Breast Cancer: Targets and Therapy Dovepress

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PERSPECTIVES

The History of Breast Cancer Early Detection: 1865 – 2020

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Summary: Early detection is a relative newcomer in medicine, with its efficacy relying not only on therapy but also on the availability of evidence supporting the advantage of treatment at an earlier stage. Late 19th century histologic evidence that cancer begins as a single primary focus and Halsted's centrifugal theory of stepwise spread (breast, regional nodes, and systemic distribution) provided the rationale for both en bloc surgery and the lifesaving benefit of early detection. Clinicians soon noticed exceptions to this ordered timeline, and pathologists identified histological features that questioned its primacy; however, Bernard Fisher spearheaded the initial challenge. His groundbreaking hypothesis that breast cancer was systemic from its inception was supported indirectly by the 3rd arm of National Surgical Adjuvant Breast and Bowel Project (NSABP) B04 and B06. These trials bolster his contention that a patient's fate was dependent on shed cells rather than the extent of the operation; however, the breast cancer wars of the 1970s focused on competing local treatments. When follow-up data revealed equivalent survival results, it established lumpectomy/radiation as equal to mastectomy, but overlooked Fisher's attack on Halsted's theory. Two mid-20th century medical innovations also played a role in the history of early detection: population-based screening by detecting cancer before it became clinically evident, and repurposing systemic treatment designed for metastatic recurrence into adjuvant chemotherapy. This review illustrates how these advances have led to the incremental acceptance of Fisher's hypothesis and recognition that invasive cancer cannot be equated with localized disease, regardless of how early it might be detected.

Keywords: early detection of breast cancer, Bernard Fisher, Halsted, mammography, liquid biopsy, circulating tumor cells

Introduction: The Emergence of Early Detection in Breast Cancer

Early detection, a relative newcomer in medical history, fundamentally requires not only effective treatment, but also evidence that earlier interventions yield better outcomes. The advent of general anesthesia and improved surgical hemostasis enabled surgeons to safely excise tumors. However, two leading medical textbooks in the late 1800s, expressed skepticism regarding the curability of breast cancer through surgery. At that time, breast cancer was thought to be a systemic disease of multiple origins, a notion stemming from Galen's theory that black bile causes incurable cancer.[1] However, this prospect shifted when microscopic studies revealed that cancer originates as a single localized growth and can be cured if completely removed.[2] This discovery has marked a significant shift in our understanding of the origin of breast cancer. Despite this, early radical surgical techniques sparked debated, particularly over the need for extensive resections, which laid the groundwork for developing more targeted approaches to early detection.

The Halstedian Legacy: Radical Surgery and Early Detection

In the late 19th century, many techniques were described for the "complete" removal of breast cancer. In 1867, total mastectomy became widely advocated, emphasizing that "mammary cancer requires careful extirpation of the entire organ" and that disease lymphatics should be routinely removed.[3,4] This practice gained traction in Germany in 1875, when anatomist Heinrich Wilhelm Waldeyer demonstrated through careful microscopic studies that cancer begins as a single primary focus and can be cured if completely removed.[5] Building on this, the complete removal of the entire

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breast was recommended, regardless of the tumor's size.[4] In the United States during the 1880s, axillary dissection – often referred to as "cleaning out the axilla" – was routinely performed alongside breast removal.[4,6] Despite many surgeons advocating for extensive resection of breast and surrounding tissue, there was no clear consensus on the extent of an adequate oncologic breast cancer resection until William Halstead (Figure 1) published, "The results of operations for the cure of cancer of the breast performed at the Johns Hopkins Hospital from June 1889 – January 1894"[7] Halsted introduced the "radical mastectomy", an en bloc resection of all suspected tissues, including both pectoral muscles and entire axilla.[7] Halsted refined Waldeyer's earlier concept and proposed the 'centrifugal theory' of cancer spread, which suggested that cancer extends to ever-growing arcs emanating from a central focus.[7] Halsted's theory provides the rationale for the early detection of cancer; however, it also complicates its evolution by justifying more radical surgeries. The larger the operative circle, the higher is the likelihood of complete removal. Halsted's influence permeated the entire generation of American physicians who advocated for more radical surgery.

