Title: Quantifying the Contribution of Earlier Detection and Advances in Treatment on the Gain 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 relative contribution of earlier detection versus advances in breast cancer treatment. We quantify the contributions of these two factors, accounting for concurrent advances in the treatment of other diseases, to 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, which require fewer assumptions than simulation-based studies, to calculate the gain in life expectancy and quantified the three constituent components of this gain: [1] earlier detection, [2] advances in breast cancer treatment, and [3] advances in the treatment of other diseases. We additionally quantify which age groups contributed the most to the overall contribution of earlier detection.

Results. Life expectancy increased 10.94 years between 1975 and 2002 for a 40-year old newly diagnosed breast cancer patient. Advances in breast cancer treatment contributed more to this gain in life expectancy than earlier detection: 6.79 years (62%) versus 2.92 years (27%). Advances in the treatment of other diseases contributed the remaining 1.25 years to this gain (11%). By age group, earlier detection contributed approximately equally to the gain in life expectancy among 40-49 year olds (0.56 years) as it did for 50-59 and 60-69 year olds (0.45 and 0.41 years, respectively.

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

**1. INTRODUCTION**

Mammography screening, which offers the promise of earlier detection, has become the subject of intense public and scientific controversy.1–10 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 that insurers must follow the 2002—not the 2009—USPSTF recommendation.

The controversy over screening persists because of disagreement over the precise contributions of screening and advances in breast cancer treatment on reductions in breast cancer mortality and the resulting improvement in the survival of breast cancer patients over time. Quantifying these contributions requires the simultaneous assessment of three components: [1] changes in the distribution of stage at diagnosis over time because women diagnosed at earlier stages typically live longer than women diagnosed at later stages, [2] better breast cancer treatments that reduce fatality rates from breast cancer, and [3] better prevention and treatment of other diseases that are the leading causes of death among women diagnosed with early stage breast cancer (e.g., cardiovascular disease [CVD]). Previous research only estimated the contribution of screening and attributed the remainder to the contribution of breast cancer treatment.11 Thus, this study was vulnerable to overestimating the contribution of breast cancer treatment because it failed to account for the substantial improvements in the treatment of other diseases that independently increased survival among the growing number of women diagnosed with early stage breast cancer. Other studies only focus on the reduction in breast cancer mortality rates rather than reductions in overall mortality rates and, consequently, inherently ignored the substantial improvements in the prevention and treatment of other diseases.1,12  Thus, these studies could not quantify the contribution of screening on the increase in overall survival of breast cancer patients over time.

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, advances in breast cancer treatment, and advances in the treatment of other diseases. We extend and improve prior research in three ways: (a) our analytic approach capture the interrelationship of these three components, (b) we base our results on the observed mortality experience of actual breast cancer patients rather than on simulation of the progression of breast cancer, and (c) we utilize case fatality rates that avoids biases inherent in survival time data. We measure earlier detection, which resulted from more widespread screening and advances in screening technology,13 by the changes over time in the distribution of tumor sizes of newly diagnosed breast cancer patients. We measure advances in breast cancer treatment and treatment of other diseases, which resulted from improvements in the delivery of existing treatments and development of novel treatments,14,15 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, which directly addresses the controversy over the value of screening at different ages. We focus on contributions to the gain in life expectancy, rather than the 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 vary the assumed level of overdiagnosis and re-quantify contributions to the gain in life expectancy.

**2. METHODS**

**2.1 Analytic Methods**. We describe our analytic approach in Figure 1, which consists of two main steps. The first step estimates the contribution of earlier detection to gains in life expectancy (component [1]). We began with all-cause incidence-based case fatality rates by tumor size. An incidence-based case fatality rate (hereafter “fatality rates”) for a specific cohort of newly diagnosed breast cancer patients equals the ratio of the number of deaths occurring for this cohort and the total number of person-years lived by this cohort up to 10 years beyond their diagnosis (eAppendix A).16,17  We then adjusted these fatality rates for overdiagnosis, as described in Section 2.3. The adjusted tumor size-specific fatality rates served as the input to demographic life tables that produced tumor size-specific life expectancies in 1975 and 2002 (see eAppendix C for example of life table calculations). We calculated the overall life expectancy for each time period as the weighted average of the tumor-size specific life expectancies, where the weights corresponded to the annual distribution of incident breast cancers by tumor size. The gain in life expectancy was then computed as the difference in overall life expectancy between 1975 and 2002. Next, we utilized an established demographic method (Kitagawa decomposition18) to estimate how much of this gain in overall life expectancy was due to changes in the annual distribution of incident breast cancers by tumor size (i.e., more small tumors over time) and improvements in adjusted all-cause fatality rates.

