneer physician, largely self-taught, utterly devoted to investigation applications of the 'new ray' and to the maintenance of his very extensive private practice. He was not the first to develop fluoroscopy, but he was certainly among the first. He was, however, recognized as one of the earliest radiation therapy specialists in this city and perhaps in the United States." (Chicago Radiological Society).

There have been some who have questioned whether Grubbe actually treated a patient with breast cancer in 1896. See Paul C. Hodge's book *The Life and Times of Emil Grubbe*.

References: Du Moulin (1993), Ekmektzoglou (2009), Mukherjee (2002).



Emil Grubbe, 1949, X-Ray Treatment. Its Origin, Birth and Early History, St Paul and Minneapolis, MN: The Bruce Publishing Company. From the author's medical book collection.

1899: Marie Curie

Discovered polonium and then radium which was to transform breast cancer treatment.

Marie Slowdowska Curie (1867–1934) was a pioneering physicist and chemist whose discoveries of radioactivity, polonium and radium transformed both science and medicine, including the treatment of cancer.

Working under extraordinarily difficult conditions, she was the first to isolate radioactive isotopes and to quantify their effects, coining the term “radioactivity” and laying the experimental groundwork for nuclear physics and radiotherapy.

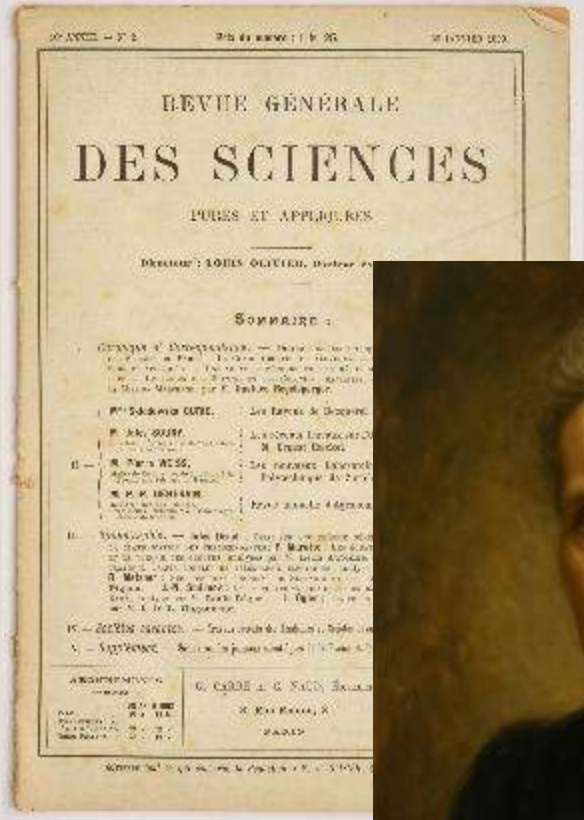
Her meticulous studies of radium’s emission of penetrating rays led directly to the development of radiation therapy for malignant tumors, most notably breast cancer, in the early 20th century.

During World War I, she also created mobile X-ray units (“Petites Curies”) to provide frontline medical imaging for wounded soldiers, saving countless lives.

Curie’s work—recognized by two Nobel Prizes in Physics (1903) and Chemistry (1911)—opened a new era of scientific and medical innovation, bridging pure research and clinical application and making her one of the foundational figures in both modern physics and cancer treatment.

She later died of the effects of radiation from substances she handled as a scientist.

References: Ben-Dror (2022), De Moulin (1993), DeVita and Rosenberg (2012), Ekmektzoglou (2009), Hajdu (2012), Olson (2002, p. 88).


REVUE GÉNÉRALE
DES SCIENCES
PURES ET APPLIQUÉES

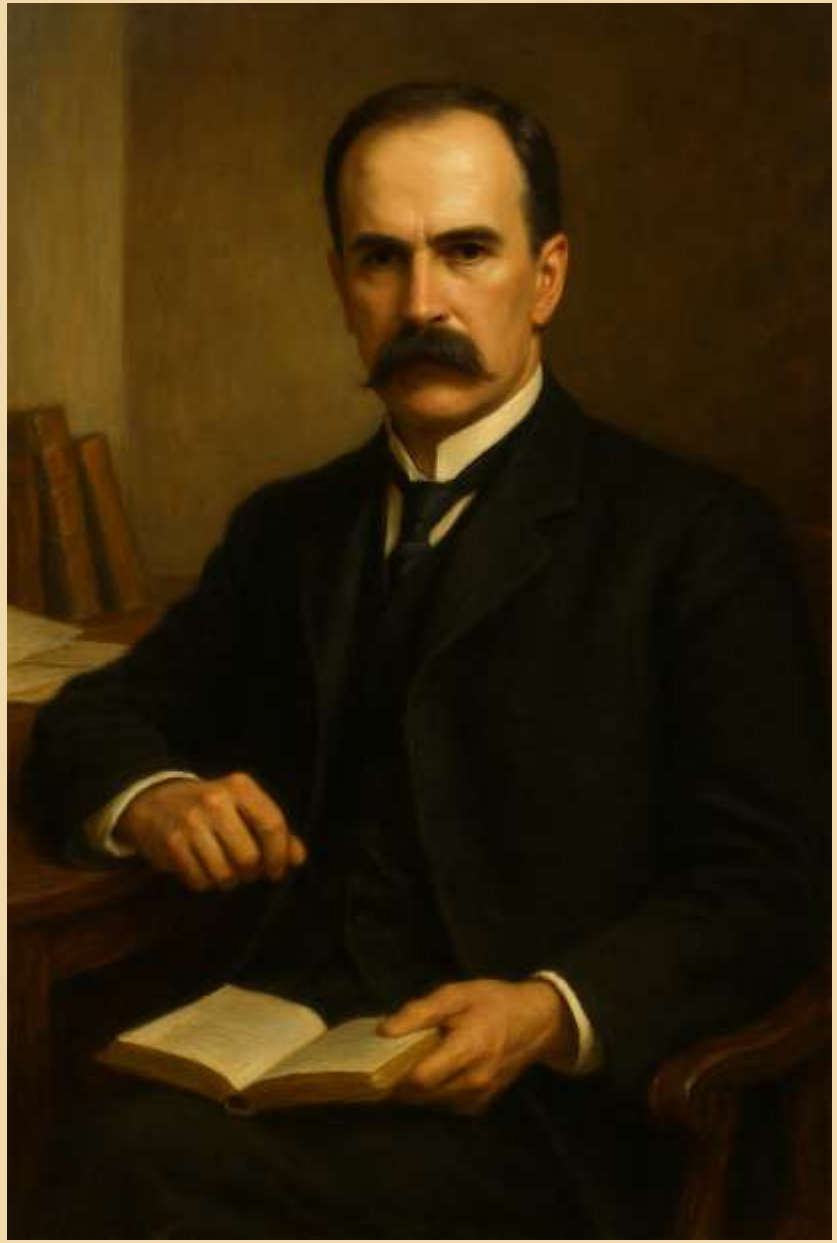
Marie Slodowska Curie, 1899, *Les Rayons de Becquerel et le Polonium. In Revue Generale Des Sciences Pures et Appliquees,* Paris: Directeur: Louis Olivier, No. 2, First edition. From the author’s medical library.

1901: William Osler

Advocated a holistic approach to breast cancer management.

William Osler's 1901 paper, "The Medical Aspects of Carcinoma of the Breast, with a Note on the Spontaneous Disappearance of Secondary Growths," published in the *American Journal of the Medical Sciences*, reflected his keen observational approach to cancer as both a systemic and clinical disease. In this study, Osler—then one of the most respected physicians in the world—examined breast cancer not merely as a surgical problem but as a multifaceted systemic illness that affected the entire organism. He reviewed the natural history of the disease, patterns of metastasis and constitutional symptoms, noting that breast carcinoma frequently spread to the liver, lungs and bones, often long after apparent local control. Osler emphasized that medical practitioners must view cancer through a broad clinical lens rather than treating it as a purely local lesion, foreshadowing later biological and systemic models of cancer behavior that emerged in the twentieth century.

The paper's most striking feature was Osler's account of a rare and carefully documented case of spontaneous regression of metastatic breast cancer. He described a patient with advanced disease in whom secondary growths in the skin and lymph nodes unexpectedly diminished and even disappeared without treatment—a phenomenon he treated with cautious skepticism but scientific curiosity. Osler presented this as an exceptional event that underscored the mystery and variability of cancer's natural course, urging further study into the body's intrinsic resistance mechanisms. He did not associate this regression with immune response or infection as had been done by his contemporary William Coley.



