Quantifying the Contribution of Earlier Detection and Advancements in Treatment on Gains in Life Expectancy for US Breast Cancer Patients Since 1975

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Abstract

Background. The intense controversy over mammography screening arose and persists, in part, because of disagreement over the precise contribution of earlier detection versus advancements in breast cancer treatment. We quantify the contributions of these two factors, as well as advancements in the treatment of other diseases, on the gain in life expectancy among breast cancer patients since 1975.

Methods. We obtained annual incidence-based case fatality rates for 664,000 breast cancer patients aged 40 years and older from the Surveillance, Epidemiology, and End Results registries, 1975 to 2012. We used life-table methods to calculate the gain in life expectancy and quantified the three constituent components of this gain: [1] earlier detection, [2] advancements in breast cancer treatment, and [3] advancements in the treatment of other diseases. We additionally quantify which age groups contributed the most to the overall contribution of earlier detection. We assumed a 10% overdiagnosis level for tumors 3cm, and varied the level up to 97% for <1cm tumors and up to 52% for 1-3cm tumors in a sensitivity analysis.

Results. Life expectancy increased 10.94 years between 1975 and 2002 for a 40-year old newly diagnosed breast cancer patient. Advancements in breast cancer treatment contributed more to this gain in life expectancy than earlier detection: 6.79 years (62%) versus 2.92 years (27%). Advancements in the treatment of other diseases contributed the remaining 1.25 years to this gain (11%). By age group, earlier detection among 40-49 year olds contributed more to the overall contribution of earlier detection (0.56 years) than 50-59 and 60-69 year olds (0.45 and 0.41 years, respectively). We reached nearly identical substantive conclusions varying the level of overdiagnosis.

Conclusion. Life expectancy among breast cancer patients increased over time primarily because of advancements in breast cancer treatment, although the contribution of earlier detection was not trivial.

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1 Introduction

Mammography screening has become the subject of intense public and scientific controversy (1−7). In 2002, for example, the US Preventive Services Task Force (USPSTF) recommended routine mammography screening among women aged 40-49 years. But in 2009, the USPSTF revised and downgraded its earlier recommendation based on evidence from randomized trials and simulation-based studies. The lower grade issued by the USPSTF led to public outcry and prompted Congress to intervene and pass an amendment to the Patient Protection and Affordable Care Act stipulating insurers follow the 2002and not the 2009USPSTF recommendation.

The controversy over screening arose and persists, in part, because of disagreement over its value and the precise contributions of earlier detection and advancements in breast cancer treatment. For example, the efficacy of screening among women aged 39 to 49 years from 8 large randomized trials varied from 0% to 30% mortality reduction (8). Yet, the trials randomized on the invitation to screenrather than screening itselfand may not generalize to the US population of women because of limited external validity. The seven Cancer Intervention and Surveillance Modeling Network (CISNET) simulation-based models concluded a wide range for the contribution of screening to reductions in breast cancer mortality rates from 1975 to 2000: 28% to 65% (1). Sun et al. (2010) concluded earlier detection contributed 17% of the estimated gain in breast cancer survival time between 1988 and 2000 and attributed the remaining 83% to advancements in breast cancer treatment (9). However, this study may have overestimated the contribution of advancements in cancer treatment because it did not separate death from breast cancer and death from competing causes (e.g., cardiovascular disease [CVD]).

In this study, we address these research gaps and quantify the contribution of the three factors that affect the gain in life expectancy among breast cancer patients: earlier detection,

advancements in breast cancer treatment, and advancements in the treatment of other diseases. We measure earlier detection, which resulted from more widespread screening and advancements in screening technology (10), by the changes over time in tumor sizes of newly diagnosed breast cancer patients. We measure advancements in breast cancer treatment and treatment of other diseases by reductions in case fatality rates from breast cancer and competing causes of death, respectively. We also quantify how the contribution of earlier detection to gains in life expectancy varied by age at diagnosis. We utilize an established demographic method based on the observed mortality experience of breast cancer patients (11, 12). We quantify the contributions to the gain in life expectancy, rather than declines in breast cancer mortality rates, to account for concurrent improvements in mortality from competing causes of death and changes in the age structure of the US female population. Finally, we consider the effect of overdiagnosis on the gain in life expectancy and its three constituent components.

2 Methods

2.1 Patient Data

We obtained incidence and mortality data for breast cancer from the US National Cancer Institutes Surveillance, Epidemiology, and End Results (SEER) 9 registry database between 1975 and 2012. The SEER 9 registries, which cover 10% of the US population, form the largest, most representative and longest running national cancer incidence database. SEER captures virtually all cancers occurring in the geographic areas covered by the registries; a persons entry into the registries begins with their diagnosis and ends, if relevant, with their death. We analyzed 663,860 breast cancer cases diagnosed between 1975 and 2012 and included only the first matching record for each person, as well as cases with both malignant and non-malignant behavior (e.g., ductal carcinoma in situ). SEER classifies breast cancer as the cause of death based on

the death certificate, the identity of a primary tumor, and relevant comorbidities. We placed a further requirement: the breast cancer death must have occurred within 10 years of diagnosis (13, 14). By allowing this 10-year time window between diagnosis and death, we calculated incidence-based case fatality rates between 1975 and 2002 for 422,141 cases. We categorized tumor size into five categories: <1cm, 1-2cm, 2-3cm, 3-5cm, and 5cm based on the extent of disease (determined by clinical and operative/pathological assessment).

An incidence-based case fatality rate for a specific cohort of newly diagnosed breast cancer patients equals the ratio of the number of deaths occurring for this cohort up to 10 years beyond their diagnosis and the total number of person-years lived by this cohort up to 10 years beyond their diagnosis (Supplementary Materials, Section A). We calculated incidence-based case fatality rates by age group at diagnosis (40-44 to 100+ years), year of diagnosis (1975-2002), tumor size (<1cm, 1-2cm, 2-3cm, 3-5cm, 5cm), and cause of death (breast cancer and competing causes of death). We also calculated the proportion of incident cancer cases by tumor size at diagnosis and year of diagnosis.

