Title: Quantifying the Contribution of Earlier Detection and Advancements in 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.

**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 2002—not the 2009—USPSTF recommendation.

The controversy over screening persists, in part, because of disagreement over the precise contributions of earlier detection and advancements in breast cancer treatment on reductions in breast cancer mortality. 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: between 28% and 65% (1975-2000).1 Additionally, the CISNET models are based on the hypothetical experience of a simulated cohort of breast cancer patients inherently untestable assumptions on the natural history of breast cancer.8 Sun et al. (2010) concluded earlier detection contributed 17% of the estimated gain in breast cancer survival time and attributed the remaining 83% to advancements in breast cancer treatment (1988-2000).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 could have led to 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 base on results on the observed mortality experience of actual breast cancer patients, rather than on simulation. We measure earlier detection, which resulted in part 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 focus on 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 Surveillance, Epidemiology, and End Results (SEER) 9 registry database, 1975 to 2012. The SEER 9 registries, which cover ~10% of the US population, form the largest, most representative and longest running national cancer incidence database. 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 breast cancer patients and, thus, study their actual mortality experience. 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 Appendix, 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**. First, we adjust case fatality rates and the annual share of cases by tumor size to overdiagnosis. 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.11 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 over the 10-year period after diagnosis. They do, however, contribute to the denominator of the case fatality rate by artificially increasing exposure. Thus, we adjust case fatality 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 inflate 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 Appendix, Section B).

Second, we create demographic life-tables for each tumor size and year, which take as input adjusted all-cause case fatality rates and output life expectancy. Life-tables accounts for the age distribution of the population by transforming these rates into probabilities of survival.12 Overall life expectancy equals the weighted sum of tumor size-specific life expectancies, where the weights equal the annual share of each tumor size.

Third, we utilize a demographic method13 to disaggregate and quantify how much of the gain in overall life expectancy over time resulted from the change in the share of tumor sizes versus from the change in tumor size-specific case fatality rates (all-cause). Fourth, we utilize a related demographic method14,15 to further 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. Finally, we utilize the same demographic methods to further disaggregate these three contributions by age group. We do not report any sampling uncertainty in the gain in life expectancy or its three constituent components because our calculations use registry and vital statistics data that fully capture the mortality experience of defined populations.16 We mathematically describe the demographic methods in Supplementary Appendix Sections D-G.

As a conceptual example of these methods, consider three mutually exclusive and exhaustive categories of tumor size: 1, 2, and 3 (e.g., <1cm, 1-2cm, and ≥2cm). Suppose the distribution of tumor size at cancer diagnosis remains constant between times 1 and 2 (Figure 1, Panel A), tumor size-specific case fatality rates from breast cancer decrease between times 1 and 2 (Figure 1, Panel B), and tumor size-specific case fatality rates from competing causes of death remain constant between times 1 and 2 (Figure 1, Panel B). Tumor size-specific life expectancy increases between times 1 and 2 because tumor size-specific case fatality rates from breast cancer decreased over the time period (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 (Figure 1, Panel D).

In actuality, all three constituent factors change over time and contribute to the gain in life expectancy. For example, 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 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.17–21 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 2, 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 2, 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 2, 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.** The decrease in size-specific case fatality rates from breast cancer and other diseases led to an increase in size-specific life expectancies. The growing share of smaller size tumors placed greater weight on the life expectancies for these tumors, compared to those of larger sized tumors.  These two patterns led to an increase of 10.94 years in overall life expectancy for a 40-year old newly diagnosed breast cancer patient between 1975 and 2002 (Figure 3).  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.** Across all ages, earlier detection contributed 2.92 years of life to the 10.94-year gain in life expectancy (Table 1). By age group, earlier detection among 40-49, 50-59, 60-69, 70-79, and 80-89 year olds contributed nearly equally in absolute terms to the overall contribution of earlier detection: between 0.41 to 0.72 years of life. In other words, earlier detection in these decades of life each contributed to between 3.7% and 6.6% to the gain in life expectancy.