Challenges to Radical Surgery: The Rise of Systemic Theories

It was not until the early 20th century that doubts regarding the effectiveness of radical surgery for breast cancer began to emerge in European medical societies. In 1924, Keynes published, "The Radium Treatment of Primary Carcinoma of the Breast", in which he showed non-operative improvements in the treatment of breast cancer using radiation therapy.[8] This nonsurgical intervention challenged the conventional approach to radical surgery and sparked further skepticism across Europe. In France, radiation therapy had frequently become the primary treatment for breast cancer, diverging from the reliance on radical surgery. Against the backdrop of World War II, the shortage of surgeons qualified to perform radical mastectomy presented an opportunity for innovation. Robert McWhirter, a Scottish radiologist, emerged as a pioneer who combined limited surgery with radiation, making him the first non-surgeon to treat breast cancer.[9] However, the controversy surrounding radiation therapy versus radical surgery overlooked the essential aspects of Halsted's approach. Halsted emphasized the significance of meticulous breast examinations, sometimes lasting up to an hour, to detect even

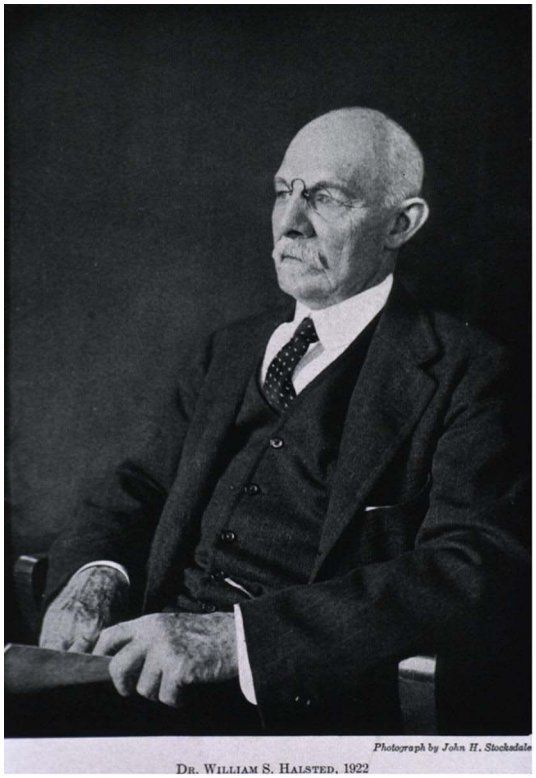

Figure 1 William Stewart Halsted (1852–1922): A prominent American surgeon who introduced radical mastectomy as a treatment for breast cancer in the late 19th century, setting a foundation for improved survival rates. *Obtained from National Library of Medicine.*

the smallest possible tumors. The concept of centrifugal theory, which relies on timely intervention with its expanding arcs, suggests that a cure is possible if the cancer can be removed before spreading beyond the circle encompassing the regional lymph nodes. Therefore, the challenges posed by Halsted's theory played an integral role in the history of early detection.

Bernard Fisher's Paradigm Shift: Breast Cancer as a Systemic Disease

While Halsted's centrifugal theory linked early detection and radical surgery, doubts about this approach persisted for decades. It was not until the 1970s that a significant challenge emerged, led by Bernard Fisher of Pittsburgh (Figure 2). Fisher proposed a groundbreaking hypothesized: that breast cancer is a systemic disease even at its earliest stages.[10] His hypothesis, which contradicted Halsted's focus on local control, was supported by two major prospective randomized control trials conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP) trials.[11,12] These trials led Fisher to conclude that the extent of local treatment is irrelevant because the fate of the patient is determined by cells shed prior to treatment.[9] The first trial, NSAPB-04, which examined axillary treatment, was largely forgotten. However, the second trial, B-06, gained significant attention because it demonstrated that breast-conservative surgery combined with radiation was just as effective as mastectomy in terms of survival outcomes.[11]