2.2 Analytic Methods

For our primary analysis, we assume an overdiagnosis level of 10% for tumor sizes 3cm based on results from the Malm, Sweden randomized trial (15). Overdiagnosed cases do not contribute to the numerator of the case fatality rate because these subclinical cases would likely never lead to death from breast cancer in a patients lifetime nor, consequently, over the 10-year period after diagnosis. They do, however, contribute to the denominator of the case fatality rate by artificially increasing exposure and raising life expectancy. Thus, we adjust case fatality mortality rates for these smaller sized tumors by removing the person-years these overdiagnosed cases contributed to the denominator. Specifically, we multiplied the observed case fatality rate by the inverse of the complement of the overdiagnosis level. Overdiagnosed cases also increase

the annual share of smaller sized tumors. We adjust the share by subtracting the overdiagnosed cases from the annual count of incident cancers and recalculating the distribution by tumor size (Supplementary Materials, Section B).

Using an established demographic method, we first isolate the contribution of earlier detection by creating separate life-tables for each tumor size and for each year based on all-cause mortality (11, 12, 16). A life-table estimates life expectancy as a function of case fatality rates and accounts for the age distribution of the population by transforming these rates into probabilities of survival (17). Overall life expectancy equals the weighted sum of tumor size-specific life expectancies, where the weights correspond to the annual share of each tumor size. The change in overall life expectancy over time is a function of the change in tumor size-specific case fatality rates and the change in the share of tumor sizes. Second, we isolate the contribution of advancements in breast cancer treatment and advancements in the treatment of other diseases by creating separate life-tables for each tumor size and for each year based only on case fatality rates from breast cancer and only on case fatality rates from competing causes of death (further details shown in Supplementary Materials, Sections D-G).

The shift toward smaller sized tumors at diagnosis occurs when incidence rates for these tumors increase more over time than the incidence rates of larger sized tumors. Growth of the share of smaller sized tumors implies an increase in their contribution to gains in life expectancy, while shrinkage of the share of larger sized tumors implies a decrease in their contribution.

To assess the robustness of our findings to the overdiagnosis level, we conducted two sensitivity analyses. First, we varied the overdiagnosis level from 0% (theoretical minimum) to 52% for all tumors 3cm. We set the upper bound based on the highest estimate from randomized screening trials and observational studies (1822). Second, we individually varied the overdiagnosis level from 0% to 97% for tumors <1cm and from 0% to 52% for 1-3cm tumors. We set the

upper bound based on the smallest percentage of patients diagnosed with <1cm tumors who subsequently died of breast cancer within 10 years (3%).

3 Results

3.1 Incidence Rates, Size Distribution, and Case Fatality Rates

The incidence rate of <1cm and 1-2cm tumors increased between 1975 and 2002 (Figure 1, Panel A). For example, the incidence rate of <1cm tumors rose from 42 to 350 cases per 100,000 over this time period. In contrast to these smaller sized tumors, the incidence rates of 2-3cm, 3-5cm and 5cm increased from 1975, peaked around 1984, and decreased thereafter. The annual share of the <1cm and 1-2cm tumors grew over time because their incidence rates increased more than those of larger sized tumors (Figure 1, Panel B). For example, the annual share grew from 5% to 21% for <1cm tumors and shrank from 15% to 10% for 5cm tumors.

Case fatality rates from breast cancer decreased more, in absolute terms, for larger than smaller sized tumors between 1975 and 2002 (Figure 1, Panel C). For example, the rate decreased from 101 to 59 deaths per 100,000 for 5cm tumors while the rate decreased from 18 to 5 deaths per 100,000 for <1cm tumors. Case fatality rates from competing causes of death also decreased over time, although they exhibited less variation among tumor sizes.

3.2 Gains in Life Expectancy

Life expectancy increased 10.94 years between 1975 and 2002 for a 40-year old newly diagnosed breast cancer patient (Figure 2). First, the temporal shift towards smaller sized tumors contributed 2.92 years to the gain in life expectancy (27%). This 2.92 year net contribution results from offsetting trends in the share of cancers by tumor size: increasing contributions from the growing share of smaller sized tumors and decreasing contributions from the shrinking share of larger sized tumors. Second, improvements in case fatality rates from breast cancer contributed

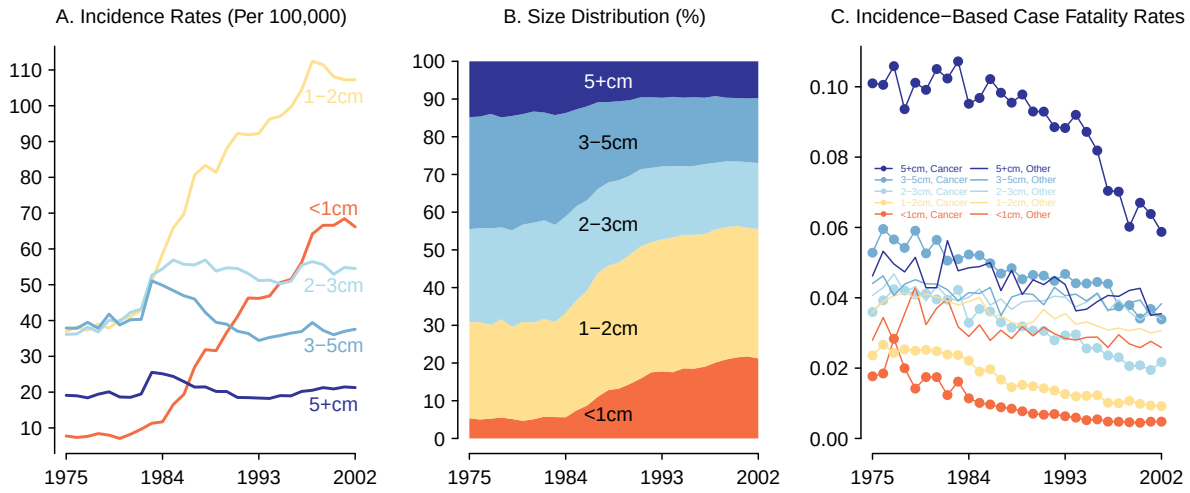

Figure 1: Breast Cancer Incidence Rates, Tumor Size Distribution, and Case Fatality Rates. (A) Incidence rates (cases per 100,000 person-years) by tumor size, 1975-2002. (B) Annual share of incident breast cancer cases by tumor size, 1975-2002. (C) Incidence-based case fatality rates from breast cancer and from all other causes of death, 1975-2002.