William Osler, 1901, *The medical aspects of carcinoma of the breast, with a note on the spontaneous diappearance of secondary growths.* Offprint
First edition.

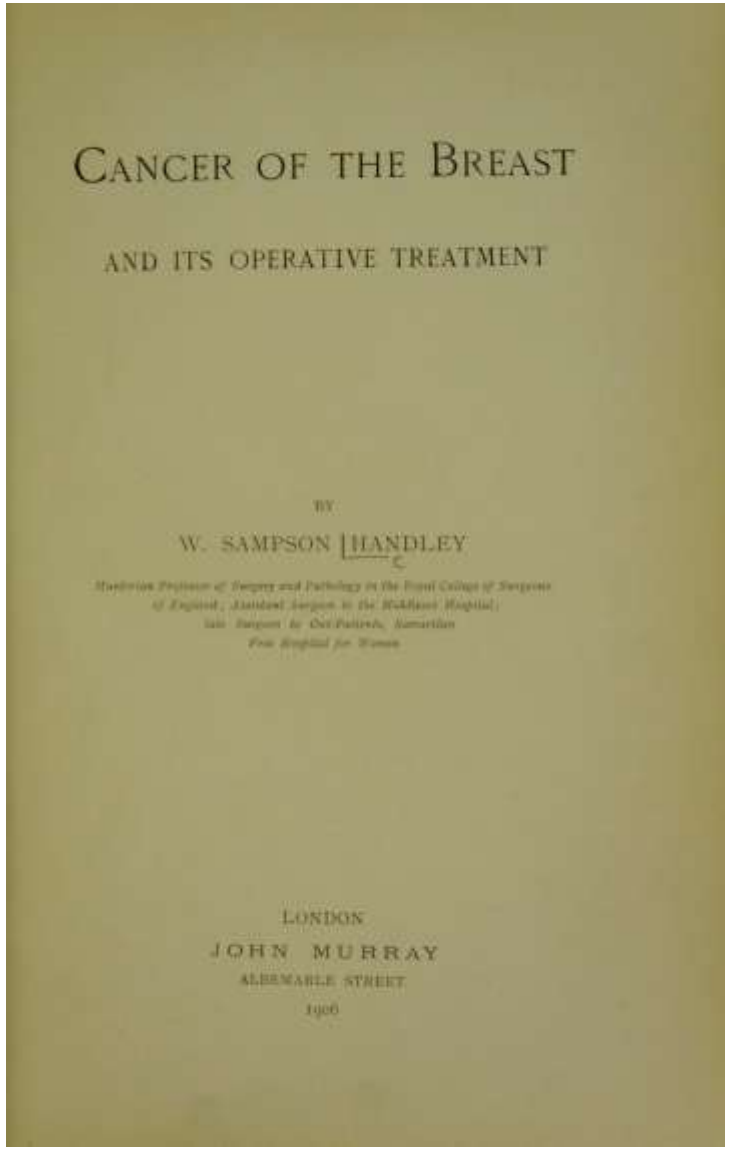
1906: Sampson Handley

Argued for lymph node involvement in breast metastasis.

Samuel (Sampson) Handley (1853–1940) was a distinguished British surgeon whose work on the pathology and surgical treatment of breast cancer profoundly influenced early twentieth-century oncology. Educated at St. Bartholomew's Hospital and later a professor of surgery at the University of London, Handley devoted much of his career to understanding how breast cancer spread. In his landmark 1906 monograph, *Cancer of the Breast and Its Operative Treatment*, he advanced the theory of "lymphatic permeation", arguing that breast cancer metastasized through the lymphatic channels in a continuous manner rather than by discrete embolic spread. This concept provided a pathological rationale for the radical surgical excision of lymphatic drainage areas, reinforcing and extending Halsted's ideas on *en bloc* resection. Handley emphasized meticulous dissection of the axillary and internal mammary lymph nodes and the removal of surrounding fascial planes, believing this could eradicate local spread and improve survival.

Although later research showed that systemic metastasis often occurs earlier than Handley supposed, his theories nonetheless had a lasting impact on surgical oncology. His detailed anatomical studies of the breast's lymphatic system improved understanding of cancer dissemination and helped refine operative planning for decades. Moreover, Handley's insistence on integrating pathological precision with surgical technique marked a turning point in breast cancer surgery, bridging the empirical operations of the nineteenth century with the scientific oncology of the modern era.

References: Ekmektzoglou (2009), Olson (2002, p. 69).



Sampson Handley, 1906, Cancer of the Breast and its Operative Treatment, London: John Muray. From the Wellcome Collection.

1910: Paul Ehrlich and Sahachiro Hata

First to describe chemotherapy. This work marked the beginning targeted drug therapies – an idea that eventually transformed breast cancer.

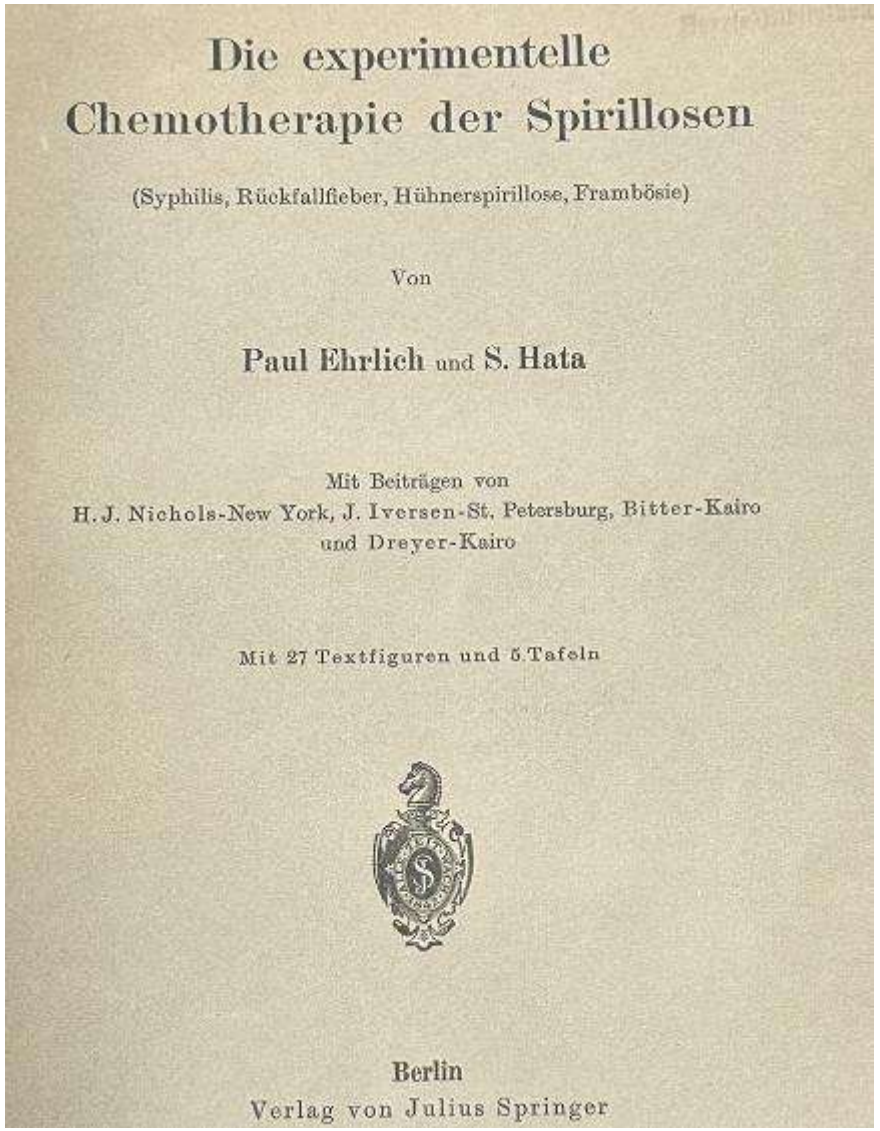
In 1910, Paul Ehrlich and his Japanese collaborator Sahachiro Hata achieved a historic breakthrough in targeted drug therapy with their discovery of Salvarsan (arsphenamine), the first effective treatment for syphilis.

Although this work did not directly impact cancer treatment, it revolutionized medical thinking about how diseases—including cancer—could be attacked selectively at the cellular level.

Ehrlich and Hata introduced the visionary concept of the “magic bullet” (Zauberkugel)—a compound that could seek out and destroy disease-causing cells without harming normal tissues. This idea laid the intellectual foundation for chemotherapy and, by extension, modern targeted cancer therapy.