The second step estimates the contribution of advances in breast cancer treatment (component [2]) and advances in the treatment of other diseases (component [3]) on gains in life expectancy. We also began with fatality rates by tumor size but now distinguished causes of death (breast cancer and all other causes). We then adjusted these rates for overdiagnosis. The adjusted tumor size- and cause-specific fatality rates served as the input to demographic life tables (one for breast cancer and the other for all other causes) that produce corresponding life-years in 1975 and 2002. We then utilized a related demographic method (Beltrán-Sánchez et al. decomposition19) to estimate how much of the contribution of improvements in adjusted all-cause fatality rates was due to improvements in adjusted fatality rates from breast cancer and improvements in adjusted fatality rates from all other causes. The sum of these two estimates equaled the total contribution from improvements in adjusted all-cause case fatality rates. The three components, all of which we derive from life tables, sums to the total gain in life expectancy. We did not report any sampling uncertainty in the gain in life expectancy or its three constituent components because our calculations used registry data that fully captured the mortality experience of defined populations, rather than sample data.17 We mathematically describe the methods in eAppendix D-G.

**2.2 Patient Data.** We obtained incidence and mortality data for breast cancer from the SEER 9 registry database (1975-2012). 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. We included 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. By allowing this 10-year time window between diagnosis and death, we mitigated potential lead time bias by limiting the length of time over which a death labeled as breast cancer on the death certificate would be categorized as a breast cancer death in our analysis. We calculated fatality rates for 422,141 breast cancer patients by age group at diagnosis (40-44 to ≥100 years), year of diagnosis (1975-2002), tumor size determined by clinical and operative/pathological assessment (<1cm, 1-2cm, 2-3cm, 3-5cm, ≥5cm), and cause of death (breast cancer or competing causes of death). We also calculated the distribution of incident cancer cases by tumor size at diagnosis and year of diagnosis. We calculate incidence-based case fatality rates, rather than death certificate-based mortality rates, because the former enables us to separate the rates by tumor size at diagnosis. These tumor size-specific fatality rates, along with the distribution of incident cases by tumor size, serve as the input to the methods described in Section 2.1.

**2.3 Adjustment for Overdiagnosis.** Overdiagnosis is the detection of asymptomatic breast cancers that are non-growing or so slow-growing that they would never present symptomatically during a women’s lifetime.20 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.21 We adjust case fatality rates (both all-cause and cause-specific) for these smaller sized tumors by removing the person-years overdiagnosed cases contributed to the denominator of the rates (eAppendix B). We also adjust the annual proportion of smaller sized tumors by subtracting the overdiagnosed cases from the annual count of incident cancers and recalculating the distribution by tumor size. We conducted two sensitivity analyses on the overdiagnosis level. First, we varied the level up to 52% for all tumors ≤3cm based on the highest estimate from randomized screening trials and observational studies.22–26 Second, we varied the level up to 97% for tumors <1cm (because 97% of patients diagnosed with <1cm tumors did not die of breast cancer within 10 years and, thus, could have been overdiagnosed) and up to 52% for 1-3cm tumors.

**3. RESULTS**

**3.1. Incidence Rates, Proportion of Tumor Sizes, and Case Fatality Rates.** Both the incidence rate and proportion of <1cm and 1-2cm tumors increased between 1975 and 2002 (Figure 2, Panels A and B).  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 proportion of the <1cm and 1-2cm tumors grew over time because their incidence rates increased more than those of larger sized tumors.