6.79 years to the gain in life expectancy (62%). Specifically, reductions in case fatality rates from breast cancer contributed 1.12 years for <1cm tumors, 2.36 years for 1-2cm tumors, 1.12 years for 2-3cm tumors, 1.52 years for 3-5cm tumors, and 0.66 years for 5cm tumors. Third, reductions in case fatality rates from competing causes of death across all tumor sizes contributed the remaining 1.25 years to the gain in life expectancy (11%).

3.3 Contribution by Age Group to Earlier Detection

The contribution of the temporal shift towards smaller sized tumors (2.92 years) represents the net of 5.02 years from <1cm tumors and 2.43 years from 1-2cm tumors (growing shares) and -4.79 years from 2-3cm, 3-5cm, and 5cm tumors (shrinking shares, Table 1). Of the overall contribution of the growing share of <1 cm tumors, 50-59 years olds contributed the most followed by 60-69 and 70-79 years olds. Similarly, of the overall contribution of the growing share of 1-2 cm tumors, 70-79 years olds contributed the most followed by 60-69 and 50-59 years

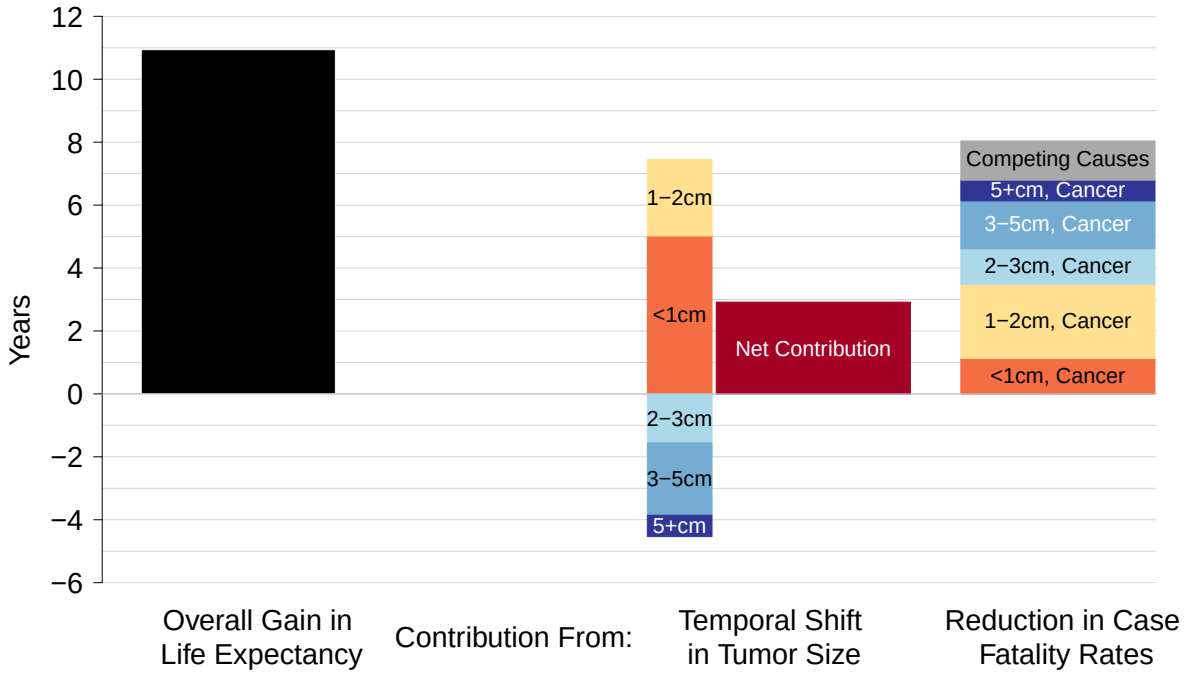

Figure 2: Contribution of Earlier Detection, Advancements in Breast Cancer Treatment, and Advancements in Treatment of Competing Diseases on Gain in Life Expectancy. Overall gain in life expectancy and the contribution of the temporal shift in tumor size (by tumor size and net contribution) and reductions in case fatality rates from breast cancer and competing causes of death.

olds. Combining the effect of growing shares of smaller sized tumors and shrinking shares of larger sized tumors, earlier detection in 70-79 year olds contributed the most among all age groups to the net contribution of earlier detection.

3.4 Varying Level of Overdiagnosis

Our primary analysis assumed an overdiagnosis level of 10% among <1cm, 1-2cm, and 2-3cm tumors. In secondary analysis, we varied the overdiagnosis level among these tumors sizes between 0% and 52% (Figure 3). As the overdiagnosis level increased, the proportionate contribution from reductions in case fatality rates from breast cancer increased while the proportionate contribution from earlier detection decreased. For example, at a 20% overdiagnosis level, the

	Age Group (Years)							
Tumor Size	40-49	50-59	60-69	70-79	80-89	90-99	≥100	Total
<1cm	0.71	1.35	1.29	1.14	0.49	0.04	0.00	5.02
1-2cm	0.29	0.47	0.60	0.62	0.38	0.08	0.00	2.43
2-3cm, 3-5 cm, 5cm	-0.44	-1.37	-1.48	-1.04	-0.23	0.01	0.00	-4.54
Total	0.56	0.45	0.41	0.72	0.65	0.12	0.01	2.92

Table 1: Contribution of Earlier Detection by Age Group. Note: cm=centimeters.

contributions to the 10.31-year gain in life expectancy were 66% from reductions in case fatality rates from breast cancer, 23% from the temporal shift to smaller sized tumors, and 12% from reductions in case fatality rates from competing causes of death. We also independently varied the overdiagnosis level for <1cm tumors and 1-3cm tumors and reached similar conclusions (Supplementary Materials Section H).