Although evidence showed that delaying treatment of microscopic cancer in axilla or breast did not affect survival for up to 20 years, it was often disregarded because women not only wanted to survive, but survive with intact breasts. Radiation after lumpectomy, while not improving overall survival rates, was shown to reduces local recurrence and the need for salvage mastectomies.[11] This transformed Fisher from a man with a paradigm-shifting hypothesis to a feminist hero, as he proved that lumpectomy combined with radiation was as effective as mastectomy in the treatment of early breast cancer. However, Fisher expressed his frustration over the lack of recognition for the broader implications of his trials, stating,

> "Unfortunately, many clinicians have perceived these trials solely as administrative exercises conducted to compare the outcomes of patients subjected to different local regional treatments. There is considerably less awareness that these studies simultaneously tested the worth of two separate hypotheses associated with the biology of tumor metastases."[10]

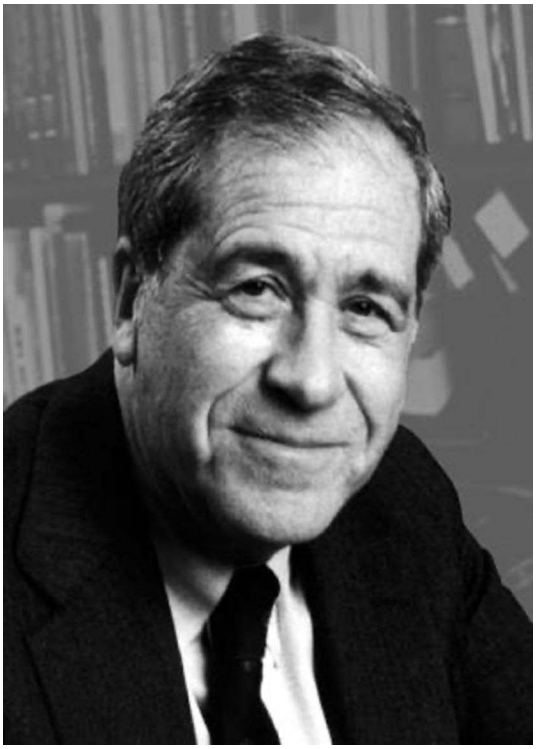

Figure 2 Bernard Fisher (1929–2002): An influential American surgeon and researcher who conducted landmark studies in the mid-20th century that challenged the prevailing notion of radical mastectomy, advocating for use of systemic therapy at early stages and breast-conserving surgeries. *Image provided by University of Pittsburgh*.

The Role of Tumor Biology in Treatment Outcomes

Although Bernard Fisher is widely acknowledged as one of the early proponents who directly challenged Halsted's centrifugal theory, it is important to recognize that he was not the first to hypothesize a systemic component at the time of initial diagnosis. Willy Meyer, best known for his role as a co-developer of radical mastectomy in New York, was actually the first physician to put forth this concept. Meyer devised a technique distinct from Halsted's approach, and his predominantly local practice allowed him to closely follow up with his patients over extended periods. In his 1916 summary, Meyer acknowledged the inherent limitations of radical mastectomy, stating,

> "The same careful and thorough operation carried out in two patients in identically the same way by the same surgeon may prove a complete cure in one while in the other it may be followed by rapid local and regionary recurrence or general metastases. The ultimate fate of these patients is not dependent upon the surgeon's work, but is determined by certain conditions."[13]

Over the subsequent 14 years, Meyer further expanded on these insights, culminating in his 1931 book titled, "Cancer - Its Origin, Its Development, and Its Self-Perpetuation. The Therapy of Operable and Inoperable Cancer in light of a Systemic Conception of Malignancy".[14] Despite his recognition of the shortcomings of the local treatment, Meyer's ideas failed to gain traction. This was largely due to the lack of support for his systemic treatment, which involved induced acidosis, a method both ineffective and dangerous. Meyer et al did not consider the systemic conception of malignancy contradictory to either radical surgery or early detection. However, Meyer's observation that "the virulence of the original disease" determined "the ultimate fate of these patients" prompted pathologists to begin correlating clinical outcomes with the gross and microscopic features of resected tumors.

