Title: Quantifying the Contribution of Earlier Detection and Advancements in Treatment on Gains in Life Expectancy for US Breast Cancer Patients, 1975 to 2002

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Word Count:

**ABSTRACT**

**Importance**.  Previous studies yield conflicting results on whether improvements in breast cancer mortality rates result from [1] more widespread mammography screening or [2] advancements in treatment.  By knowing the relative contribution of screening versus treatment on improvements in breast cancer mortality, we can more effectively focus cancer care.

**Objective**.  To assess how much of the gain in life expectancy over time among breast cancer patients resulted from shifts in the stage of diagnosis versus improvements in mortality rates from breast cancer and competing causes of death.

**Design, Setting, and Participants**. Retrospective cohort evaluation of 1.7 million patients aged 40-84 years diagnosed with breast, cervical, colorectal, and prostate cancer; 1973-2011; using the US Surveillance, Epidemiology, and End Results registries.

**Main Outcomes and Measures**.  The gain in life expectancy over time that resulted from shifts in the stage at diagnosis, improvements in mortality rates from cancer, and improvements in mortality rates from other causes of death.

**Results**:  Life expectancy for breast cancer patients increased by 13.4 years between 1973 and 2001: 30.6% from shifts to earlier stages at diagnosis, 48.5% from improvements in breast cancer mortality rates, and 20.1% from improvements in mortality rates of other diseases.

**Conclusions and Relevance**.  Life expectancy for breast cancer patients primarily increased because of improvements in treatment of cancer, rather than screening.

**INTRODUCTION**

US breast cancer mortality rates declined by 32% between 1975 and 2012: from 69.4 to 47.4 deaths per 100,000 person-years. The contribution of mammography screening to this decline has become the subject of intense public and scientific controversy.1–5 For example, medical researchers now question the previously held dogmatic belief that mammography screening saves lives by detecting cancer at earlier and more treatable stages.6 In 2002, the US Preventive Services Task Force (USPSTF) recommended routine mammography screening among women aged 40-49 years. 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 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 wide disagreement on the value of screening. For example, the efficacy of screening among women aged 39 to 49 years from 8 large randomized trials varied from 0% to 30% mortality reduction.7 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 an even wider range for the contribution of screening to reductions in breast cancer mortality rates: between 28% and 65%.1 The debate over the value of screening also implicitly involves the relative contributions of screening versus treatment. Sun et al. (2010) concluded earlier detection contributed to 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.8 Yet, this study may have overestimated the contribution of advancements in cancer treatment because it did not separate death from breast cancer and death from other competing causes of death (e.g., cardiovascular disease).

In this study, we address these research gaps and quantify the contribution of the three factors that could have led to reductions in mortality rates among breast cancer patients and the resulting gains in life expectancy: [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,9 by the change over time in the tumor sizes of newly diagnosed breast cancer patients. We measure advancements in breast cancer treatment and treatment of other diseases by the reduction over time 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 US breast cancer patients.10,11 We quantify the contributions to gains in life expectancy, rather than declines in breast cancer mortality rates, to account for changes in the age structure of the US female population over time. Finally, we consider the effect of overdiagnosis and lead-time bias on gains 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 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 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 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 incident cancer cases. We categorized tumor size into the following 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. For example, 556 women aged 65-69 years were diagnosed with <1cm breast cancer in 2001. Between 2001 and 2011, 22 of these women died of breast cancer and another 107 died of a competing cause of death. This entire cohort lived a total of 5099.5 person-years over the 10-year period. Thus, the incidence-based case fatality rate from breast cancer equaled 22/5099.5 and the incidence-based case fatality rate from competing causes of death equaled 107/5099.5. 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 cause of death). We also calculated the proportion of incident cancer cases by tumor size at diagnosis and year of diagnosis. For example, the proportion of women diagnosed with <1cm breast cancer in 2001 equaled 4,602 out of 19,029 newly diagnosed breast cancers (24.2%).