4 Discussion

Our analysis quantifies the contribution of earlier detection, advancements in breast cancer treatment, and advancements in the treatment of other diseases on the gain in life expectancy of US breast cancer patients. We show that the majority, 63%, of the gain in life expectancy between 1975 and 2002 resulted from advancements in the breast cancer treatment, which reduced case fatality rates from breast cancer. Next, 27% of the gain resulted from earlier detection, which increased the share of smaller sized tumors over time. Finally, the remaining 12% of the gain resulted from advancements in the treatment of other diseases, which reduced case fatality rates from competing causes of death. The relative contribution of each of these three constituent components remained the same across various levels of overdiagnosis.

Our study adds to a growing body of research on the contribution of earlier detection on improvements in breast cancer outcomes (21). The seven simulation-based CISNET models estimated screening contributed to between 28% and 65% of the decline in breast cancer mortality

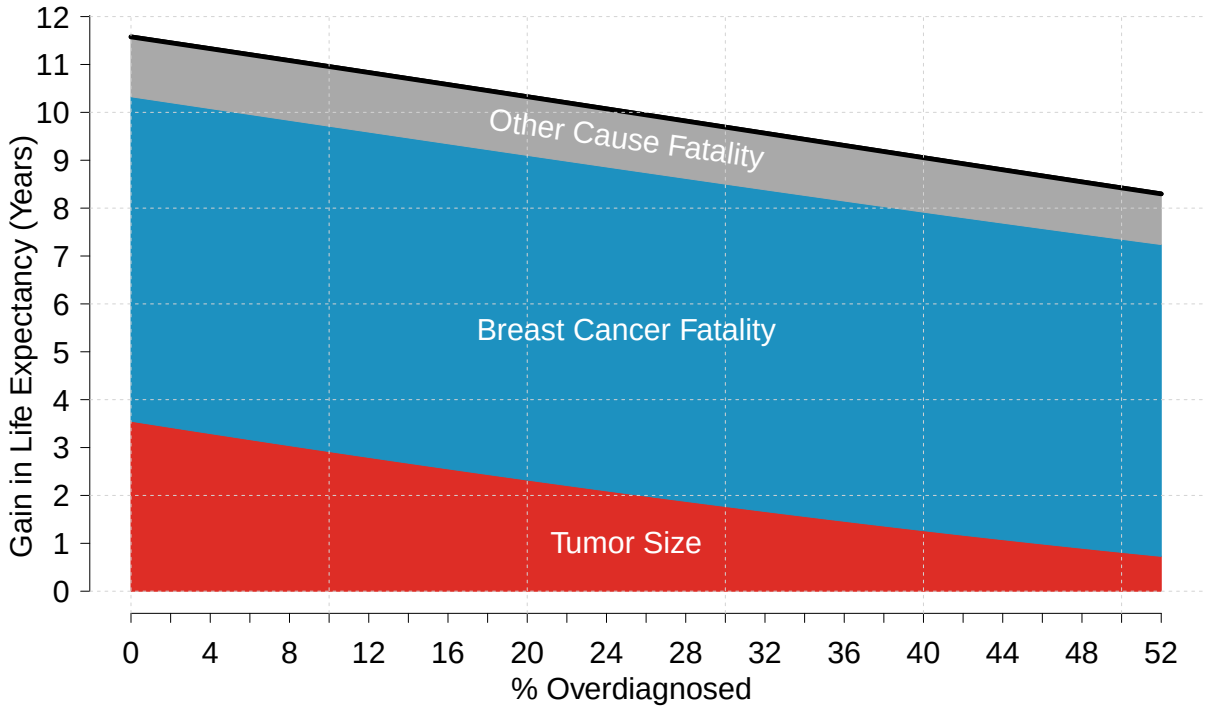

Figure 3: Contributions to Gain in Life Expectancy, Varying Level of Overdiagnosis. Overall gain in life expectancy and its constituent components (temporal shift in tumor size, reductions in case fatality rates from breast cancer, and reductions in case fatality rates from competing causes of death) varying the level of overdiagnosis for tumors 3cm from 0% to 52%.

rates between 1975 and 2000, which corresponds to an equivalent contribution of between 16% and 50% on the resulting gain in life expectancy (1). During this same time period, our estimate of the contribution of earlier detection (24%), fell on the lower end of the CISNET range. Additionally, although the incidence rates of 3-5cm and 5cm tumors remained relatively stable since 1990, this constancy does not necessarily imply screening failed to detect these largest and most problematic cancers. Screening only fails to reduce the incidence of larger sized tumors if we assume the underlying nature of these cancers is constant over time (i.e., risk factors do not change over age, time, and across cohorts). A recent analysis considered age, time, and cohort effects for metastatic cancer and concluded that the incidence rate would have increased over time in the absence of screening; screening reduced this increase to produce the constant trend

observed (23).

Our results also directly address the longstanding controversy over the value of mammography screening, especially among 40-49 year olds (2, 24). Our estimate of the benefit of screening among 40-49 year olds, which is based on the actual mortality experience of breast cancer patients, is higher than most previous estimates (25−27). We conclude that earlier detection among 40-49 year olds contributed 0.56 of the 10.94-year gain in life expectancy, or 5.16%. This contribution was greater than the corresponding contributions of 50-59 and 60-69 year olds (4.14% and 3.70%, respectively). Previous estimates of the benefits of screening among 40-49 year olds came from simulation-based studies, randomized trials, and cross-national studies. Yet, simulation studies are based on inherently untestable assumptions on the natural history of breast cancer (28). The efficacy demonstrated in randomized trials may not translate to the same level of effectiveness in actual populations because of limited external validity. And cross-national studies are ecological in nature and based on comparisons of whether women were offered screening rather than actually screened.

While the contribution from earlier detection on the gain in life expectancy was substantial, we found that the contribution from advancements in breast cancer treatment was even larger. Treatment-related advancements likely resulted from a combination of improvements in the delivery of existing treatments (e.g., breast-conserving surgery with radiotherapy) and the development of novel treatments (e.g., tamoxifen for breast cancer chemoprevention), both of which reduced case fatality rates (29, 30). The same CISNET models estimated breast cancer treatment contributed to between 35% and 72% of the decline in breast cancer mortality rates or, equivalently, between 50% and 84% of the resulting gain in life expectancy. Our estimate of the contribution of advancements in breast cancer treatment (62%) fell on the lower end of the CISNET range.