Case fatality rates from breast cancer decreased more, in absolute terms, for larger tumors 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 person-years among patients diagnosed with ≥5cm tumors and from 18 to 5 deaths per 100,000 person-years among patients diagnosed with <1cm tumors. For patients diagnosed with <1cm, 1-2cm, 2-3cm, and 3-5cm tumors, case fatality rates from other causes were higher than those from breast cancer.  Only for patients diagnosed with ≥5cm tumors were case fatality rates from breast cancer larger than those from other causes.  ~~This result highlights the importance of accounting for both causes of death (breast cancer and other causes) when assessing the gain in life expectancy for breast cancer patients.~~

**3.2. Analysis of Gains in Life Expectancy.** The decrease in tumor size-specific case fatality rates from breast cancer and other diseases led to an increase in size-specific life expectancies. The growing proportion of smaller size tumors placed greater weight on these tumors in calculating overall life expectancy, and less weight to the shrinking proportion of larger sized tumors. The decrease in fatality rates and redistribution in the proportion of tumor sizes led to a 10.94-year gain 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 this gain (27%). This 2.92 year net contribution results from offsetting trends in the distribution of cancers by tumor size: increasing contributions from the growing proportion of smaller sized tumors and decreasing contributions from the shrinking proportion 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 (as evidenced by a shift in tumor size) contributed 2.92 years of life to the 10.94-year gain in life expectancy from 1975 to 2002 (Table 1). By age group, earlier detection among 40-49, 50-59, 60-69, 70-79, and 80-89 year olds contributed approximately 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 3.8% and 6.6% to the gain in life expectancy.

**3.4. Effect 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 up to 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 gain in life expectancy equaled 10.31 years (compared to 10.94 years at a 10% overdiagnosis level): 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 (compared to 62%, 27%, and 11%, respectively, at a 10% overdiagnosis level). We also independently varied the overdiagnosis level for <1cm tumors and 1-3cm tumors and reached similar conclusions (eAppendix H).

**4. Discussion**

Our study quantifies the contribution of earlier detection and advances in breast cancer treatment on gains in life expectancy for a newly diagnosed breast cancer patient. Accurately measuring these contributions depends on accounting for improvements in the treatment of competing causes of death for breast cancer patients. Our results provide a more precise estimate of these contributions because they are based on the observed mortality experience of actual breast cancer patients without the use of simulation models and their requisite—though untestable—assumptions about the progression of breast cancer. Overall, we found the majority of the gain in life expectancy between 1975 and 2002 resulted from advances in breast cancer treatment (62%), followed by earlier detection (27%) and advances in the treatment of other diseases (11%). ~~The relative contribution of each of these three constituent components were similar across various levels of overdiagnosis.~~

Our results provide a more accurate estimate of the contribution of earlier detection and advances in cancer treatment to the gain in life expectancy than previous work. For instance, CISNET estimates two separate life expectancies, one assuming breast cancer as the only cause of death and the other assuming all other causes as the only cause of death.27 CISNET then takes the smaller of these as the actual life expectancy.27 Thus, gains in overall life expectancy from 1975 to 2002 become increasingly dominated by the cause with higher fatality rates and, hence, lower life expectancy. Empirically, mortality rates from breast cancer exceeded those from all other causes and, therefore, the life expectancy from breast cancer was lower than life expectancy from all other causes. Consequently, although CISNET appears to consider mortality rates from other causes of death, it effectively relies only on breast cancer mortality rates when estimating the gain in life expectancy. In doing so, the CISNET approach underestimates the gain in life expectancy over time, which results in biased estimates of the contributions of breast cancer treatment and earlier detection to the gain in life expectancy. In contrast, we jointly model life expectancy from the two causes of death using a competing risk approach; overall survival equals the product of survival from breast cancer and survival from all other diseases. In other words, our approach equally relies on case fatality rates from both causes of death (breast cancer and other disease) when estimating the gain in life expectancy.