For oncology, Ehrlich’s contribution was transformative conceptually rather than immediately practical. His work suggested that it might someday be possible to design agents that specifically target tumor cells. Ehrlich’s early experiments on dye-binding and cell receptors also anticipated the later development of monoclonal antibodies and receptor-specific anticancer drugs. By introducing the principles of selectivity, receptor targeting and chemical precision, Ehrlich and Hata’s 1910 discovery became a distant but essential ancestor of treatments that now define breast cancer care—from hormone therapies like tamoxifen to HER2-targeted agents like trastuzumab and CDK4/6 inhibitors.

References: Ben-Dror (2022), DeVita and Rosenberg (2012), GMN 2403, Hajdu (2012).


Die experimentelle
Chemotherapie der Spirillosen

(Syphilis, Rückfallfieber, Hühnerspirillose, Frambösie)

Von

Paul Ehrlich und S. Hata

Mit Beiträgen von
H. J. Nichols-New York, J. Iversen-St. Petersburg, Bitter-Kairo
und Dreyer-Kairo

Mit 27 Textfiguren und 5 Tafeln

Berlin
Verlag von Julius Springer

Paul Ehrlich and Sahachiro Hata, 1910 *Die experimentelle Chemotherapie der Spirillosen,* Berlin: Verlag von Julius Springer. From the author’s medical library.

1913: Albert Salomon

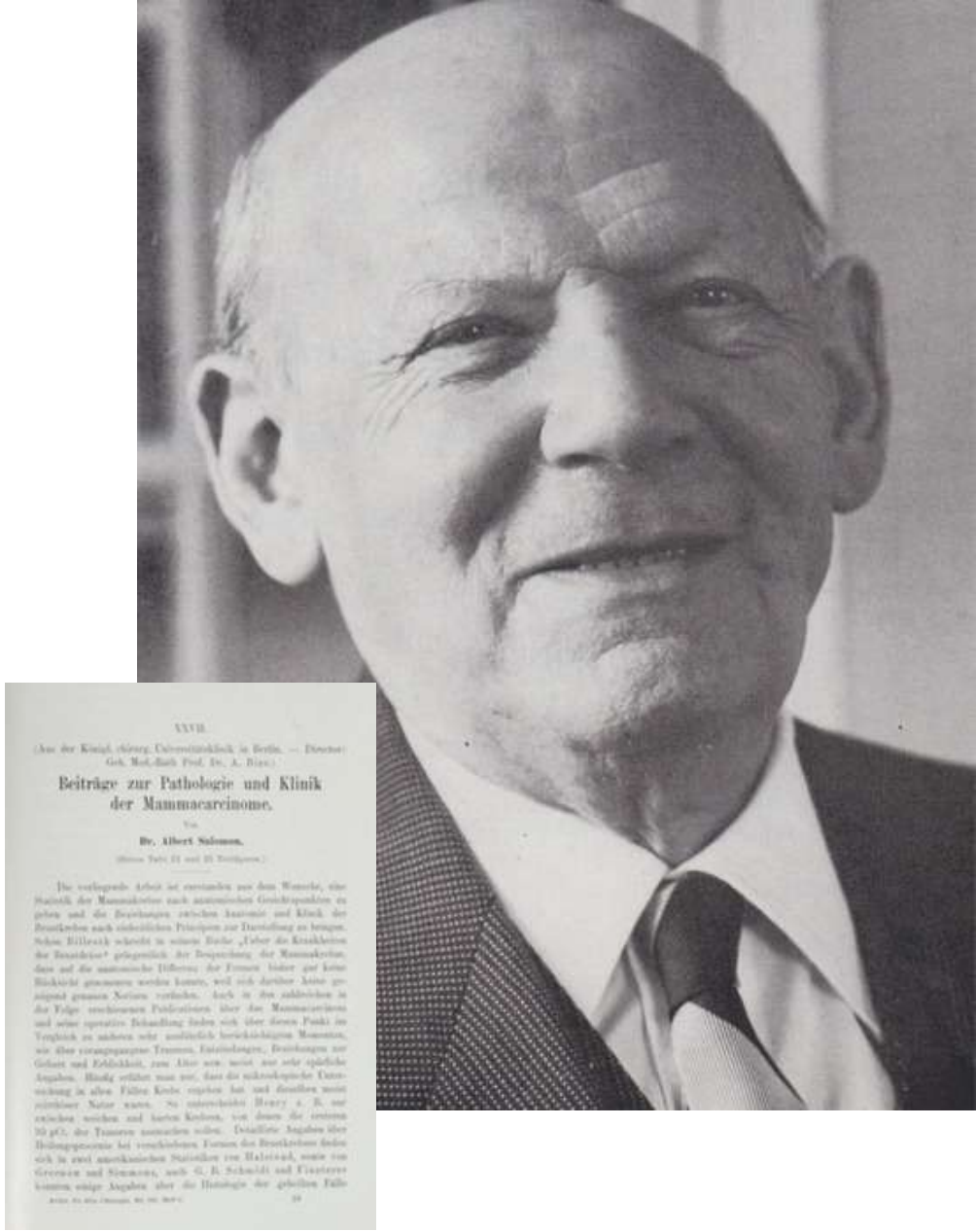
First to show how an X-ray can tell breast cancer vs. non-cancer via microcalcifications, setting up the potential for a mammogram.

Albert Salomon (1883–1976) was a German surgeon and pathologist who made the first systematic study of x-ray imaging of the breast, laying the foundation for modern mammography. In 1913, while working at the University of Berlin, Salomon examined over 3,000 mastectomy specimens using x-rays to correlate radiographic findings with histologic features of breast tumors. He demonstrated that malignant tumors produced distinctive calcifications and irregular densities on x-ray films, distinguishing them from benign lesions. This pioneering correlation between radiology and pathology showed that breast cancer could be identified through non-invasive imaging, decades before clinical mammography became a diagnostic standard.

However, Salomon never linked this new method to the idea of trying to find breast cancer in healthy women.

Although Salomon's work was largely forgotten for years—due partly to the upheavals of World War I and II—his 1913 monograph, Beiträge zur Pathologie und Klinik der Mammakarzinome, became a cornerstone of mammographic science once rediscovered in the mid-20th century. Later researchers such as Stafford L. Warren, Raúl Leborgne and Robert Egan built directly on Salomon's insights, developing clinical mammography for cancer screening in the 1930s–1950s. Salomon is now recognized as the founding figure of mammography, having been the first to prove that breast x-rays could reveal the internal morphology of cancer and thus transform both diagnosis and early detection.

References: GMN 13264, Lukong (2017).



XXVII.

(Aus der Königl. chirurg. Universitätsklinik in Berlin. — Director: Geh. Med.-Rath Prof. Dr. A. Bier.)

Beiträge zur Pathologie und Klinik der Mammacarcinome.

Von

Dr. Albert Salomon.

(Hierzu Tafel IX und 25 Textfiguren.)

Albert Salomon, 1913, Beiträge zur Pathologie und Klinik der Mammacarcinome. *Arch. klin. Chir.*, 101, 573-668.

1929: Geoffrey Keynes

This paper argues for radiation as a less destructive therapy than mastectomy but does not given statistical evidence.

In this 1929 article, Geoffrey Keynes, brother of John Maynard Keynes, reported on a series of 90 patients treated from August 1924 to April 1929 with radium therapy targeted to primary carcinomas of the breast.

Keynes reported that radium was used both pre- and post-operatively and in selected early cases as a stand-alone treatment, to target the primary carcinoma of the breast and the regional lymphatics.

He found that among patients with early, localized disease, radium therapy alone or combined with limited surgery achieved encouraging local control with less morbidity than the traditional Halsted radical mastectomy. Recurrences were common in advanced cases, but Keynes emphasized the palliative value of radium for symptom relief.

This paper helped pioneer the conservative management of breast cancer—laying groundwork for later interest in breast-preserving approaches.