Advancements in the prevention and treatment of competing causes of death, such as CVD (31, 32), also contributed to the gain in life expectancy among breast cancer patients. After breast cancer itself, other cancers and CVD were the second and third leading causes of death among breast cancer patients (33). For early stage breast cancers, which are also generally smaller sized tumors, the probability of death from other causes is considerably higher than the corresponding probability from breast cancer. Thus, improvements in the treatment of other diseases for breast cancer patients are particularly important for the gain in life expectancy because the share of smaller sized tumors grew over time.

Our study has some potential limitations. First, our results may be subject to bias from misclassification of the underlying cause of death on death certificates. This bias is unlikely to affect our results because the accuracy of breast cancer as the cause of death between medical records and death certificates exceeds 92% and is among the highest across all cancer types (34, 35). Second, our results may not be generalizable nationally to the extent that the SEER registries fail to capture national patterns in mammography screening and breast cancer mortality. The SEER 9 registries include both areas of comparatively high and low prevalence of mammography screening (36). Additionally, breast cancer mortality patterns in the SEER registries are highly representative of national breast cancer mortality patterns (37). Third, we required that breast cancer death must have occurred within 10 years of diagnosis when calculating case fatality rates to partially mitigate the effect of length bias. We vary the time interval between 8 years and 12 years and reach identical substantive conclusions (Supplementary Materials, Section I). Finally, we cannot quantify the contribution of individual types of cancer treatment because patients typically received multiple modalities for virtually the entire time period of our study (38).

In conclusion, we quantify the benefit of earlier detection and advancements in breast cancer

treatment for US breast cancer patients between 1975 and 2002. Earlier detection contributed to more than one-quarter of the observed gain in life expectancy; advancements in breast cancer treatment contributed substantially more. The value of screening is based on the balance of potential benefits of earlier detection and potential harms from overdiagnosis and overtreatment. Our study provides greater clarity to the longstanding debate on the value of mammography screening by quantifying the realized benefit of earlier detection against which its potential harms can be measured.

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Supplementary Materials

A Computation of Incidence-Based Case Fatality Rates

An incidence-based case fatality rate for a specific cohort of newly diagnosed breast cancer patients equals the ratio of [1] the number of deaths occurring for this cohort up to 10 years beyond their diagnosis and [2] the total number of person-years lived by this cohort up to 10 years beyond their diagnosis. For example, 556 women aged 65-69 years were diagnosed with <1cm breast cancer in 2001. Between 2001 and 2011, 22 of these women died of breast cancer and another 107 died of a competing cause of death. This entire cohort lived a total of 5099.5 person-years over the 10-year period. Thus, the incidence-based case fatality rate from breast cancer equaled 22/5099.5 and the incidence-based case fatality rate from competing causes of death equaled 107/5099.5. Also, the proportion of women diagnosed with <1cm breast cancer in 2001 equaled 4,602 out of 19,029 newly diagnosed breast cancers (24.2%).

B Adjustment for Overdiagnosis

Suppose 10% of the 556 women aged 65-69 years old diagnosed with <1cm breast cancer in 2001 were overdiagnosed, the observed case fatality rate from breast cancer (22/5099.5) would become 22/[5099.5 - 0.10*5099.5]. Formally, let $\mathcal{A}$ be a set of starting ages for age intervals analyzed (e.g., 40, 45, ..., $\omega = 100$ years), $\mathcal{T}$ be a set of years (e.g., 1975, ... 2002), and $\mathcal{S}$ be a set of tumor sizes at diagnosis (e.g., <1cm, 1-2cm, 2-3cm, 3-5cm, and $\geq$ 5cm). Let α_s represent the assummed level of overdiagnosis for tumor size $s \in \mathcal{S}$. Let $m_{a,t,s}$ represent the observed case fatality rate for age group $a \in \mathcal{A}$, year $t \in \mathcal{T}$, and tumor size $s \in \mathcal{S}$. Then, the case fatality rate adjusted for overdiagnosis, $m^*_{a,t,s}$, equals, $\frac{1}{1-\alpha_s} \times m_{a,t,s}$.

In 2001, the number of women diagnosed with breast cancer equaled: 4602 with <1cm

tumors, 7208 with 1-2cm tumors, 3684 with 2-3cm tumors, and 1300 with $\geq$ 5cm tumors. These counts translate to the following distribution: 24%, 38% 19%, 12%, and 7%, respectively. Suppose 10% of <1cm breast cancers were overdiagnosed (460 of 4602 women). We subtract these 460 women from the count of breast cancers in 2001 and recalculate the distribution: 22% for <1cm, 39% for 1-2cm, 20% for 2-3cm, 12% for 3-5cm, and 7% for $\geq$ 5cm. Let α_s represent the assummed level of overdiagnosis for tumor size $s \in \mathcal{S}$. Let $n_{t,s}$ represent the observed count of breast cancer cases in year t and for tumor size s. The observed distribution of incident breast cancer cases, $\pi_{t,s}$, equals $\frac{n_{t,s}}{\sum_{s\in\mathcal{S}} n_{t,s}}$. The distribution of incident breast cancer cases adjusted for overdiagnosis equals:

$$\pi^*_{t,s} = \frac{(1-\alpha_s)\times n_{t,s}}{\sum_{s\in\mathcal{S}}(1-\alpha_s)\times n_{t,s}}.$$

C Computation of Tumor Size-Specific Life Expectancy

The life expectancy of a breast cancer patient newly diagnosed at age $a^* \in \mathcal{A}$, at time t, and with tumor size s equals:

