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

Authors: Samir Soneji, PhD

Hiram Beltrán-Sánchez, PhD

Affiliations: From the Norris Cotton Cancer Center and Dartmouth Institute for Health Policy & Clinical Practice, Geisel School of Medicine at Dartmouth (SS). From the Department of Community Health Sciences and the California Center for Population Research, University of California Los Angeles (HBS).

Address correspondence to: Samir Soneji, PhD, Norris Cotton Cancer Center, One Medical Center Drive, Lebanon, NH 03766; tel. 603-650-3520; fax 603-653-0820; e-mail samir.soneji@dartmouth.edu.

Word Count: 3019

**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, accounting for concurrent 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 gain in life expectancy (0.56 years) than for 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, which offers the promise of earlier detection, has become the subject of intense public and scientific controversy. 1–9 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 screening and advancements in breast cancer treatment on reductions in breast cancer mortality. 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 lived longer than women diagnosed at later stages, [2] improvements in breast cancer treatment that reduce fatality rates from breast cancer, and [3] improvements in the 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]). Yet, previous research only estimated the contribution of screening and attributed the remainder to the contribution of treatment.1,10 Thus, these studies were vulnerable to overestimating the contribution of breast cancer treatment because they failed to account for the substantial improvements in the treatment of other diseases that independently raised survival among an increasingly larger number of women diagnosed with early stage breast cancer. For example, the seven Cancer Intervention and Surveillance Modeling Network (CISNET) simulation-based models attributed between 28% and 65% of the reduction in breast cancer mortality to screening (1975-2000) and the remainder to advancements in breast cancer treatment.1

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 extend and improve prior research in three ways: (a) our analytic approach capture the interrelationship of these three components, (b) we base on 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 in part from more widespread screening and advancements in screening technology,11 by the changes over time in the share of tumor sizes of newly diagnosed breast cancer patients. We measure advancements in breast cancer treatment and treatment of other diseases, which resulted from improvements in the delivery of existing and development of novel treatments,12,13 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 to directly address the controversy in screening women 40-49 years old. 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 implemented robustness checks to consider the effect of overdiagnosis on the gain in life expectancy and its three constituent components.

**2. METHODS**

**2.1 Analytic Methods**. We describe our analytic approach in Figure 1, which consists of two main steps. First, we began with all-cause incidence-based case fatality rates (hereafter “fatality rates”) by tumor size and adjusted them 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. 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 share 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 (Kitigawa decomposition14) to estimate how much of this gain in overall life expectancy was due to changes in the annual share of incident breast cancers by tumor size and improvements in adjusted all-cause fatality rates. We used the first estimate as a measure of the contribution of earlier detection to gains in life expectancy (component [1]).

In the second step, we also began with fatality rates by tumor size now separated by cause of death (breast cancer and all other causes). These rates were then adjusted for overdiagnosis. The adjusted tumor size- and cause-specific fatality rates served as the input to demographic life tables that produce corresponding life-years in 1975 and 2010. We then utilized a related demographic method (Beltrán-Sánchez et al. decomposition15) 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. We used the first estimate as a measure of advancements in breast cancer treatment (component [2]) and the second estimate as a measure of advancements in the treatment of other diseases (component [3]). The sum of these two estimates equaled the total contribution from improvements in adjusted all-cause case fatality rates. 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 C-G.

**2.2 Patient Data.** We obtained incidence and mortality data for breast cancer from the 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. By allowing this 10-year time window between diagnosis and death, we mitigate the potential bias of ascertainment in cause of death and calculate incidence-based case fatality rates between 1975 and 2002 for 422,141 breast cancer patients. 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 and the total number of person-years lived by this cohort up to 10 years beyond their diagnosis (eAppendix A).16,17  We calculated 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 share of incident cancer cases by tumor size at diagnosis and year of diagnosis.

**2.3 Adjustment for 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.18 We adjust case fatality rates for these smaller sized tumors (both all-cause and cause-specific) by removing the person-years overdiagnosed cases contributed to the denominator of the rates (eAppendix B). We also adjust the annual share 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.19–23 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, Share of Tumor Sizes, 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 and 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 overall life expectancy, compared to the shrinking share of larger sized tumors. The decrease in fatality rates and redistribution in the share 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 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 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 3.7% 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 gain in life expectancy equaled 10.31 years: 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 (eAppendix H).

**4. Discussion**

Our study quantifies the contribution of earlier detection and advancements in breast cancer treatment on gains in life expectancy for a 40-year old 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 on the progression of breast cancer. Overall, we found the majority of the gain in life expectancy between 1975 and 2002 resulted from advancements in breast cancer treatment (62%), followed by earlier detection (27%) and advancements in the treatment of other diseases (11%). The relative contribution of each of these three constituent components remained about equal across various levels of overdiagnosis.