The Influence of Tumor Grading on Breast Cancer Prognosis

In 1925, Greenough described a histologic classification method that quantified three factors to determine three grades of malignancy. This classification revealed a strong correlation between the tumor grades and 5-year survival rates: 63% of the lowest grade, 33% of the middle grade, and none of the highest grades were cured with radical mastectomy.[15] Similar findings were reported by Patey and Scharff, who studied 50 patients operated upon by the same surgeon between 1919 and 1923.[16] In 1950, Bloom further refined the classification by adding the number of mitoses and assigning points to a composite score, which resulted in a numerical malignancy grade.[17] This method was applied to 1409 patients treated between 1936 and 1949 and correlated with differences in survival at five, ten, and fifteen years of follow-up post-surgery.[18]

Although these survival rates were reported based on tumor grade, it was recognized that tumor grade is an inherent characteristic, independent of the time of detection. This realization led to a school of thought, emphasizing the biological behavior of individual tumors as a crucial factor in determining of treatment outcomes. A provocative study by Park and Lees concluded that "treatment, whether early or late in the disease, had little influence on survival, if at all, and more probably not at all".[19] Although this study predated Fisher's work, it raised important questions about the value of early detection in breast cancer treatment. Further skepticism were cast by McKinnon's extensive studies, which demonstrated that age-specific breast cancer mortality rates, based on vital statistics from Canada, England, and Massachusetts, remained unaffected by decades of educational programs designed to foster patients' and physicians' awareness of early intervention.[20]

This challenge to the established Halstedian orthodoxy outraged many within the surgical community.[21] However, the debate between Halsted's proponents and those favoring biological determinism was overshadowed by two significant advances in the mid-20th century that revolutionized both "early detection" and breast cancer treatment. Halsted's practice of detecting the smallest possible tumors through palpation was replaced by the concept of cancer screening before clinical symptoms were detected. Additionally, the introduction of systemic chemotherapy expanded the scope of cancer treatment beyond local control of primary tumors.

The Advent of Screening and Systemic Treatments

Screening, often viewed as population-based early detection, underwent a radical redefinition with the first screening trial. This shift began with the work of George Papanicolaou, who, through his study of tumor pathology, developed a method of scraping cervical cells to prepare slides for microscopic examination. In women with cervical cancer, he identified aberrant cells that could be readily distinguished from normal cells, leading to a 1928 publication: *New Cancer Diagnosis*.[22] In concert with other pathologists who included cellular and tissue changes in their grading systems, Papanicolaou documented gradations between normal cytology and malignancy. By 1950, he introduced a new concept of "early detection", which focused on identifying pre-invasive precursors of cancer, rather than relying solely on detecting small tumors. The 1952 National Cancer Institute Trial from Shelby County in Tennessee demonstrated the efficacy of this approach. The results were striking: invasive cancer was found in 555 women, while 557 had preinvasive lesions that were curable through colposcopy.[23] Moreover, these women were nearly 20 years younger than those diagnosed with clinically detectable disease. The precursor-based approach to early detection has shifted the time of detection forward by two decades and has transformed a once-deadly cancer into a treatable condition.[23]