Our study provides greater clarity to the contribution of earlier detection to the gain in life expectancy among breast cancer patients. The CISNET approach is to have several groups model the problem independently, which results in a range of estimates. CISNET simulated the progression of breast cancer using seven distinct models that varied between six and forty separate parameters, some of which rely on untestable assumptions of breast cancer progression from small non-invasive tumor to malignant cancer.28 CISNET estimated the contribution of earlier detection to be as low as 28% (University of Rochester model) and as high as 65% (Dana-Farber model model) to the decline in breast cancer mortality rates (1975-2000).1 This range corresponds to an equivalent contribution of between 16% and 50% on the resulting gain in life expectancy. During the same time period (1975-2000), we estimated that earlier detection made a 28% contribution to the gain in life expectancy. Additionally, Sun et al. (2010) estimated the contribution of earlier detection to be 17% of the 3.6-year gain in survival among breast cancer patients between 1988 and 2000.11 This study may have underestimated the contribution from screening because it overestimated the contribution from improved breast cancer treatment by failing to distinguish between breast cancer and other diseases as causes of death. During the same time period (1988-2000), we calculated that early detection made a 24% contribution to the gain in life expectancy, which suggests that Sun et al. estimate of 17% is too low. Overall, our calculation of the contribution of earlier detection is broadly similar to many of the CISNET models and Sun et al., although we arrive at this conclusion using methods that require fewer assumptions and are less susceptibility to bias. The general agreement of these three different approaches should increase confidence in the estimates of the relative contribution of early detection, as well as better treatment of breast cancer.

Our results also directly address the longstanding controversy over the value of screening at different ages.3,29 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%) and slightly less than the corresponding contribution of 70-79 year olds (6.58%). Thus, our results suggest earlier detection among 40-49 year olds provided approximately equal benefit, measure in the contribution to the gain in life expectancy, as it did among 50-59 and 60-69 year olds. This comparable level of contribution from earlier detection may be due, in part, because of similar increases in mammography screening rates for these age groups across time.30

Our study more accurately measures the contribution of advances in breast cancer treatment on the gain in life expectancy because it accounts for concurrent improvements in the treatment of other diseases. Just as the CISNET models estimated a wide range of the contribution of earlier detection, so too was the estimated range for the contribution of breast cancer treatment: as low as 35% (Dana-Farber model) and as high as 72% (University of Rochester model) on the decline in breast cancer mortality rates (1975-2000).1 This range corresponds to an equivalent contribution of between 50% and 84% to the resulting gain in life expectancy. During the same time period (1975-2000), we calculate a 62% contribution from advances in breast cancer treatment. Sun et al. (2010) concluded that advances in breast cancer treatment contributed 83% of the estimated gain in breast cancer survival time (1988-2000).11 Our calculation of the contribution of advances in breast cancer treatment in this time period, 64%, suggests the previous estimate may be too high because the study failed to distinguish between breast cancer and other diseases as causes of death.

Advances in the prevention and treatment of competing causes of death, such as CVD,31,32 made an increasing contribution to the gain in life expectancy among breast cancer patients from 1975 to 2002 in part because of the trend toward earlier detection. 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 usually smaller sized tumors, the probability of death from other causes is considerably higher than the corresponding probability of death from breast cancer.33 Thus, improvements in the treatment of other diseases are particularly important for the overall gain in life expectancy of breast cancer patients over the period 1975 to 2002 because the proportion of smaller sized tumors grew over this period. And as treatment of other diseases improved, so did the size of the population who could benefit most from it.