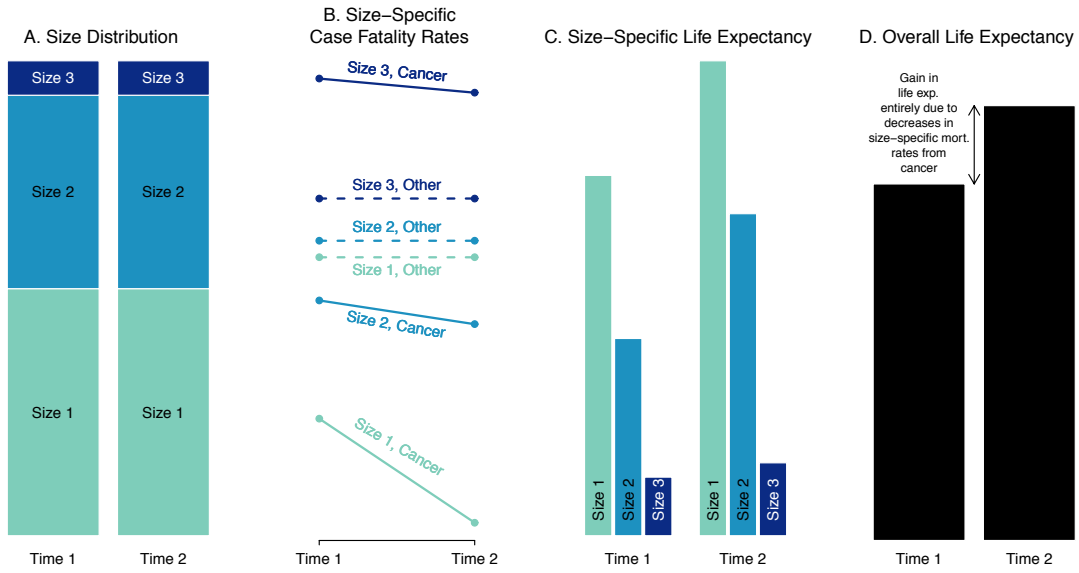
$$e_s(a^*,t) = \int_{a^*}^{\omega} e^{\left(-\int_{a*}^{a}\mu_s(y,t)\,dy\right)}da = \int_{a^*}^{\omega} e^{\left(-\sum_{a=a*}^{a} n\, m^*_{a,t,s}\right)}\,da, \tag{C.1}$$

where $\mu_s(a,t)$ and $m^*_{a,t,s}$ represent the hazard of mortality and case fatality rate adjusted for overdiagnosis, respectively; n is the width of the age interval; and ω is the starting age of the final and open-ended age interval.

D Schematic Representation of the Methodology

For simplicity, consider three mutually exclusive and exhaustive categories of tumor size: 1, 2, and 3 (e.g., <1cm, 1-2cm, and $\geq$2cm). Suppose the distribution of tumor size at cancer diagnosis remained constant between times 1 and 2 (Supplemental Figure 1, Panel A), tumor size-specific case fatality rates from breast cancer decreased between times 1 and 2 (Supplemental

Figure 1, Panel B), and tumor size-specific case fatality rates from competing causes of death remained constant between times 1 and 2 (Supplemental Figure 1, Panel B). Tumor size-specific life expectancy increased between times 1 and 2 because tumor size-specific case fatality rates from breast cancer decreased over the time period (Supplemental Figure 1, Panel C). Overall life expectancy at each time equals the weighted average of tumor size-specific life expectancy, where the weights equal the distribution of tumor sizes at cancer diagnosis at times 1 and 2, respectively. Overall life expectancy grew between times 1 and 2, and this gain was entirely due to decreases in tumor size-specific case fatality rates from breast cancer (Supplemental Figure 1, Panel D). In actuality, all three aforementioned factors change over time and contribute to the gain in life expectancy. We quantify the individual contribution of each of these three constituent components. We also utilize the same demographic method to further disaggregate these three contributions by age group in Section F.



Supplemental Figure 1: The gain in life expectancy depends on three factors: (A) changes in the tumor size distribution at cancer diagnosis, (B) changes in tumor size-specific case fatality rates from breast cancer, and (C) changes in tumor size-specific case fatality rates from competing causes of death.

E Decomposition by Tumor Size and Case Fatality Rates from Breast Cancer and Other Causes of Death

Let $\pi_s(t)$ equal the proportion of breast cancer patients diagnosed with tumor size s in year t. Let $e_s(a,t)$ equal the tumor size-specific life expectancy at age a. The overall life expectancy at age a and time t, $e(a,t)$, equals:

$$e(a,t) = \sum_{s \in \mathcal{S}} \pi_s(t)\, e_s(a,t),$$

where $\sum_{s \in \mathcal{S}} \pi_s = 1$.

The change in life expectancy at age a between times t_1 and t_2 can be decomposed using the methodology of Kitagawa (1955):

$$\begin{aligned} e(a,t_2) - e(a,t_1) &= \sum_{s \in \mathcal{S}} \left[\, \pi_s(t_2)\, e_s(a,t_2) - \pi_s(t_1)\, e_s(a,t_1)\right] \\ &= \sum_{s \in \mathcal{S}} \left[\pi_s(t_2) - \pi_s(t_1)\right] \left[\frac{e_s(a,t_1) + e_s(a,t_2)}{2}\right] + \\ &\quad \sum_{s \in \mathcal{S}} \left[e_s(a,t_2) - e_s(a,t_1)\right] \left[\frac{\pi_s(t_1) + \pi_s(t_2)}{2}\right]. \end{aligned} \tag{E.1}$$

Equation E.1 quantifies how much of the change in life expectancy at age a between times t_1 and t_2 is due to: [a] shifts in the share of cancer tumor size (first term) and [b] changes in tumor-size-specific life expectancy (second term).

We can further decompose the second term of equation E.1 by cause of death. In doing so, we can quantify how much of this change in tumor-size-specific cancer life expectancy, $e_s(a,t_2) - e_s(a,t_1)$, is due to improvements in case fatality rates from breast cancer and improvements in case fatality rates from competing causes of death. Let $\mathcal{C}$ be a set of mutually exclusive and exhaustive causes of death (e.g., breast cancer and all other causes). Let $L_{a,s,c}(t)$ represent the person-years lived in the life table based on the case fatality rate at age a, for tumor size s,

from cause $c \in \mathcal{C}$, and at time t. Similarly, let $L_{a,s,-c}(t)$ represent the person-years lived in the life table based on the case fatality rate at age a, for tumor size s, and from causes other than c $(-c)$, and at time t. Let a^* be the first starting age of $\mathcal{A}$. Then, following the approach developed by Beltrán-Sánchez et al. (2008),

$$e_s(a^*, t_2) - e_s(a^*, t_1) = \sum_{c \in \mathcal{C}} \sum_{a=a^*}^{\omega} \left[L_{a,s,c}(t_2) - L_{a,s,c}(t_1)\right] \left[\frac{L_{a,s,-c}(t_2) + L_{a,s,-c}(t_1)}{2n}\right], \qquad \text{(E.2)}$$

where n is the width of the age interval and ω is the starting age of the final and open-ended age interval.