References: Ekmektzoglou (2009), Olson (2002)

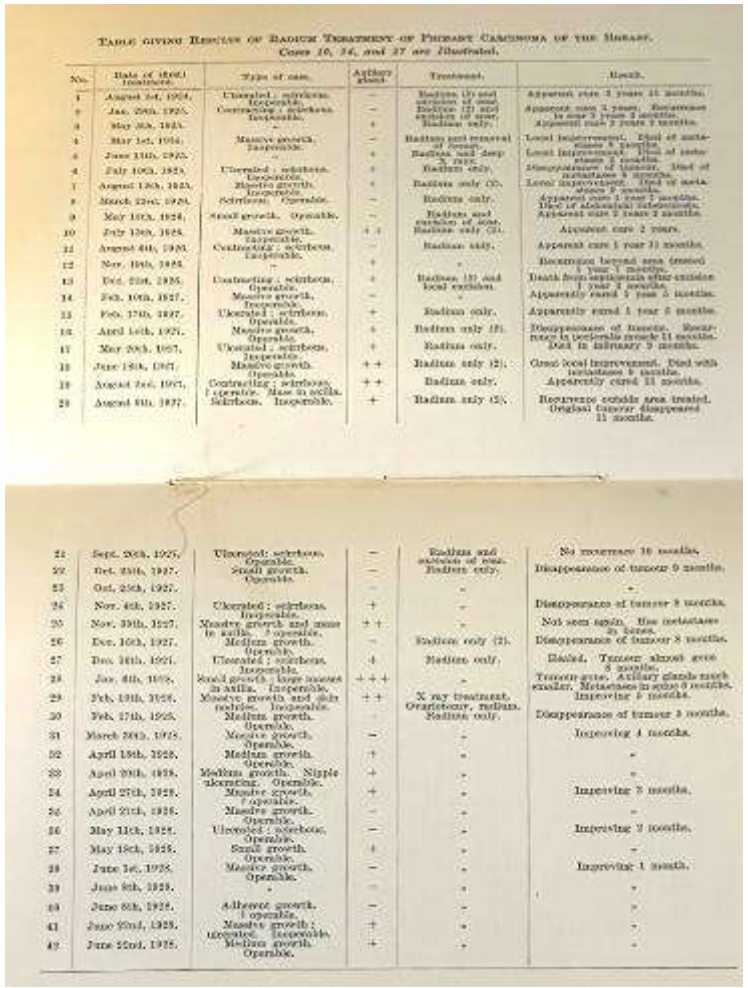
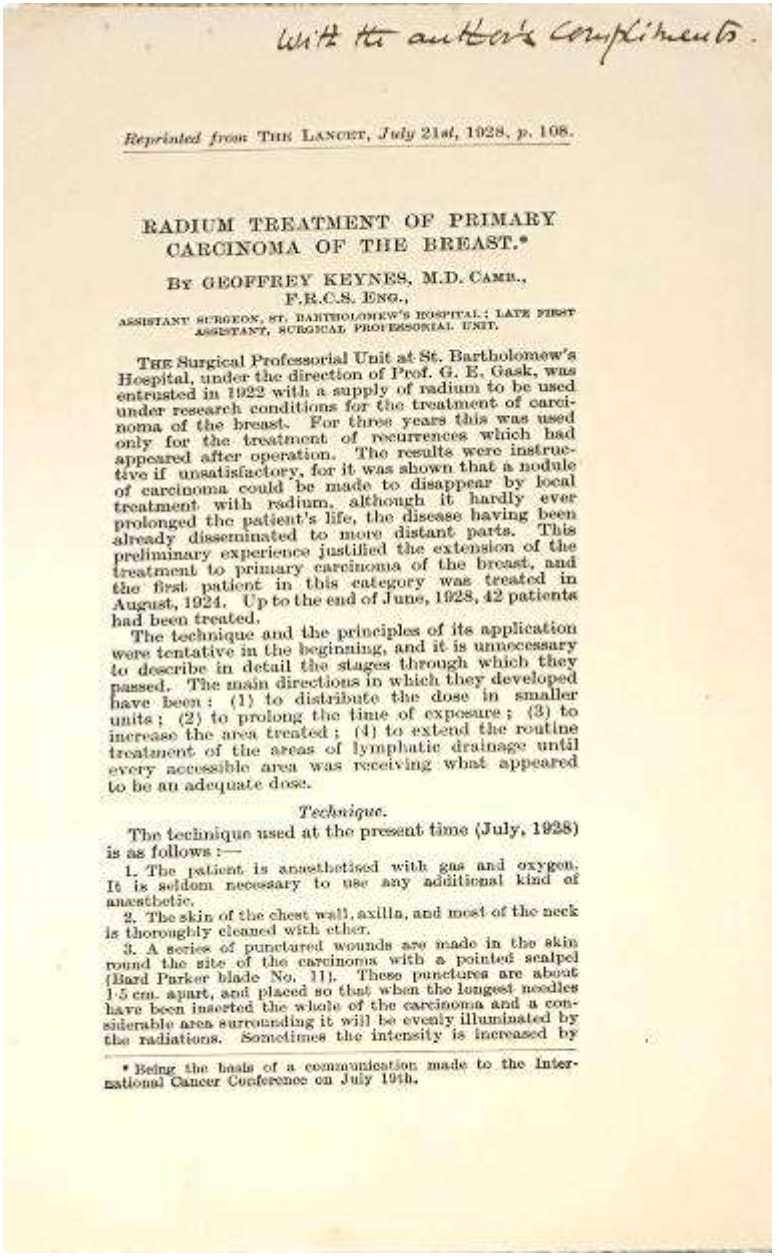


TABLE giving RESULTS OF RADIUM TREATMENT OF PRIMARY CARCINOMA OF THE BREAST.
Cases 10, 14, and 37 are illustrated.

No.	Date of (first) treatment.	Type of case.	Axillary gland.	Treatment.	Result.
1	August 3rd, 1924.	Ulcerated; sclirrhous. Inoperable.	–	Radium (3) and excision of scar.	Apparent cure 3 years 11 months.
2	Jan. 29th, 1925.	Contracting; sclirrhous. Inoperable.	–	Radium (2) and excision of scar. Radium only.	Apparent cure 3 years. Recurrence in scar 3 years 2 months.
3	May 30th, 1925.	–	+	–	Apparent cure 3 years 7 months.
4	May 1st, 1924.	Massive growth. Inoperable.	–	Radium and removal of tumour.	Local improvement. Died of metastases 8 months.
5	June 11th, 1925.	–	+	Radium and deep X rays.	Local improvement. Died of metastases 3 months.
6	July 10th, 1925.	Ulcerated; sclirrhous. Inoperable.	+	Radium only.	Disappearance of tumour. Died of metastases 8 months.
7	August 13th, 1925.	Rapidly growth. Inoperable.	+	Radium only (2).	Local improvement. Died of metastases 9 months.
8	March 22nd, 1926.	Sclirrhous. Operable.	–	Radium only.	Apparent cure 1 year 7 months. Died of accidental pneumonia.
9	May 18th, 1926.	Small growth. Operable.	–	Radium and excision of scar.	Apparent cure 2 years 2 months.
10	July 13th, 1926.	Massive growth. Inoperable.	+ +	Radium only (2).	Apparent cure 2 years.
11	August 4th, 1926.	Contracting; sclirrhous. Inoperable.	–	Radium only.	Apparent cure 1 year 11 months.
12	Nov. 10th, 1926.	–	+	–	Recurrence beyond area treated 1 year 1 months.
13	Dec. 21st, 1926.	Contracting; sclirrhous. Operable.	+	Radium (3) and local excision.	Death from septicæmia after excision 1 year 2 months.
14	Feb. 10th, 1927.	Massive growth. Inoperable.	–	–	Apparently cured 1 year 6 months.
15	Feb. 17th, 1927.	Ulcerated; sclirrhous. Operable.	+	Radium only.	Apparently cured 1 year 6 months.
16	April 14th, 1927.	Massive growth. Operable.	+	Radium only (2).	Disappearance of tumour. Recurrence in pectoralis muscle 11 months.
17	May 20th, 1927.	Ulcerated; sclirrhous. Inoperable.	+	Radium only.	Died in February 9 months.
18	June 18th, 1927.	Massive growth. Operable.	+ +	Radium only (2).	Great local improvement. Died with metastases 8 months.
19	August 2nd, 1927.	Contracting; sclirrhous. Inoperable. Mass in axilla. Sclirrhous. Inoperable.	+ +	Radium only.	Apparently cured 11 months.
20	August 8th, 1927.		+	Radium only (2).	Recurrence outside area treated. Original tumour disappeared 11 months.
21	Sept. 20th, 1927.	Ulcerated; sclirrhous. Operable.	–	Radium and excision of scar.	No recurrence 10 months.
22	Oct. 25th, 1927.	Small growth. Operable.	–	Radium only.	Disappearance of tumour 9 months.
23	Oct. 25th, 1927.	–	–	–	–
24	Nov. 4th, 1927.	Ulcerated; sclirrhous. Inoperable.	+	–	Disappearance of tumour 8 months.
25	Nov. 30th, 1927.	Massive growth and mass in axilla. Operable.	+ +	–	Not seen again. Has metastases in bones.
26	Dec. 10th, 1927.	Medium growth. Operable.	–	Radium only (2).	Disappearance of tumour 8 months.
27	Dec. 16th, 1927.	Ulcerated; sclirrhous. Inoperable.	+	Radium only.	Healed. Tumour almost gone 8 months.
28	Jan. 4th, 1928.	Small growth; large masses in axilla. Inoperable.	+ + +	–	Tumour gone. Axillary glands much smaller. Metastases in spine 9 months.
29	Feb. 10th, 1928.	Massive growth and skin nodules. Inoperable.	+ +	X ray treatment. Ovariotomy, radium. Radium only.	Improving 5 months.
30	Feb. 17th, 1928.	Medium growth. Operable.	–	–	Disappearance of tumour 3 months.
31	March 20th, 1928.	Massive growth. Operable.	–	–	Improving 4 months.
32	April 13th, 1928.	Medium growth. Operable.	+	–	–
33	April 20th, 1928.	Medium growth. Nipple ulcerating. Operable.	+	–	–
34	April 27th, 1928.	Massive growth. Inoperable.	+	–	Improving 3 months.
35	April 27th, 1928.	Massive growth. Operable.	–	–	–
36	May 11th, 1928.	Ulcerated; sclirrhous. Operable.	–	–	Improving 2 months.
37	May 18th, 1928.	Small growth. Operable.	+	–	–
38	June 1st, 1928.	Massive growth. Operable.	–	–	Improving 1 month.
39	June 8th, 1928.	–	–	–	–
40	June 8th, 1928.	Adherent growth. Operable.	–	–	–
41	June 22nd, 1928.	Massive growth; ulcerated. Inoperable.	+	–	–
42	June 22nd, 1928.	Medium growth. Operable.	+	–	–