Our results provide a more accurate estimate of the contribution of earlier detection and cancer treatment on the gain in life expectancy than previous work. For instance, CISNET estimates two separate life expectancies assuming breast cancer as the only cause of death and all other causes as the only cause of death.24 CISNET then takes the smaller of these two values as the actual life expectancy. Thus, gains in overall life expectancy over time 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. Thus, although CISNET ostensibly considers 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. This underestimation results in biased estimates of the contributions of breast cancer treatment and earlier detection on the gain in life expectancy. In contrast, we jointly model life expectancy using a competing risk approach; overall survival equals the product of survival from breast cancer and survival from all other diseases. In other words, breast cancer patients only live if they do not die of breast cancer and do not die of other causes.

Our study provides greater clarity to the contribution of earlier detection to the gain in life expectancy among breast cancer patients. CISNET estimated the contribution of earlier detection as low as 28% (University of Rochester model) and as high as 65% (Dana-Farber model model) on 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. CISNET produced such a wide range because it 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 this progression.9 During the same time period (1975-2000), we calculate a 28% contribution of earlier detection. Additionally, Sun et al. (2010) estimated earlier detection contributed 17% of the 3.6-year gain in survival among breast cancer patients between 1988 and 2000.10 Yet, this study may have underestimated the contribution from screening because it overestimated the contribution from treatment by not distinguishing between breast cancer and other diseases as causes of death. During the same time period (1988-2000), our calculation of a 24% contribution of early detection indeed suggests the estimate of Sun et al. may be too low. Finally, our study and its conclusions on the observed contribution of earlier detection starkly contrast with a recent county-based study that failed to find a relationship between screening and breast cancer mortality.10 This study was ecological in nature and focused on a single year of screening (2000) rather than assessing changes over time in screening and in mortality, as we do. 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 with less assumptions and biases.

Our results also directly address the longstanding controversy over the value of screening, especially among 40-49 year olds.3,25 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%) and slightly less than the corresponding contribution of 70-79 year olds (6.58%). The net contribution of earlier detection results from offsetting trends in the share of incident breast cancer by tumor size and age of diagnosis. Fifty to fifty-nine and 60-69 year olds captured a larger amount of the increasing contribution from the growing share of smaller sized tumors than 40-49 and 70-79 year olds. Yet they also captured a larger amount of the decreasing contribution from the shrinking share of larger sized tumors. Thus, the net result of these offsetting trends led to a larger contribution of earlier detection to the gain in life expectancy among 40-49 and 70-79 year olds than 50-59 and 60-69 years olds.

Our study more accurately measures the contribution of advancements 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% on the resulting gain in life expectancy. During the same time period (1975-2000), we calculate a 62% contribution from advancements in breast cancer treatment. Sun et al. (2010) concluded advancements in breast cancer treatment contributed 83% of the estimated gain in breast cancer survival time (1988-2000).10 Our calculation of the contribution of advancements 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.

Yet, 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, we base cohorts on year of breast cancer diagnosis, rather than on year of birth. Thus, our life table methods and the resulting estimates of life expectancy assume women experience over their entire life the fatality rates of their year of breast cancer diagnosis. This assumption may lead to a conservative estimate of the gain in life expectancy between 1975 and 2002 because age-specific fatality rates declined over this time period. Second, 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 mitigate the ascertainment bias in cause of death. 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.29 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 how diagnosis occurred. Finally, we focus on the broadest time period possible, 1975-2002, and do not quantify the contribution of earlier detection and advancements in breast cancer treatment after the introduction of a specific innovation (e.g., trastuzumab [Herceptin®]). The diffusion of novel chemotherapy agents, imaging modalities, and new clinical and surgical techniques occurs slowly over time rather than immediately after introduction.30,31

In conclusion, more widespread screening increased the share of small-sized tumors among newly diagnosed breast cancer patients. At the same time, incremental improvements in medical care have reduced the risk of death among breast cancer patients from breast cancer itself. As patients lived longer, they also benefited from advances in other diseases, such as cardiovascular disease. We apply existing demographic methodologies to disentangle the precise contribution of earlier detection and advancements in breast cancer treatment on the gain in life expectancy, accounting for concurrent advancements in the treatment of other diseases. 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.

**Acknowledgements**: We thank Jonathan Skinner, Harold Sox, and H. Gilbert Welch for helpful comments and suggestions.

**Funding Statement:** Dr. Soneji was supported by the National Center For Advancing Translational Sciences grant number KL2TR001088 and the American Lung Association. Dr. Beltrán-Sánchez was supported by the National Institute of Aging (R24HD047873 and P30AG017266).

**Competing Interests Statement**: Both authors report no potential competing interests.

**Contributorship Statement:** S. Soneji and H. Beltrán-Sánchez were involved in study design, data collection, statistical analysis, and preparation of the article.

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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 share 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 share (earlier detection), contribution from changes in case fatality rates from breast cancer (advancements in breast cancer treatment), and contribution from changes in case fatality rates from other causes (advancements 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 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 3. 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 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 | Percentage |
| 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 |