**2.2 Analytic Methods**. For our primary analysis, we assume an overdiagnosis rate of 10% for tumor sizes ≤3cm based on the results of the Malmö, Sweden randomized trial.12 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, which artificially lowers the case fatality rate and raises 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 by multiplying the observed case fatality rate by the inverse of the complement of the overdiagnosis level. For example, if 10% of the 556 women aged 65-69 years old diagnosed with <1cm breast cancer in 2001 were overdiagnosed, the observed case fatality rate from breast cancer (22/11,591) would become 22/[11,591 - (1-0.10)\*11,591].

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.13 We create separate life tables for each tumor size and for each year, which produces an annual tumor size-specific life expectancies. Overall life expectancy equals the weighted sum of tumor size-specific life expectancies, where the weights correspond to the annual share of each tumor size. The smaller the share for a given tumor size, the less weight it exerts on overall life expectancy. Gains in life expectancy among breast cancer patients over time depend on three factors: [1] shifts toward smaller sized tumors at diagnosis, [2] reductions in case fatality rates from breast cancer, and [3] reductions in case fatality rates from competing causes of death.

The shift toward smaller sized tumors at diagnosis occurs when incidence rates for smaller sized tumors increases more over time than the incidence rates of larger sized tumors. The growth of the share of smaller sized tumors implies an increase in their contribution to gains in overall life expectancy, while the shrinkage of the share of larger sized tumors implies a reduction in their contributions. Using an established demographic method, we calculated how much of the change in life expectancy over time was the result of changes in the aforementioned three factors.10,11,14 We schematically represent our approach in Figure 1 and fully describe it in the Supplementary Appendix.

For simplicity, 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 2, Panel B), and tumor size-specific case fatality rates from competing causes of death remain constant between times 1 and 2 (Figure 2, 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 2, 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 2, Panel D). In actuality, all three aforementioned factors change over time and contribute to gains in life expectancy. We quantify the individual contribution of each of these three constituent components. We also utilize the same demographic method to further disaggregate these three contributions by age group.

To assess the robustness of our findings to the overdiagnosis level, we vary the level from 0% to 31% (the level estimated by Bleyer and Welch [2012]15) among tumors ≤3 cm and recalculate the gain in life expectancy. We then quantify the contribution to these gains in life expectancy from changes in the distribution of tumor size over time, changes in case fatality rates from breast cancer, and changes in case fatality rates from competing causes of death. We also separately vary the overdiagnosis level from 0 to 90% for <1cm tumors and from 0 to 31% for 1-2cm and 2-3cm tumors and perform the analysis described above.

