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Trends in Metastatic Breast and Prostate Cancer — Lessons in Cancer Dynamics

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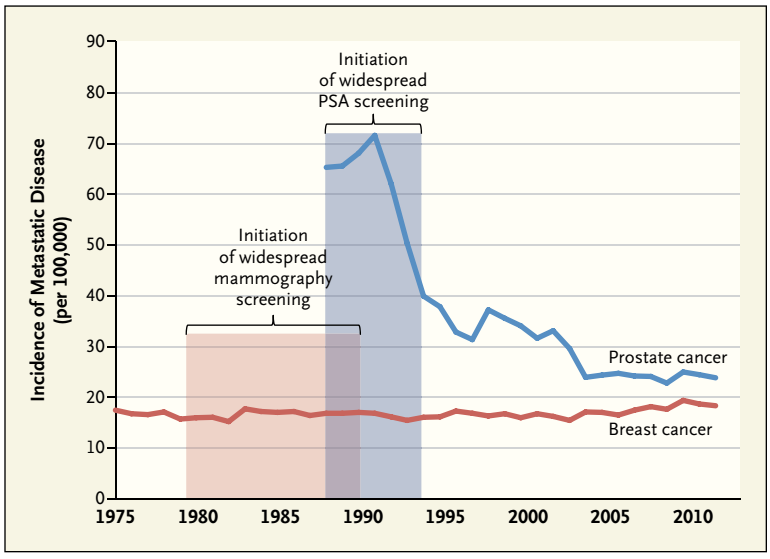
Patients who present with metastatic cancer serve as powerful motivators for efforts to detect cancer early. Screening offers hope that cancer can be detected in an early, localized phase when it's more amenable to treatment. This hope is based on a paradigm attributed to William Stewart Halsted, which holds that cancer arises at a single location, grows there, and eventually migrates to local lymph nodes and then to more distant organs. If the Halstedian paradigm is correct, effective screening should allow cancers destined to metastasize to be identified at an earlier stage and reduce the incidence of cancers that first present as metastatic disease. Such a stage shift is typically viewed as necessary but not sufficient to enable screening to reduce mortality.

We considered two cancers — breast and prostate — for which screening has been particularly prominent. The Surveillance, Epidemiology, and End Results (SEER) program provides data on the incidence of metastatic cancer — a metric that includes only cases in which cancer is first diagnosed when a patient presents with metastases, not those in which early-stage cancer is diagnosed and then progresses to metastatic disease. The incidence of metastatic breast cancer has been stable since 1975 (see graph). In contrast, the incidence of metastatic prostate cancer has decreased by half since 1988. Although SEER data aren't available for earlier years, data from the Seattle–Puget Sound registry suggest that the incidence of metastatic prostate cancer was stable before 1988.[1]

What explains these discordant trends? The stable incidence of metastatic breast cancer suggests two things. First, the underlying probability of developing this form of breast cancer is itself stable. Second, screening mammography has been unable to identify at an earlier stage, before symptoms appear, cancers that are destined to become metastatic. In fact, the mean age at diagnosis among women 40 years of age or older hasn't changed over the past 37 years, remaining at 63.7 years. Either mammography isn't sensitive enough to identify these cancers early or they don't fit the Halstedian paradigm of steady progression. The lack of change in the incidence of metastatic disease is consistent with the hypothesis that breast cancer is a systemic disease by the time it's detectable — a paradigm typically attributed to Bernard Fisher.

In contrast, the steep decline in the incidence of metastatic



Incidence of Cancer That Was Metastatic at First Presentation, United States, 1975–2012.

Data are for breast cancer (SEER historic stage distant) among women 40 years of age or older and prostate cancer (American Joint Committee Stage IV) among men 40 years of age or older.

prostate cancer is most likely the result of prostate-specific antigen (PSA) screening. The rapid uptake of PSA screening led to a dramatic spike in overall prostate cancer diagnoses during the early 1990s[2] — one that's unrivaled in U.S. cancer data. Although the decline in the incidence of metastatic disease could have been caused by an intervention to reduce prostate cancer risk or a reduction in an environmental carcinogen, for example, it's hard to imagine another factor changing and exerting an effect so quickly. Data on patient age further support the hypothesis that PSA screening leads to earlier diagnosis of cancers destined to become metastatic: the mean age at diagnosis for men 40 years of age or older has fallen by 2 years, from 71.8 to 69.8 years.