with the author's compliments.

Reprinted from THE LANCET, *July 21st, 1928, p. 108.*

RADIUM TREATMENT OF PRIMARY CARCINOMA OF THE BREAST.*

BY GEOFFREY KEYNES, M.D. CAMB., F.R.C.S. ENG.,
ASSISTANT SURGEON, ST. BARTHOLOMEW'S HOSPITAL; LATE FIRST ASSISTANT, SURGICAL PROFESSORIAL UNIT.

THE Surgical Professorial Unit at St. Bartholomew's Hospital, under the direction of Prof. G. E. Gask, was entrusted in 1922 with a supply of radium to be used under research conditions for the treatment of carcinoma of the breast. For three years this was used only for the treatment of recurrences which had appeared after operation. The results were instructive if unsatisfactory, for it was shown that a nodule of carcinoma could be made to disappear by local treatment with radium, although it hardly ever prolonged the patient's life, the disease having been already disseminated to more distant parts. This preliminary experience justified the extension of the treatment to primary carcinoma of the breast, and the first patient in this category was treated in August, 1924. Up to the end of June, 1928, 42 patients had been treated.

The technique and the principles of its application were tentative in the beginning, and it is unnecessary to describe in detail the stages through which they passed. The main directions in which they developed have been: (1) to distribute the dose in smaller units; (2) to prolong the time of exposure; (3) to increase the area treated; (4) to extend the routine treatment of the areas of lymphatic drainage until every accessible area was receiving what appeared to be an adequate dose.

Technique.

The technique used at the present time (July, 1928) is as follows:—

1. The patient is anæsthetised with gas and oxygen. It is seldom necessary to use any additional kind of anæsthetic.
2. The skin of the chest wall, axilla, and most of the neck is thoroughly cleaned with ether.
3. A series of punctured wounds are made in the skin round the site of the carcinoma with a pointed scalpel (Bard Parker blade No. 11). These punctures are about 1·5 cm. apart, and placed so that when the longest needles have been inserted the whole of the carcinoma and a considerable area surrounding it will be evenly illuminated by the radiations. Sometimes the intensity is increased by

* Being the basis of a communication made to the International Cancer Conference on July 19th.

Geoffrey Keynes, 1929, Radium Treatment of Primary Carcinoma of the Breast, *Lancet*, Inscribed by Keynes. From the author's medical library.

1932: Geoffrey Keynes

Argued that radium treatment could match mastectomy results.

In his 1932 paper, Keynes reported his experience treating carcinoma of the breast using a combination approach: surgical excision of the primary tumor plus the insertion of radium needles (so-called “interstitial radium”) into the the residual breast tissue, axilla and supraclavicular areas. He presented a relatively large case series (171 patients) subdivided by clinical class (e.g. no palpable lymph nodes vs palpable nodes vs inoperable) and followed them over time to assess survival.

Keynes argued that this method could achieve outcomes comparable to radical mastectomy (which was then the standard surgical practice) but with less mutilation. He pointed out that many failures of radical surgery stemmed from undetected residual disease in the breast bed and lymphatic zones, which might be better addressed by adding radium treatment locally.

References: Ekmektzoglou (2009), Lukong (2017), Olson (2002).

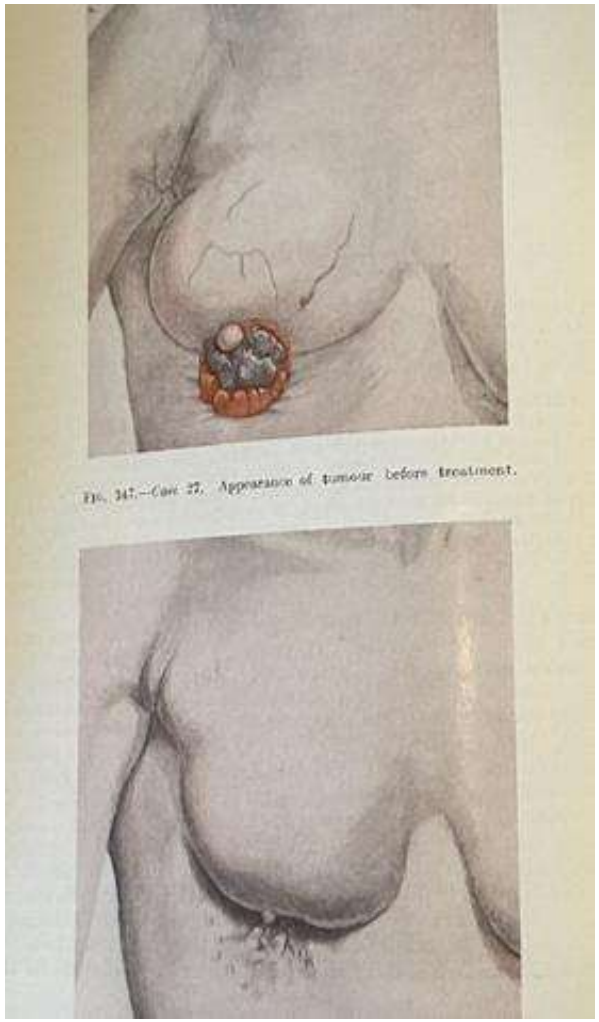
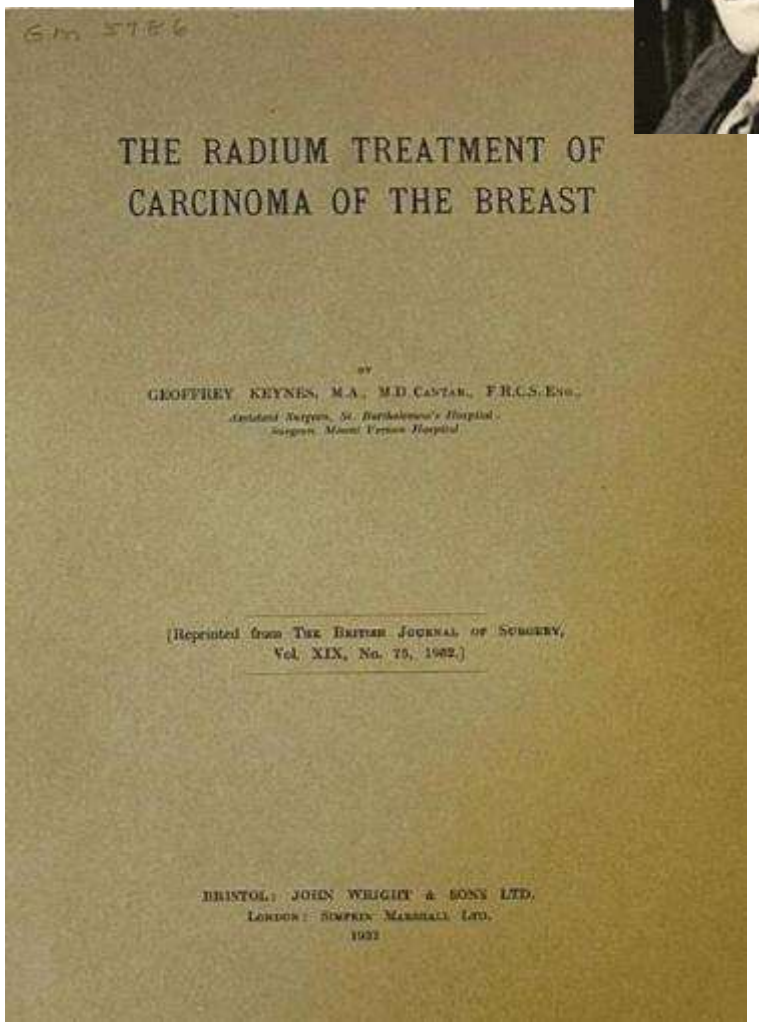


FIG. 347.—Case 27. Appearance of tumour before treatment.