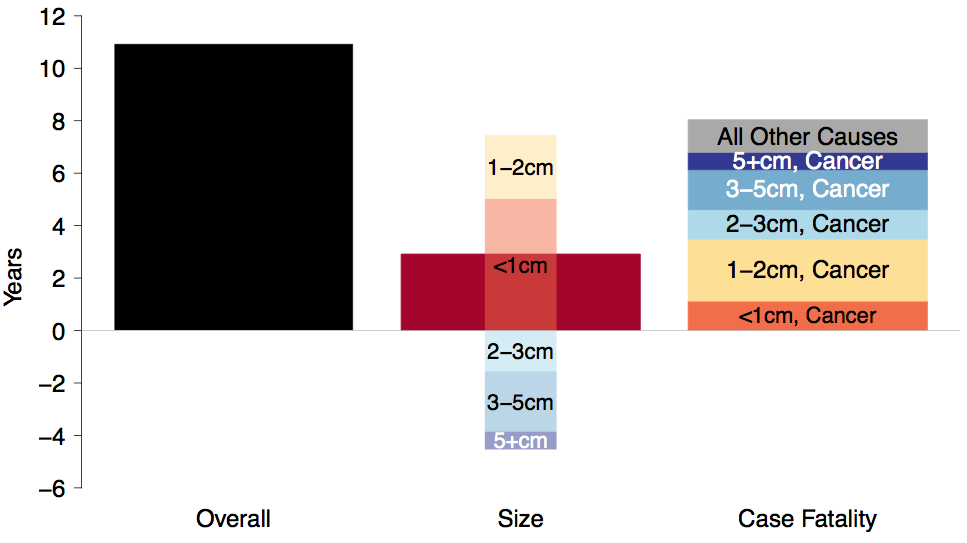
**3. RESULTS**

**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. The steepest gain occurred in the five-year period between 1984 and 1988. Likewise, the incidence rate of 1-2 cm breast cancer increased from 200 to 567 cases per 100,000; the steepest gain occurred between 1983 and 1987. In contrast to these smaller sized tumors, the incidence rate of 2-3cm breast cancers increased from 195 cases per 100,000 in 1975 to a peak level of 308 cases per 100,000 in 1985 and decreased modestly thereafter. The incidence rate of 3-5cm breast cancer increased from 204 cases per 100,000 in 1975 to its peak peak level of 277 cases per 100,000 in 1983 and decreased thereafter. Finally, the incidence rate of 5+cm breast cancer increased from 103 cases per 100,000 in 1975 to its peak level of 138 cases per 100,000 in 1983 and fluctuated between 98 to 114 cases per 100,000 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 from 25% to 34% for 1-2cm tumors between 1975 to 2002. 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 5+cm 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 2, Panel C). For example, the rate decreased from 101 to 59 deaths per 100,000 for 5+cm 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 and exhibited less variation among tumor sizes over time than the case fatality rates from breast cancer.

**3.2. Gains in Life Expectancy.** Overall, life expectancy increased 10.94 years between 1975 and 2002 for a 40-year old newly diagnosed breast cancer patient (Figure 3). First, the temporal shift towards smaller sized tumors contributed 2.92 years to the 10.94 year 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 overall 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 5+cm tumors. Third, reductions in case fatality rates from competing causes of death across all tumor sizes contributed the remaining 1.25 years to the overall 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, 2.43 years from 1-2cm tumors and -4.79 years from 2-3cm, 3-5cm, and 5+cm tumors (Table 1). Fifty to fifty-nine year olds contributed the most to the overall contribution of the growing share of <1cm tumors on this gain in life expectancy, followed by 60-69 and 70-79 year olds. Similarly, 70-79 year olds contributed the most to the overall contribution of the growing share of 1-2cm tumors on the gain in life expectancy followed by 60-69 and 50-59 year 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 overall gain in life expectancy.

**3.4. Overdiagnosis and Lead-Time Bias.** 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 31% (Figure 4). As the percentage of overdiagnosis among these tumors sizes increased, the overall gain in life expectancy decreased because case fatality rates (from both breast cancer and competing causes of death) increased. For example, as the overdiagnosis level among tumors ≤3cm increased from 10% to 20%, the gain in life expectancy decreased from 10.94 years to 10.31 years. At any overdiagnosis level, the reductions in case fatality rates from breast cancer contributed the largest proportion to the overall gain in life expectancy, followed by the temporal shift to smaller sized tumors and then by reductions in case fatality rates from competing causes of death. At a 20% overdiagnosis level, the contributions to the 10.31 year gain in life expectancy were: 6.78 years from reductions in case fatality rates from breast cancer (66%), 2.32 years from the temporal shift to smaller sized tumors (23%), and 1.23 years from reductions in case fatality rates from competing causes of death (12%). We also separately vary the overdiagnosis level for <1cm tumors and 1-3cm (1-2cm and 2-3cm) tumors in Appendix Figure X and reach nearly identical substantive conclusions on the relative contribution of the three constituent components to gains in life expectancy.