Our study has some potential limitations. First, our life table methods and the resulting estimates of life expectancy assume that women experience a set of fatality rates, which vary by age, based on their year of breast cancer diagnosis rather than on their year of birth.  For example, the life expectancy of a 40-year-old woman diagnosed with 1-2cm breast cancer in 1990 is based on the case fatality rates of 40-44-year-old, 45-49-year-old, …, ≥100-year-old women diagnosed with similarly sized tumors also in 1990 (‘period life expectancy’).  In reality, the life expectancy of this 40-44-year-old woman diagnosed in 1990 would be based on the survival times from diagnosis to death of her birth cohort (‘cohort life expectancy’ equals the area under this survival curve).  The limitation of period life expectancy notwithstanding, it is commonly reported summary of a population’s mortality because cohort life expectancy can only be computed after all individuals have died.  Empirically, case fatality rates for cohort life expectancy were at most 20% smaller than the case fatality rates for period life (eAppendix J).  This difference between period- and cohort-based case fatality rates corresponds to a gain in life expectancy of 10.88 years between 1975 and 2002 (compared to 10.94 years in our primary analysis) with the following contributions: 62% from advances in breast cancer treatment, 28% from earlier detection, and 11% from advances in the treatment of other diseases (compared to 61%, 27%, and 11% in our primary analysis).  Second, we required that breast cancer death must have occurred within 10 years of diagnosis when calculating case fatality rates to partially mitigate lead time bias. We vary the time interval between 8 years and 12 years and reach identical substantive conclusions (eAppendix I). Third, we cannot quantify the contribution of individual types of treatment because patients typically received multiple modalities. Fourth, we cannot quantify the contribution of specific factors that produced the observed effectiveness of detection (e.g., more widespread screening among *BRCA* mutation carriers, improved standards in the interpretation of mammograms, and improvements in clinical breast examination) because SEER does not capture screening information or the circumstances leading to diagnosis. ~~Fifth, we focus on the broadest time period possible, 1975-2002, which begins with the start of the SEER 9 registries and ends 10 years before the final year of data registry data (2012) to allow for the 10-year window to calculate incidence-based case fatality rates.~~ Finally, we do not quantify the contribution of earlier detection and advances in breast cancer treatment after the introduction of a specific innovation. The diffusion of novel chemotherapy agents, imaging modalities, and new clinical and surgical techniques occurs slowly over time rather than immediately after introduction.34,35

In conclusion, several factors contributed to the gain in life expectancy for breast cancer patients.  More widespread screening increased the proportion of small-sized tumors among newly diagnosed breast cancer patients. At the same time, incremental improvements in medical care reduced the risk of death among breast cancer patients from breast cancer itself. As patients lived longer, they also benefited from advances in treating other diseases, such as CVD. We apply existing demographic methods to disentangle the precise contribution of earlier detection and advances in breast cancer treatment on the gain in life expectancy, accounting for concurrent advances in the treatment of other diseases. Earlier detection contributed to more than one-quarter of the observed gain in life expectancy (27%); advances in breast cancer treatment contributed substantially more (62%), and advances in treatment of other disease contributed the least (11%). The value of screening is based on the balance of potential benefits of earlier detection and potential harms from overdiagnosis and overtreatment. Our study assessed the benefit of early detection on its contribution to the gain in life expectancy.  When the harms are also measured in gains in life expectancy, it will be possible to directly measure the balance of benefits and harms. This common approach may clarify the controversy about whether mammography confers net benefit.

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**Figure Titles and Legends**

Figure 1. Overview of Analytic Method

Incidence-based case fatality rates (all-cause, breast cancer, and all other causes) and the annual distribution of incident breast cancer by tumor size serve as inputs to the demographic-based methods that estimate the constituent components of the gain in life expectancy: contribution from change in tumor-size distribution (earlier detection), contribution from changes in case fatality rates from breast cancer (advances in breast cancer treatment), and contribution from changes in case fatality rates from other causes (advances in treatment of other diseases).

Figure 2. 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 distribution 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 3. Contribution of Earlier Detection, Advances in Breast Cancer Treatment, and Advances 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 4. 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

|  |  |  |
| --- | --- | --- |
| Age Group (Years Old) | Contribution to Gain in Life Expectancy | |
| Years of Life  (1) | Percentage Contribution  (2)=100\*(1)/10.94 |
| 40-49 | 0.56 | 5.12 |
| 50-59 | 0.45 | 4.11 |
| 60-69 | 0.41 | 3.75 |
| 70-79 | 0.72 | 6.58 |
| 80-89 | 0.65 | 5.94 |
| 90-99 | 0.12 | 1.10 |
| ≥100 | 0.01 | 0.09 |
| Total | 2.92 | 26.69 |