Less mutilation with radium treatment than mastectomy.



THE RADIUM TREATMENT OF CARCINOMA OF THE BREAST

BY

GEOFFREY KEYNES, M.A., M.D. CANTAB., F.R.C.S. ENG.,

Assistant Surgeon, St. Bartholomew's Hospital;
Surgeon, Mount Vernon Hospital.

(Reprinted from THE BRITISH JOURNAL OF SURGERY, Vol. XIX, No. 75, 1932.)

BRISTOL: JOHN WRIGHT & SONS LTD.
LONDON: SIMPKIN MARSHALL LTD.
1932

Geoffrey Keynes, 1932, *The Radium Treatment of Carcinoma of the Breast, Journal Reprint from British Journal of Surgery*, Vol XIX, 1932. First edition. From the author’s medical library.

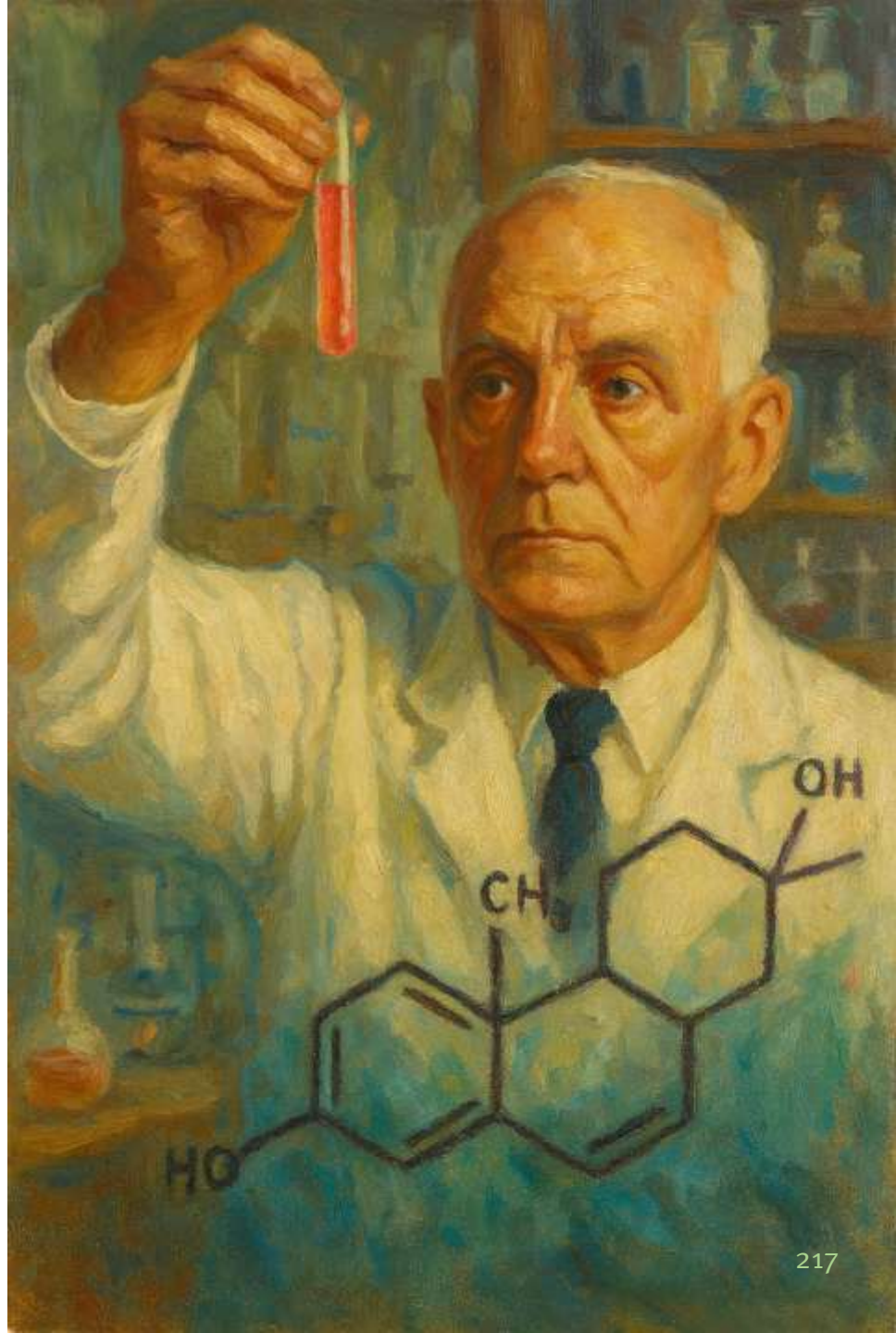
1941: Charles B. Huggins

First linked prostate cancer to hormones. Later showed that breast cancer linked to hormones. His work earned a Nobel Prize and was highly influential in the development of endocrine therapies for breast cancer.

Charles B. Huggins, a Canadian-born surgeon and researcher at the University of Chicago, revolutionized cancer therapy by demonstrating that some tumors depend on hormones for their growth. In 1941, he showed that prostate cancer could be controlled by suppressing testosterone production through surgical castration or estrogen administration—marking the first time that a systemic, rather than purely surgical, intervention could shrink malignant tumors. This discovery established the principle that hormonal environments could directly influence tumor behavior and opened an entirely new field of endocrine therapy in oncology.

In the following decades, Huggins extended this hormonal framework to breast cancer, revealing that estrogens serve as key growth drivers in many mammary tumors. He demonstrated that reducing estrogen levels or countering their effects—sometimes even by increasing androgen activity—could cause breast tumors to regress. These findings laid the biological foundation for the later development of selective estrogen receptor modulators and aromatase inhibitors, which remain mainstays of breast cancer treatment today. Huggins' work transformed the understanding of cancer as a hormonally regulated disease and permanently changed the course of cancer medicine.

References: ASCO Foundation (2025). Benadada et al. (2024), Olson (2002, p. 81).



Charles Huggins and Clarence Hodges, 1941, "I. The Effect of Castration, of Estrogen and of Androgen Injection on Serum Phosphatases in Metastatic Carcinoma of the Prostate," *Cancer Research*. pp. 293-297.

1944: Alexander Haddow

Showed that synthetic estrogens can cause regression of breast cancer.

Alexander Haddow's 1944 paper was one of the first systematic demonstrations that hormonal manipulation could influence the course of breast cancer. Haddow and his colleagues administered synthetic estrogens—primarily stilboestrol—to women with advanced breast carcinoma, many of whom had exhausted other treatment options. Surprisingly, in a subset of these patients, tumor regression and clinical improvement were observed. This finding was paradoxical, as estrogens were known to promote the growth of some breast cancers, yet under certain circumstances (particularly in postmenopausal women), they appeared to induce tumor involution. Haddow proposed that the physiological stress of hormonal imbalance could selectively damage malignant cells—a principle that foreshadowed later strategies of endocrine therapy.

The implications of Haddow's work were far-reaching. His study laid the experimental foundation for modern hormonal therapy in breast cancer, influencing subsequent research that led to the development of anti-estrogens (such as tamoxifen) and aromatase inhibitors. It demonstrated that systemic therapy could be rationally designed to exploit the biological dependence of tumors on hormonal environments, marking an early shift from purely surgical approaches to targeted biochemical interventions. Haddow's insight into the dual nature of hormones—capable of both promoting and suppressing cancer—helped launch decades of research into receptor biology and endocrine responsiveness.

References: GMN 2659.3

BRITISH MEDICAL JOURNAL

Alexander Haddow et al., 1944, "Influence of Synthetic Oestrogens upon Advanced Malignant Disease", *British Medical Journal*, 2:393–398. Source: Royal College of Physicians.

