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

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**ABSTRACT (Word Count: 288)**

**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.

**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 2002—and not the 2009—USPSTF recommendation.

The controversy over screening arose and persists, in part, because of disagreement over the value of screening and disagreement over 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 a 0% to 30% mortality reduction.8 Yet, the trials randomized on the invitation to screen—rather than screening itself—and 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: between 28% and 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 of death (e.g., cardiovascular disease [CVD]).

In this study, we address these research gaps and quantify the contribution of the three factors that could have led to the gain in life expectancy among breast cancer patients: [1] earlier detection, [2] advancements in breast cancer treatment, and [3] 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 Institute’s 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 of the cancers occurring in the geographic areas covered by the registries; a person’s 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.3,4 By allowing this 10-year time window between diagnosis and death, we were able to calculate 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 [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. 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. Supplementary Materials, Section A, describes the calculation of incidence-based case fatality rates.

**2.2 Analytic Methods**. For our primary analysis, we assume an overdiagnosis level of 10% for tumor sizes ≤3cm based on the results of the Malmö, Sweden randomized trial.13 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 patient’s 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).

We estimated life expectancy at age 40 using a life-table that uses as input the all-cause incidence-based case fatality rates from a cohort of patients diagnosed with breast cancer in a particular year. A life-table accounts for the age distribution of the population by transforming case fatality rates into probabilities of survival.14 We create separate life tables for each tumor size and for each year, which produces annual tumor size-specific life expectancies (Supplementary Materials, Section C). 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. Hiram – I think we need a sentence that briefly describes the cause-deleted life tables and associated decrement life tables. Using an established demographic method, we calculated how much of the change in life expectancy over time was the result of : [1] shifts toward smaller sized tumors at diagnosis from earlier detection, [2] reductions in case fatality rates from breast cancer from advancements in breast cancer treatment, and [3] reductions in case fatality rates from competing causes of death from advancements in the treatment of other diseases.11,12,15 We schematically represent our approach in Supplementary Materials Sections D-G.

The shift toward smaller sized tumors at diagnosis occurs when incidence rates for smaller sized 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 overall 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% to 52% for all tumors ≤3cm. We set the lower bound at its theoretical minimum of 0% and the upper bound based on the highest estimate from randomized screening trials and observational studies.16–20 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~~. The steepest gain occurred between 1984 and 1988.~~ 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. In contrast, the annual share decreased from 25% to 17% for 2-3cm tumors, from 30% to 17% for 3-5cm tumors, and from 15% to 10% for ≥5cm tumors.

Case fatality rates from breast cancer decreased more, in absolute terms, for larger sized tumors 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 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 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 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 in life expectancy resulted from earlier detection, which increased the share of smaller sized tumors over time. Finally, the remaining 12% of the gain in life expectancy 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 the 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.19 The seven simulation-based CISNET models estimated screening contributed to between 28% and 65% of the decline in breast cancer mortality 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 stationary 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.21

Our results also directly address the longstanding controversy over the value of mammography screening, especially among 40-49 year olds.2,22 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.23–25 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) and smaller than the corresponding contributions of 70-79 and 80-89 year olds (6.54% and 5.93%, 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.26 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.27,28 The same CISNET models also 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 upper end of the CISNET range.

Advancements in the prevention and treatment of competing causes of death, such as CVD,29,30 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.31 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, which may affect its internal and external validity. 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.32,33 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.34 Additionally, breast cancer mortality patterns in the SEER registries are highly representative of national breast cancer mortality patterns.35 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 treatment because patients typically received multiple modalities for virtually the entire time period of our study.36

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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**Figure Titles and Legends**

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.

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.

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 ≤1cm from 0% to 52% and for tumors 1-3cm from 0% to 35%.

Table 1. Contribution of Earlier Detection by Age Group

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Age Group (Years) | | | | | | | |  | |
| Tumor Size | 40-49 | 50-59 | 60-69 | 70-79 | 80-89 | 90-99 | ≥100 | Total | |
| <1 cm | 0.71 | 1.35 | 1.29 | 1.14 | 0.49 | 0.04 | 0.00 | 5.02 | |
| 1-2 cm | 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 | |

Note: cm=centimeter.