**4. Discussion**

Our methods provide a more accurate means to quantify the contribution of earlier detection, advancements in breast cancer treatment, and concurrent advancements in the treatment of other diseases on the gains life expectancy of breast cancer patients. We show that the majority, 63%, of 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, 25% 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 relative contribution of detection and treatment on improvements in breast cancer outcomes. For example, Sun et al. (2010) estimated earlier detection contributed to 20% of the 3.6-year gain in survival among breast cancer patients between 1988 and 2000, and attributed the remaining 80% to improvements in breast cancer treatment.8 We reach a similar conclusion on the contribution of earlier detection between 1988 and 2000 (24%), but estimate a smaller contribution from improvements in breast cancer treatment (64%) because we separately consider death from breast cancer and death from competing causes. 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 the CISNET range. CISNET 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 advancements in breast cancer treatment (62%) fell on the upper end of CISNET range.

Our results also directly address the longstanding controversy over the value of mammography screening, especially among 40-49 year olds.2,16 The value of screening is based on the balance of potential benefits of earlier detection and potential harms from overdiagnosis and overtreatment. We quantify the realized benefits based on the actual mortality experience of breast cancer patient. 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.17 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 gains in life expectancy was substantial, we found that the contribution from advancements in breast cancer treatment was even larger. Treatment-related advancements resulted from a combination of improvements in the delivery of existing treatments and development of novel treatments, both of which reduced case fatality rates. Additionally, breast cancer treatment has involved multiple modes of treatment for virtually the entire time period of our study.26 Thus,

Advancements included multiagent adjuvant chemotherapy, hormonal therapy, and breast-conserving surgery with radiotherapy.18 For example, the Food and Drug Administration approved tamoxifen for breast cancer chemoprevention in 1998.

Finally, although we can quantify the contribution of advancements in breast cancer treatment on gains in life expectancy, we cannot further disaggregate the individual contributions of breast cancer surgery, radiation therapy, chemotherapy, targeted therapy, and hormonal therapy.

Advancements in the prevention and treatment of competing causes of death, such as cardiovascular disease (CVD),19,20 also contributed to gains in life expectancy among breast cancer patients. After breast cancer itself, other cancers and CVD were the second and third leading causes of death of women diagnosed with breast cancer.21 For early stage breast cancers, which are also generally small sized tumors, the probability of death from other causes was considerably higher than the corresponding probability from breast cancer. Thus, improvements in competing causes of death for cancer patients are particularly important for gains 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 was among the highest across all cancer types.22,23 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.24 Additionally, breast cancer mortality patterns in the SEER registries are highly representative of national breast cancer mortality patterns.25 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 5 years and 15 years, by 2.5 year increments, and reach identical substantive conclusions on the relative contribution of advancements in cancer treatment, earlier detection, and advancements in the care of competing causes of death (Appendix Table X).

Future research may expand on our findings by considering the contribution of reductions in case fatality rates from breast cancer before and after the NIH consensus statement on breast conserving surgery (1990) or approval of trastuzumab (1988). Additionally, our methodology may be applied to other cancers. For example, the contribution of earlier detection to gains in life expectancy may be greater for colorectal cancer than for breast cancer.

In conclusion, earlier detection increased the annual share of smaller sized tumors among incident breast cancer cases while advancements in breast cancer treatment reduced case-fatality rates from breast cancer. Based on the observed mortality experience of women diagnosed with breast cancer between 1975 and 2002, we conclude life expectancy increased by 10.7 years over the time period. Furthermore, advancements in breast cancer treatment contributed most to this gain in life expectancy, followed by earlier detection and advancements in the treatment of competing causes of death. We reached an identical conclusion varying the level of overdiagnosis. Our results indicate that cancer treatment contributed twice as much as earlier detection on increasing average length of life of breast cancer patients. FINAL SENTENCE.

**Acknowledgements**: We thank X for helpful comments and suggestions.

**Funding Statement:** Dr. Soneji was supported by the National Center For Advancing Translational Sciences grant number KL2TR001088, ALA, R21. Dr. Beltrán-Sánchez was supported by X.

**Competing Interests Statement**: All 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 Title and Legend**

Figure 1.

Figure 2.

Figure 3.

Table 1.

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|  | 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, 5+cm | -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.