The initial success of the first cervical cancer screening trial generated considerable interest in addressing the widespread issue of breast cancer. When Egan introduced mammography to the United States in 1952, earlier detection was predicated on its ability to detect tumors before they were palpable. However, unlike Papanicolaou's cytological approach, mammography focused on detecting invasive cancers in their early stages. Subsequently, the first mammography trial in the United States was conducted in 1963.[24] At that time, early cancer detection was universally recognized as live-saving, and any opposition from biologic determinists was largely ignored. The trial was expected to yield a foregone conclusion of a 30% relative reduction in breast cancer mortality among the screened women.[24] However, despite the trial being discredited owing to improper randomization and the use of a virtual surrogate control group, the positive outcomes had a profound impact on the adoption of mammography in the United States. This impact was further amplified by American Cancer Society's promotional efforts and subsequent patient advocacy. However, later trials in Europe and Canada produced conflicting results, leading to contentious debate on trial methodologies.[25,26] Consequently, the focus shifted from mortality reduction to assessment of the balance between potential benefits and harm.

While early cancer detection has been widely acknowledged as a life-saving approach, it also creates a dichotomy between patients: those caught early enough to and to those who are no longer localized and has spread. This unique advantage is based on the stepwise timeline proposed by Halsted, which emphasizes the interval of localized disease before it becomes systemic.

Cushman Haagensen: Bridging Early Detection and Systemic Treatment

Among the few physicians who fully grasped the implications of Bernard Fisher's critique of Halsted is Cushman Haagensen (Figure 3). Haagensen made significant contributions to breast cancer treatment by integrating pathology with surgical practice. As both a pathologist and clinician, Haagensen recognized the significance of occult metastases and aimed to refine Halsted's theory by establishing operability criteria based on staging. Haagensen was among the few who recognized that Fisher's criticism of centrifugal theory not only challenged radical surgery, but also questioned the fundamental principles of early detection. Fisher complained that his hypotheses were ignored, seemingly overlooking Haagensen's response to the first B-04 trial. Haagensen vehemently opposed discharging women with untreated cancer, even in microscopic form (as explored in the third arm of both the B-04 and 06 trials), which he considered a criminal act. He also emphasized the absence of bloodstream metastases in his patients who underwent surgery between 1935 and 1972, many of whom remained well for 20, 30, or even 40 years after surgery.[27] These views positioned Haagensen as a rare voice, recognizing the dual challenge posed by Fisher to radical surgery and the concept of early detection.

Subsequent developments necessitated a reevaluation of both "bloodstream metastases" and Halsted's theory. Despite the significance of Haagensen's data, his contributions have often been overlooked. Haagensen's commitment to lifelong follow-up was initially expressed in his book "*A Hundred Years of Medicine*" published in 1943, in which he urged physicians not to relinquish their responsibility when patients left the hospital ward.[2] Taking this commitment seriously, he hired two research secretaries who traveled across the country to check patients or collect their death certificates for

Figure 3 Cushman Davis Haagensen (1921–2013): A pioneering surgeon, researcher, and pathologist, was a key leader in breast cancer treatment. Dr. Haagensen's meticulous study of tumor histopathology advanced our understanding of breast cancer biology and some of his authored books, including "Diseases of the Breast", continue to shape breast cancer diagnosis and treatment worldwide. *Image obtained from Journal of the Florida Medical Association, v. 35*, n. *9, p. 570.; MMS ID 991436771340667 6; NLM ID 101436771*.

those who had not returned for postoperative visits. His meticulous collection of survival data allowed a detailed understanding of long-term outcomes in breast cancer patients provided crucial evidence that rules out the idea of bloodstream metastases from many of his patients.[28]

However, in his farewell lecture in 1988, Haagensen shared an unexpected finding: "Our patients continued to die of carcinoma throughout the entire follow-up period of 10 to 50 years". This aspect of the treatment of breast carcinoma has not been previously reported because no one has a long follow-up period.[29] This finding was unexpected because it contradicted the time-dependent centrifugal theory, which suggests that at some point, all patients destined to experience a recurrence would have done so, leaving only long-term survivors who were "cured". Ongoing breast cancer mortality indicated that no one was truly "cured", and long-term survivors were not necessarily "caught in time". As Haagensen put it, there was 'evidence that for some women, the disease progressed exceedingly slowly'.[29] Though largely ignored during his lifetime, his insights would later be recognition in mainstream medicine, culminating in the opening sentence of a recent article in the *New England of Journal Medicine*, which reads: 'The risk of recurrence of hormone positive early breast cancer continues indefinitely.'[30]