We perform the decomposition starting at age 40; the final decomposition equation equals:

$$\begin{aligned} e(40, t_2) - e(40, t_1) &= \sum_{s \in \mathcal{S}} \left[\, \pi_s(t_2)\, e_s(40, t_2) - \pi_s(t_1)\, e_s(40, t_1)\right] \\ &= \sum_{s \in \mathcal{S}} \left[\pi_s(t_2) - \pi_s(t_1)\right] \left[\frac{e_s(40, t_1) + e_s(40, t_2)}{2}\right] + \sum_{s \in \mathcal{S}} \left[\texttt{Diff}_\texttt{e}\right] \left[\frac{\pi_s(t_1) + \pi_s(t_2)}{2}\right], \end{aligned}$$

where $\texttt{Diff}_\texttt{e}$ is given by (E.2) evaluated at $a^* = 40$.

F Decomposition by Tumor Size, Case Fatality Rates from Breast Cancer and Other Causes of Death, and Age Group

As previously defined $\pi_s(t)$ equals the proportion of cancer patients with tumor size s in year t. This proportion can also be computed by age group such that $\pi_s(t) = \sum_{a \in \mathcal{A}} \pi_{s,a}(t)$ and $\sum_{s \in \mathcal{S}} \pi_s = 1$. Then, the change in life expectancy at age a between times t_1 and t_2 can be

estimated as:

$$
\begin{aligned}
e(40,t_2) - e(40,t_1) &= \sum_{s\in\mathcal{S}} \left[\, \pi_s(t_2)\, e_s(40,t_2) - \pi_s(t_1)\, e_s(40,t_1)\right] \\
&= \sum_{s\in\mathcal{S}} \left[\sum_{a\in\mathcal{A}} \pi_{s,a}(t_2)\, e_s(40,t_2) - \sum_{a\in\mathcal{A}} \pi_{s,a}(t_1)\, e_s(40,t_1) \right] \\
&= \sum_{s\in\mathcal{S}} \left[\pi_{s,40}(t_2)\, e_s(40,t_2) - \pi_{s,40}(t_1)\, e_s(40,t_1)\right] + \\
&\quad \sum_{s\in\mathcal{S}} \left[\pi_{s,45}(t_2)\, e_s(40,t_2) - \pi_{s,45}(t_1)\, e_s(40,t_1)\right] + \\
&\quad \vdots \\
&\quad \sum_{s\in\mathcal{S}} \left[\pi_{s,\omega}(t_2)\, e_s(40,t_\omega) - \pi_{s,\omega}(t_1)\, e_s(40,t_1)\right].
\end{aligned}
$$

Each summation in the above equation can be written as follows based on equation (E.1):

$$
\begin{aligned}
&e(40,t_2) - e(40,t_1) = \\
&\sum_{s\in\mathcal{S}} \left[\pi_{s,40}(t_2) - \pi_{s,40}(t_1)\right] \left[\frac{e_s(40,t_1) + e_s(40,t_2)}{2}\right] + \sum_{s\in\mathcal{S}} \left[e_s(40,t_2) - e_s(40,t_1)\right] \left[\frac{\pi_{s,40}(t_1) + \pi_{s,40}(t_2)}{2}\right] + \\
&\sum_{s\in\mathcal{S}} \left[\pi_{s,45}(t_2) - \pi_{s,45}(t_1)\right] \left[\frac{e_s(40,t_1) + e_s(40,t_2)}{2}\right] + \sum_{s\in\mathcal{S}} \left[e_s(40,t_2) - e_s(40,t_1)\right] \left[\frac{\pi_{s,45}(t_1) + \pi_{s,45}(t_2)}{2}\right] + \\
&\qquad\qquad \vdots \\
&\sum_{s\in\mathcal{S}} \left[\pi_{s,\omega}(t_2) - \pi_{s,\omega}(t_1)\right] \left[\frac{e_s(40,t_1) + e_s(40,t_2)}{2}\right] + \sum_{s\in\mathcal{S}} \left[e_s(40,t_2) - e_s(40,t_1)\right] \left[\frac{\pi_{s,\omega}(t_1) + \pi_{s,\omega}(t_2)}{2}\right] = \\
&\sum_{s\in\mathcal{S}} \left[\mathtt{Diff}_{\pi,40}\right] \bar{\mathtt{e}}_{\mathtt{s}} + \sum_{s\in\mathcal{S}} \left[\mathtt{Diff}_{\pi,45}\right] \bar{\mathtt{e}}_{\mathtt{s}} + \cdots + \sum_{s\in\mathcal{S}} \left[\mathtt{Diff}_{\pi,\omega}\right] \bar{\mathtt{e}}_{\mathtt{s}} + \sum_{s\in\mathcal{S}} \left[e_s(40,t_2) - e_s(40,t_1)\right] \left[\frac{\pi_s(t_1) + \pi_s(t_2)}{2}\right]
\end{aligned}
\tag{F.1}
$$

where $\mathtt{Diff}_{\pi,\mathtt{a}} = \pi_{s,a}(t_2) - \pi_{s,a}(t_1)$ and $\bar{\mathtt{e}}_{\mathtt{i}} = \frac{e_s(40,t_1)+e_s(40,t_2)}{2}$.