**3.4. Varying Level of Overdiagnosis.** In the primary analysis, we assumed the overdiagnosis level for ≤3cm tumors equaled 10%. In secondary analysis, we varied the overdiagnosis level among these tumors sizes between 0% and 52% (Figure 4). 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 Appendix Section H).

**4. Discussion**

Our study quantifies the contribution of earlier detection and advancements in breast cancer treatment on gains in life expectancy.  We show that accurately measuring these contributions depends on accounting for improvements in the treatment of competing causes of death for breast cancer patients.  Our results also provide a precise estimate of these contributions because they are based on the observed mortality experience of actual breast cancer patients.  Overall, we found the majority of the gain in life expectancy between 1975 and 2002 resulted from advancements in breast cancer treatment (63%), followed by earlier detection (27%) and advancements in the treatment of other diseases (10%).  The relative contribution of each of these three constituent components remained the same across various levels of overdiagnosis.

Our study precisely quantifies the effect of earlier detection on the gain in life expectancy for breast cancer patients.  Previous estimates of this effect from the seven CISNET models ranged between 16% and 50% when translated on the scale of life expectancy.1 This wide range resulted from the varying set of assumptions in the models and the inherent uncertainty in simulating the mortality experience of a hypothetical cohort of breast cancer patients.  Sun et al. (2010) estimated earlier detection contributed 17% of the 3.6-year gain in survival among breast cancer patients between 1988 and 2000 using survival time data.9  We reach a similar conclusion on the contribution of earlier detection between 1988 and 2000, 24%, although our methods rely on incidence-based case fatality rates and not survival time data, which are inherently subject to the lead- and length-time biases. Our calculation of the observed effect of earlier detection contrasts with a recent county-based study that failed to find a relationship between screening and breast cancer mortality.7 This study was ecological in nature and focused on a single year of screening (2000) rather than assessing the relationship of changes in screening over time and changes in mortality over time.

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 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.22

Our results also directly address the longstanding controversy over the value of screening, especially among 40-49 year olds.2,23 We calculate earlier detection among 40-49 year olds conferred about the same level of benefit, in terms of years of life expectancy gained, as older age groups. For example, earlier detection among 40-49 year olds contributed 5.16% of the 10.94-year gain in life expectancy, which was slightly greater than the corresponding contribution of 50-59 year olds (4.11%) and 60-69 year olds (3.75%). Our calculation of the observed benefit of earlier detection among 40-49 year olds starkly contrasts with estimates from cross-national studies. These 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 and the development of novel treatments, both of which reduced case fatality rates.24,25 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 upper end of the CISNET range. Sun overestimated the contribution of advancements in breast cancer treatment.

Advancements in the prevention and treatment of competing causes of death, such as CVD,26,27 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.28 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.28 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; 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.29,30 Second, our results may not be generalizable nationally to the extent that SEER fails 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 screening.31 Additionally, breast cancer mortality patterns in the SEER registries are highly representative of national mortality patterns.32 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 Appendix, Section I). Finally, we cannot quantify the contribution of individual types of treatment because patients typically received multiple modalities.33

In conclusion, the substantial gain in life expectancy for breast cancer patients observed since 1975 likely resulted from co-occurring and incremental improvements in detection, breast cancer treatment, and the treatment of other diseases. We utilize new methodologies to disentangle the precise contribution of each of these three factors. 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 ≤3cm from 0% to 52%.

Table 1. Contribution of Earlier Detection on Gain in Life Expectancy by Tumor Size & Age Group (Years of Life)

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Age Group (Years Old) | | | | | | | |  | |
| Tumor Size | 40-49 | 50-59 | 60-69 | 70-79 | 80-89 | 90-99 | ≥100 | Total | |
| Total | 0.56 | 0.45 | 0.41 | 0.72 | 0.65 | 0.12 | 0.01 | 2.92 | |

Note: cm=centimeter.