Haagensen's meticulous work not only questioned the assumptions of localized treatment, but also foreshadowed the importance of systemic therapies in managing breast cancer. As treatment evolved, the focus increasingly shifted from local control to a more integrated approach that incorporated of systemic therapies. Fisher's hypothesis received only minimal support from NSABP trials, but more convincing evidence came from an unexpected source: internists armed with drugs capable of targeting cancer cells throughout the body. Chemotherapy, initially conceived as a treatment for metastatic recurrence, was given a new name, adjuvant chemotherapy, and repurposed as an initial treatment even for small tumors confined to the breast (stage 1). The presence of circulating tumor cells in the bloodstream of cancer patients was described as early as 1869 by Thomas Ashworth; however, their relevance became apparent in the mid-1990s with the advent of high-gradient dielectrophoretic separators that demonstrated their existence early in the disease

course.[31,32] The survival benefit resulting from adjuvant chemotherapy provided the first direct evidence that viable cancer cells were shed at the time of the initial diagnosis.

The Genetic Revolution and the Future of Early Detection

The genetic revolution of the 21st century, which enabled researchers to model carcinogenesis based on molecular changes in genes, has provided support for both biological determinants and Fisher's hypothesis of cancer behavior from the inception of the disease. Although each patient's cancer is unique owing to the distinct cancer genome, essential alterations in cell physiology collectively define malignancy, including sustained growth, limitless replicative function, tissue invasion, and metastasis. It is crucial to note that these alterations not only characterize malignant cells, but also dictate their behavior. The biological behavior of cancer – ranging from the degree of virulence, as proposed by Willy Meyer, to the present-day molecular insights – now surpasses traditional detection methods.[33] Fisher was the first to hypothesize that cancer's behavior contradicted Halsted's stepwise timeline of localized disease progressing to systemic spread. While this was a bold hypothesis at the time of its presentation, it was eventually validated by systemic treatments, both adjuvant and neoadjuvant, which gained prominence over local control. Support that had previously gone unrecognized emerged from screening trials, once it became evident that only detecting precursors could guarantee the localized disease needed for early detection to truly save lives.

Conclusion

The evolution of breast cancer treatment, from radical surgery to systemic therapies, reflects a profound shift in our understanding of the disease. Initially, the concept of early detection as a lifesaving measure for breast cancer was founded on Halsted's centrifugal theory, which proposed that the complete removal of localized tumors could prevent systemic spread. However, throughout the 20th century, this theory faced substantial challenges, particularly by pioneers such as Bernard Fisher. Through clinical trials, Fisher demonstrated that breast cancer is a systemic disease right from its inception, questioning the necessity of radical surgeries, but also emphasized the importance of biologic factors in determining treatment outcomes.

This review traces the transition from a focus on local control to broader understanding of cancer's systemic nature, with tumor biology emerging as a crucial determinant of patient prognosis. Innovations in screening, such as the introduction of mammography, extended the timeline for early detection, but also raised questions about the notion of "early" in light of advancements in molecular biology and the genetics. As we move into the era of molecular biology, it is increasingly clear that the focus on early detection must shift. No longer is the focus solely on finding localized disease; instead, we now recognize the at the biologic behavior of cancer at the molecular level plays a pivotal role in treatment decisions. The future of breast cancer management lies in integrating these systemic insights with innovations in detection and treatment, such as the potential for blood-based screening tests for cancer, which could revolutionize how and when we detect cancer. This will alter the paradigm in which the origin of the cancer is no longer the primary focus of screening.

Disclosure

The authors report no conflicts of interest in this work.

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