The terms of equation(F.1) that include $\mathtt{Diff}_{\pi,40} \ldots \mathtt{Diff}_{\pi,\omega}$ correspond to the contribution of changes in the share of tumor size by age group to the change in cancer life expectancy between times t_1 and t_2. We can additionally estimate the contribution of changes in case fatality rates from breast cancer and competing causes of death to changes in tumor-size-specific life

expectancy by age. The last term of (F.1) can be written as follows, based on equation (E.2):

$$e_s(40,t_2) - e_s(40,t_1) = \sum_{c\in\mathcal{C}} \sum_{a=40}^{\omega} \left[L_{a,s,c}(t_2) - L_{a,s,c}(t_1)\right] \left[\frac{L_{a,s,-c}(t_2) + L_{a,s,-c}(t_1)}{2n}\right]. \tag{F.2}$$

G Assuming Constant Mortality Within Age Intervals

Let $M_{a,a+n}$ represent the mortality rate between ages a and $a+n$ and let $\mu(a)$ represent the hazard of mortality at age a. Then, the number (or proportion) of survivors at age $a+n$ in the life table, l_{a+n}, equals (Preston et al. (2000)):

$$l_{a+n} = l_a\, e^{-\int_a^{a+n} \mu(x)\,dx} = l_a\, e^{-n\, M_{a,a+n}}.$$

Then, the number of person-years lived between ages a and $a+n$ equals:

$${}_nL_a = l_a \int_a^{a+n} e^{-M_{a,a+n}(s-a)} ds = l_a \left(\frac{-1}{M_{a,a+n}}(e^{-n\, M_{a,a+n}} - 1)\right). \tag{G.1}$$

Suppose the age interval is $n = 5$ years wide, then equation (G.1) equals:

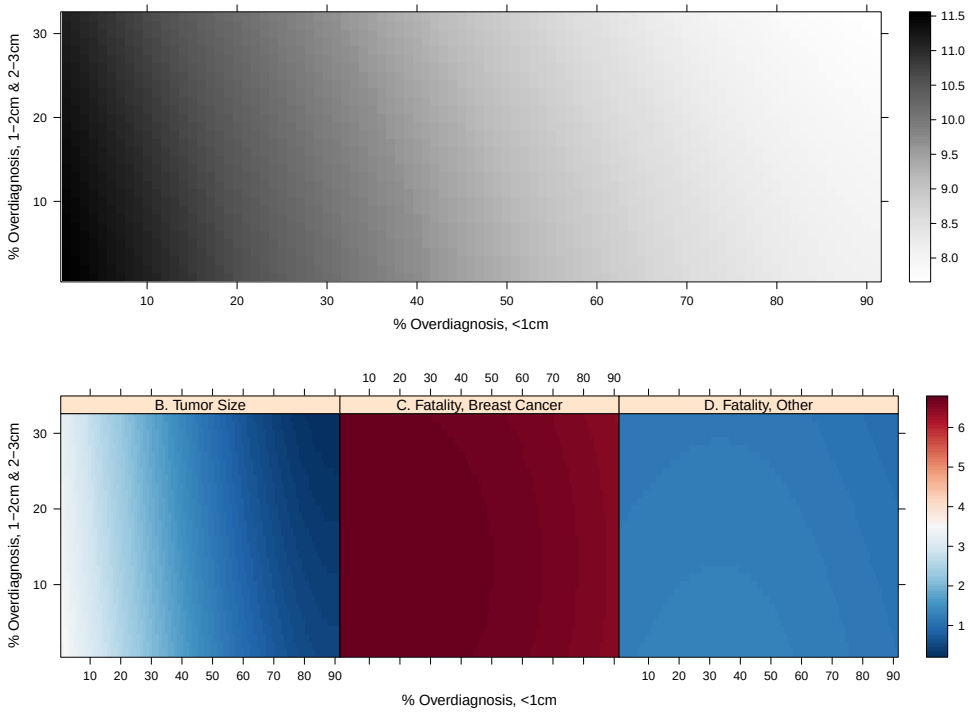
$${}_5L_a = l_a \left(\frac{-1}{M_{a,a+5}}(e^{-5\, M_{a,a+5}} - 1)\right).$$

For the last and open-ended age group (e.g., $\geq$100 years), we can assume there are no person-years lived beyond a certain time (say no more than 10 years) to compute ${}_\infty L_{100}$ as:

$${}_\infty L_{100} = l_{100} \left(\frac{-1}{M_{100+}}(e^{-10\, M_{100+}} - 1)\right).$$

H Varying Overdiagnosis Level for <1cm and $1-3$cm Tumors

We individually varied the overdiagnosis level from 0% to 97% for tumors <1cm and from 0% to 52% for 1-3cm tumors. We set the upper bound based on the smallest percentage of patients diagnosed with <1cm tumors who subsequently died of breast cancer within 10 years (3%). For example, at overdiagnosis levels of 97% for <1cm tumors and 35% for 1-3cm tumors, the contribution to the 7.58-year gain in life expectancy were: 6.40 years from reductions in case fatality rates from breast cancer (84%), 0.22 years from the temporal shift to smaller sized tumors (3%), and 0.98 years from reductions in case fatality rates from competing causes of death (13%).



Supplemental Figure 2: Gain in life expectancy (top panel) and contributions of the temporal shift to smaller sized tumors (bottom left), temporal reductions in case fatality rates from breast cancer (bottom center), and temporal reductions in case fatality rates from competing causes of death (bottom right) varying the overdiagnosis level for <1cm tumors (0% to 90%) and 1-3cm tumors (0% to 31%). The color scale for the top (bottom) panel indicates the number of years of the gain in life expectancy (contribution to the gain).

I Varying Time Intervals Between Diagnosis and Death

Time Interval	Gain in Life Expectancy	Tumor Size	Reductions in Case Fatality Rates from Breast Cancer	Reductions in Case Fatality Rates from Competing Causes
8	11.23	3.15 (28%)	7.07 (63%)	1.03 (9%)
9	10.93	3.09 (28%)	6.76 (62%)	1.09 (10%)
10	10.69	2.99 (28%)	6.57 (61%)	1.15 (11%)
11	10.38	2.78 (27%)	6.27 (60%)	1.35 (13%)
12	10.28	2.65 (26%)	6.05 (59%)	1.59 (15%)

Supplemental Table 1: Gain in life expectancy and contribution of the temporal shift to smaller sized tumors, temporal reductions in case fatality rates from breast cancer, and temporal reductions in case fatality rates from competing causes of death, 1975-2000, varying time interval between breast cancer diagnosis and death. Note: Yrs=years.

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