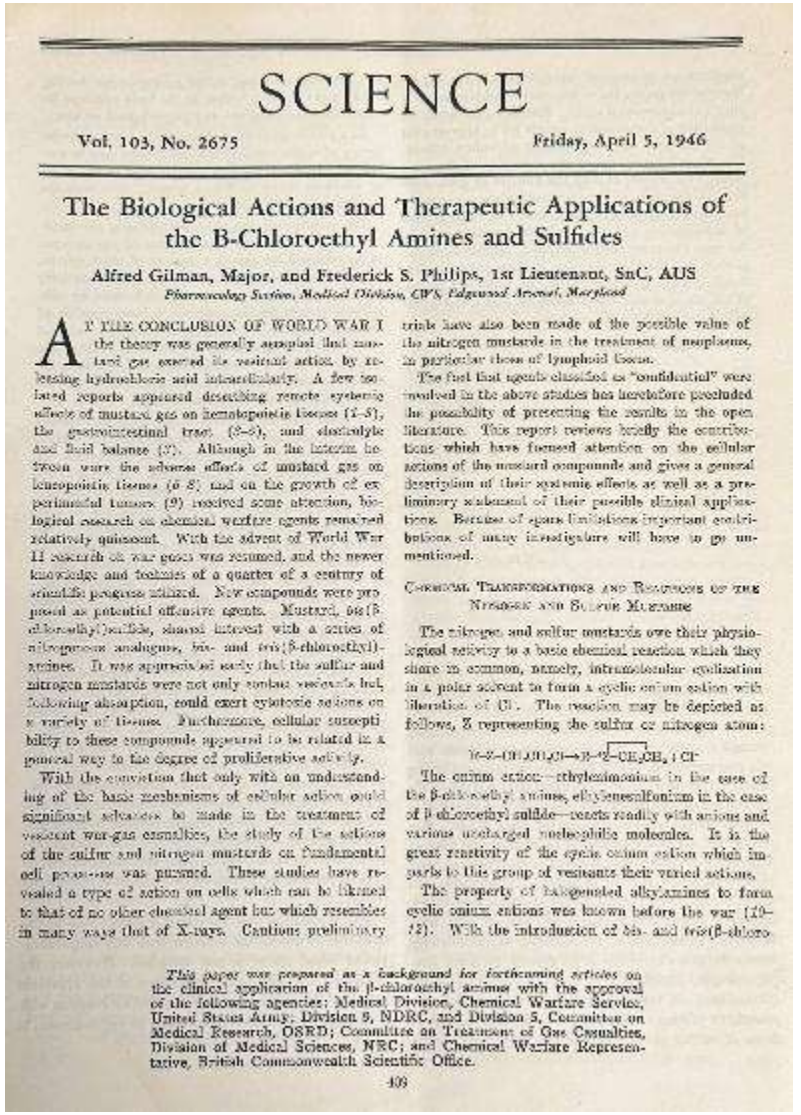
1946: Alfred Gilman and Frederick Philips

This work inaugurated a new era in oncology, showing that chemical agents could systematically suppress malignant growth and setting the stage for decades of discovery of chemotherapies.

The development of nitrogen mustard as a chemotherapy marked the beginning of modern cancer pharmacology—a direct outgrowth of wartime chemical weapons research. During World War II, physicians and pharmacologists, including Louis Goodman and Alfred Gilman at Yale, observed that soldiers exposed to sulfur mustard gas (a chemical warfare agent) suffered profound suppression of their bone marrow and lymphoid tissues. This cytotoxic effect on rapidly dividing cells led researchers to hypothesize that a related compound, nitrogen mustard (methyl-bis(β-chloroethyl)amine), might selectively target rapidly proliferating cancer cells, especially lymphomas. In 1942, the first human trials using nitrogen mustard were conducted under military secrecy at Yale–New Haven Hospital, treating a patient with advanced non-Hodgkin lymphoma and producing dramatic—though temporary—tumor regression.

In their 1946 paper, Alfred Gilman and Frederick S. Philips provided the first comprehensive scientific account of these agents' pharmacology and clinical potential. The authors described how the β-chloroethyl amines acted as alkylating agents, forming highly reactive intermediates that crosslinked DNA and inhibited cell division. They detailed the compounds' toxicity profile, mechanism of action and observed tumor responses, noting particularly their effects on lymphoid malignancies and other rapidly growing tissues. This article was both a scientific milestone and a public revelation—translating secret wartime research into the literature and introducing chemotherapy as a therapeutic discipline.

References: Conant (2020), DeVita and Rosenberg (2012), Einhorn (1985), Gilman (1963), GMN 3788, Olson (2002).



SCIENCE

Vol. 103, No. 2675 Friday, April 5, 1946

The Biological Actions and Therapeutic Applications of the B-Chloroethyl Amines and Sulfides

Alfred Gilman, Major, and Frederick S. Philips, 1st Lieutenant, SnC, AUS

Pharmacology Section, Medical Division, CWS, Edgewood Arsenal, Maryland

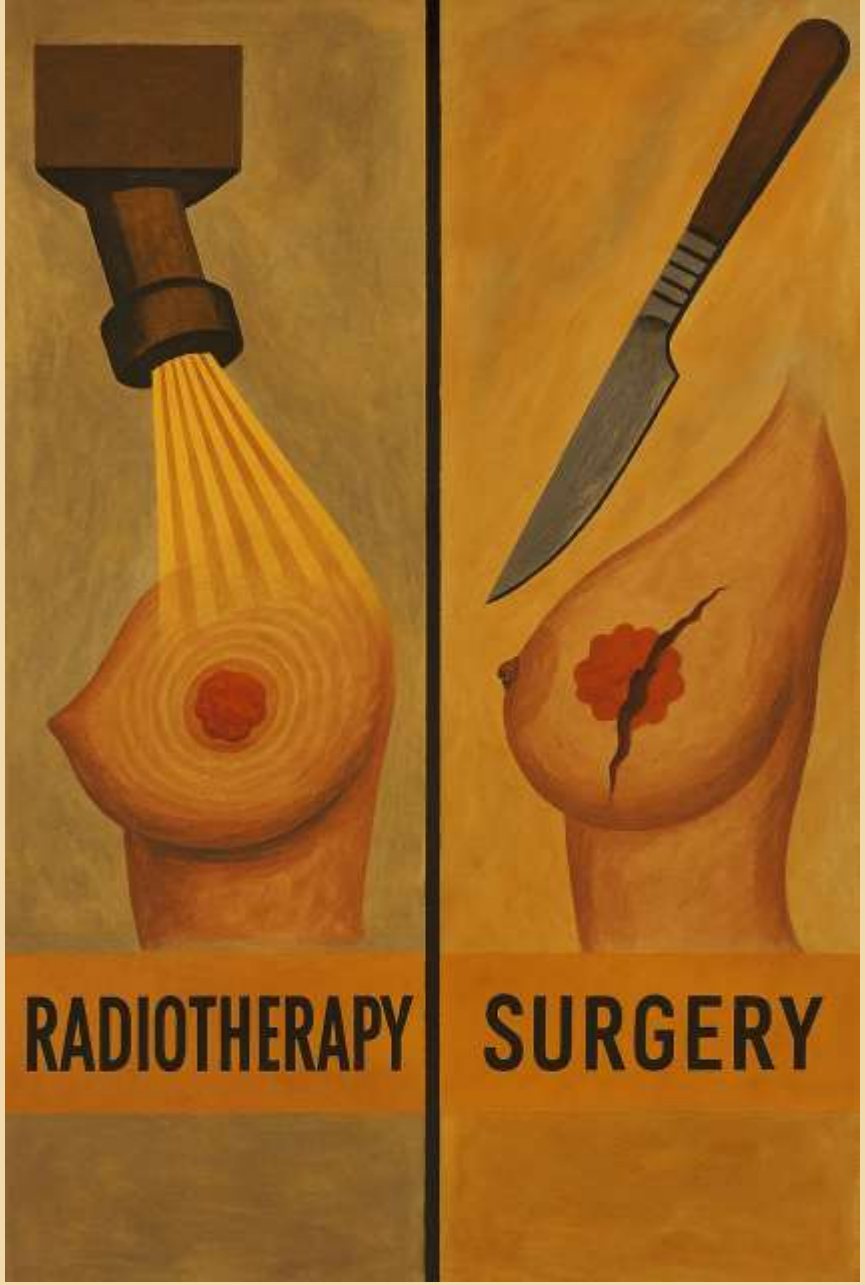
Alfred Gilman and Frederick S. Philips, 1946, "The Biological Actions and Therapeutic Applications of the B-Chloroethyl Amines and Sulfides," *Science,* Volume 103, pp. 409-415. From the author's medical library.