Thus, prostate cancer destined to become metastatic appears to fit the Halstedian paradigm: steadily progressing disease that allows time for screening to find it at an earlier stage. It's important to point out, however, that although such a stage shift is a prerequisite for screening to reduce mortality, it doesn't by itself mean that mortality will reliably decline. For example, although the European Randomized Study of Screening for Prostate Cancer showed that PSA screening almost halved the risk of metastatic prostate cancer presentation, screening reduced the risk of death from prostate cancer only by about one fifth.[3] Unfortunately, many men who are diagnosed with localized prostate cancer have disease recurrence despite therapy. This finding suggests that microscopic metastases may develop very early in the course of disease and is more consistent with Fisher's paradigm than with Halsted's.

Although these discordant trends could reflect distinct disease dynamics, they could also be the result of different screening strategies. Mammography represents an anatomical search for a structural abnormality; PSA screening uses a biochemical assay to detect a tumor marker. It's possible that the latter is a much more sensitive indicator of disease burden. Were a similar breast-cancer assay discovered — and a similar organwide sampling strategy used (the typical prostate biopsy now involves at least 10 needle cores throughout the organ) — then perhaps fewer women would present with metastatic breast cancer. Again, whether mortality would therefore decline is a separate question.

Samuel Hellman proposed a third paradigm: that for each type of cancer there are multiple paths to metastasis.[4] Aggressive, poorly differentiated cancers tend toward the Fisher paradigm; localized, well-differentiated cancers tend toward that of Halsted. There's evidence of such variability in breast cancer. Whereas breast cancers destined to present as metastatic disease have not been amenable to early-detection efforts, metastatic progression from disease that is local or regional at presentation can be detected earlier than it once was — albeit with no change in the risk of death.[5] Earlier diagnosis may be possible for women with cancers that would ultimately become metastatic — but not for some women presenting with metastases — because the two groups have different disease dynamics.

Although prostate cancer may in general be a slowly progressing disease that allows ample time for early detection, there is also evidence of variability. The incidence of metastatic prostate cancer has stabilized during the past decade at a rate similar to that seen in breast cancer. This finding suggests a similarity between the two diseases: both appear to include a subgroup of

cases that first present as a systemic disease. Because early-detection efforts will never be successful for patients with such cases, disease dynamics can have a profound effect on the efficacy of screening.

Given the increasing enthusiasm for genomic, proteomic, and immunosignature testing to enhance early cancer detection, we believe it will be critical to consider the variability in cancer dynamics. Some cancers will be systemic at the outset, some will progress and some will not. Conflating these types of lesions could result in screening programs that are not helpful and administration of treatment that is either not needed or not effective. As Hellman concluded two decades ago, "The lesson from all this is the value of clinical investigation to study the natural history of disease."[4]

An audio interview with Dr. Welch is available at NEJM.org

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Hospital Charity Care — Effects of New Community-Benefit Requirements

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The Internal Revenue Service (IRS) recently finalized new requirements for nonprofit hospitals to maintain their tax-exempt status under the Affordable Care Act (ACA).[1] Section 501(r) of the Internal Revenue Code now requires each hospital to establish a written financial-assistance policy that applies to all "emergency and medically necessary care." Through these policies, hospitals must strive to ensure that patients who qualify for fully or partially subsidized charity care can apply for and receive it, are charged reasonable amounts, and are not subject to extraordinary bill-collection practices when they have outstanding medical debt. Hospitals are also required to assess the health needs of their community every 3 years. Failure to comply with Section 501(r) could result in a $50,000 excise tax, losing tax-exempt status, or both, once the requirements are fully implemented in 2016.[1]

Section 501(r) arose from longstanding concerns over whether nonprofit hospitals provide sufficient community benefits — and specifically charity care — to justify their tax-exempt status, valued at $24.6 billion in 2011.[2] Key policymakers, such as Senator Charles Grassley (R-IA), believe that some nonprofit hospitals provide insufficient charity care and use "extremely punitive" measures to collect unpaid medical bills from low-income patients.[3] A 2013 study by Young and colleagues showed that charity care represented only 2% of hospital operating expenses on average, or roughly a quarter of total expenditures on community benefits.[4] After unsuccessful attempts to require nonprofit hospitals to spend at least 5% of revenues on charity care,[5] the architects of Section 501(r) envisioned greater oversight in increasing the provision of charity care. Measured against these hopes, the effect of the new requirement on charity care is likely to be mixed.

Policymakers, hospital leaders, and practicing physicians face key questions about Section 501(r). How have hospitals responded to the requirements, which became effective when the ACA was enacted? How will compliance with the new requirements affect the provision of charity care, and how will its effects differ between states that have chosen to expand Medicaid under the ACA and those that have chosen not to? Although the ACA should greatly