1948: Robert McWhirter

Showed radiation could achieve the same survival rates as radical mastectomy after Keynes gave up the fight.

JJ Newmark: "On 7 January 1948, a meeting was held at the Royal Society of Medicine in London. Its purpose was to settle a controversy. Robert McWhirter, an Edinburgh-based radiotherapist, had been invited to defend the scandalous position advocated by Geoffrey Keynes ten years previously: that radical mastectomy offered no survival advantage when compared to simple mastectomy plus local radiotherapy. The negative publicity surrounding the meeting proved overwhelming for Keynes and he abandoned his research. Indeed, the events of the meeting may have been quietly buried were it not for McWhirter who, over the following decade, pursued Keynes' research. He refined his technique, sparing patients the disfiguring and painful radical mastectomy without compromising overall survival. Later, he garnered support from other researchers, which led to a series of papers confirming his original findings. Towards the end of his career, he also made contributions to service organisation and hormone therapy, eventually holding the Presidency of the Faculty of Radiologists. By keeping the controversy alive, McWhirter was instrumental in overturning 60 years of surgical dogma. He remains a pivotal figure in the history of breast cancer." Daniel de Moulin (p. 111): A method somewhat comparable to the one just mentioned is simple mastectomy – ablatio simplex – followed by radical irradiation. Its proponent is Robert McWhirter (b. 1904), radiotherapist in Edinburgh. In TNM Stage I patients, he argued, radical mastectomy would overshoot the mark, whereas in Stage II, the same procedure might be inadequate since the disease often spreads beyond the axilla when the lymph nodes are involved.[298] The McWhirter technique gave rise to a flood of papers, both for and against, it seems to have its adherents especially in Great Britain.

References: Ekmektzoglou (2009), Lukong (2017), Olson (2002, p. 91).



Robert McWhirter, 1948, “Value of Simple Mastectomy in Treating Cancer of the Breast," *British Journal of Radiology*, Volume 31, p. 599-610. From the author’s medical library.

Appendix 2: References

Detail on Citations in this Report

THE MIDDLESEX HOSPITAL, 1876. (*See page 465.*)

From the Wellcome Institute Collection: In 1792 the Middlesex Hospital (pictured here in 1876) established Britain's first cancer wards. It was one of the world's earliest clinical institutions dedicated to the care and treatment of cancer patients, and there were two wards, one for women and one for men. While most hospitals in this period refused to admit patients with chronic and incurable diseases like cancer, the Middlesex insisted that patients could stay until "relieved by art or released by death". The hospital not only provided treatment for people living with cancer, but allowed surgeons and physicians to study the disease, its causes, characteristics and potential cures.

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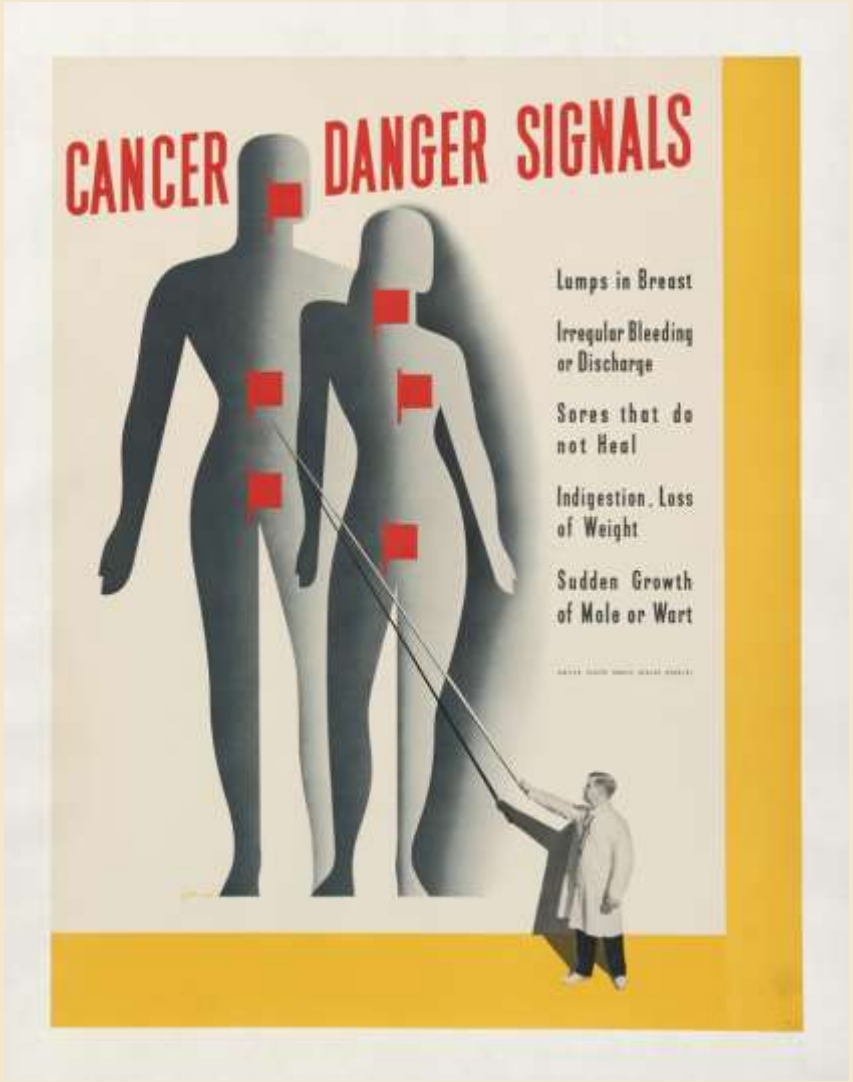
Appendix 3: Accessing Stifel Reports

Our Investment Banking Reports (and Subscription Process)



From the Wellcome Institute Collection: The first effective chemotherapies were developed in the 1940s. However, public health professionals and doctors both continued to think that prevention and early detection offered patients greater opportunities for survival than treatment. In the middle of the 20th century, governments in Europe and North America developed comprehensive public health campaigns designed to educate people about the early warning signs of cancers. The campaigns prompted the public to seek medical advice early and often and make 'healthy' decisions about what they ate, how much they exercised, and whether they smoked.

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Aug 18, 2025 (Cardiovascular Drugs)
Jul 14, 2025 (Top 40 Pharma)
Jun 23, 2025 (Science and Truth)
May 12, 2025 (MFN Policy)
May 5, 2025 (NIH Cuts, China Tariffs)
Apr 28, 2025 (Eyes on Washington DC)
Apr 21, 2025 (FDA Shifts, Buyside Update)
Apr 14, 2025 (Wild Week in Market)
Apr 7, 2025 (Biotech Market Break)
Mar 31, 2025 (China Biotech Update)
Mar 24, 2025 (Healthcare Reform)
Feb 24, 2025 (Retail Pharma Trends)
Feb 10, 2025 (Pharma Earnings)
Jan 27, 2025 (Women's Health, Obesity)
Dec 17, 2024 (Biotech Blues)
Nov 25, 2024 (Biotech Balance Sheets)
Nov 18, 2024 (New Administration)
Nov 4, 2024 (Election, Obesity)
Oct 21, 2024 (China, Pfizer)
Oct 7, 2024 (VC update)
Sep 23, 2024 (The Fed Rate Cut)
Sep 9, 2024 (Sector Outlook)
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July 8, 2024 (Obesity Market Update)
June 17, 2024 (Lab Market)
June 8, 2024 (Oncology Review)
May 27, 2024 (GLP-1's)
May 20, 2024 (Returning Capital)
May 13, 2024 (Brain, AlphaFold 3)
May 6, 2024 (Earnings, Obesity)
April 29, 2024 (M&A, Japan)
April 22, 2024 (Pharma Pricing)
April 15, 2024 (AI in Pharma)
April 8, 2024 (The Buyside)
April 1, 2024 (Biotech Balance Sheets)
March 25, 2024 (Women's Health)
March 18, 2024 (Inflammasome)
March 11, 2024 (IRA, Immunology)
March 4, 2024 (Biotech Employment)
Feb 26, 2024 (Biotech Strategy)
Feb 19, 2024 (Big Drugs, Autoantibodies)
Feb 12, 2024 (Fibrosis, Endometriosis)
Feb 5, 2024 (Severe Disease in Women)
Jan 29, 2024 (Pharma R&D Productivity)
Dec 18, 2023 (Expectations for Future)
Dec 11, 2023 (ASH, R&D Days)
Dec 4, 2023 (Big Pharma, CEA)
November 20, 2023 (M&A)
November 13, 2023 (AHA, Bear Market)
November 7, 2023 (Unmet Needs)
October 30, 2023 (ADCs)
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