Title: Quantifying the Contribution of Earlier Detection and Advances 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: 3598

## ABSTRACT

Importance: 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.

Objective: To quantify the contributions of earlier detection and advances in breast cancer treatment, accounting for concurrent advances in the treatment of other diseases, to the gain in life expectancy among breast cancer patients since 1975.

Design: Longitudinal analyses of consecutive annual cohorts of women diagnosed with breast cancer between 1975 and 2002. Each cohort followed forward for 10 years and cause of death, if applicable, categorized as breast cancer or all other causes. The date of final follow-up was December 31, 2012.

Setting: United States, 1975 to 2012.

Participants: Newly diagnosed breast cancer patients with both malignant and non-malignant (e.g., ductal carcinoma in situ) behavior who resided in 1 of 9 population-based registries of the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) program (N = 422,141). Patients categorized by age, year, and tumor size at diagnosis determined by clinical and operative/pathological assessment (<1cm, 1-2cm, 2-3cm, 3-5cm, ≥5cm), and cause of death (breast cancer and all other causes).

Main Outcomes and Measures: The gain in life expectancy of newly diagnosed breast cancer patients between 1975 and 2002 and the contribution to this gain from: [1] earlier detection, [2] advances in breast cancer treatment, and [3] advances in the treatment of other diseases.

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).

Conclusions and Relevance: Life expectancy among breast cancer patients increased over time primarily because of advances in breast cancer treatment, although earlier detection also contributed substantially.

## 1. INTRODUCTION

Mammography screening has become the subject of intense 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 the survival of breast cancer patients. Quantifying these contributions requires 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 leading causes of death. A previous study only estimated the contribution of screening and attributed the remainder to the contribution of breast cancer treatment.[11] We hypothesized that this study overestimated the contribution of breast cancer treatment because it failed to consider 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 (e.g., cardiovascular disease [CVD]). Other studies only focus on the reduction in breast

cancer-specific mortality rates rather than reductions in overall mortality rates and, consequently, ignored the substantial improvements in the prevention and treatment of other diseases.[1,12] Thus, these studies could not quantify the contribution of screening to the increase in survival of breast cancer patients over time.

In this study, we address these research gaps and quantify the contribution of the three components that could have led to the gain in life expectancy among breast cancer patients. We extend and improve prior research in three ways: (a) our analytic approach mathematically accounts for the effects of these 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, thus avoiding biases inherent in survival time data (e.g., length-time bias). We measure earlier detection, which resulted from more widespread screening and advances in screening technology,[13] through 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] through reductions in tumor size-specific 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

105 changes in the age structure of the US female population. Finally, we vary the assumed
106 prevalence of overdiagnosis and re-quantify contributions to the gain in life expectancy.
107
108 **2. METHODS**
109 **2.1 Analytic Methods**. Our analytic approach consists of two main steps
110 (Figure 1). The first step estimates the contribution of earlier detection to gains in life
111 expectancy (component [1]). We began with all-cause incidence-based case fatality
112 rates (hereafter "fatality rates") by tumor size (Section 2.2). We adjusted these fatality
113 rates for overdiagnosis because overdiagnosed cases artificially lower observed fatality
114 rates (Section 2.3 and eAppendix B). The adjusted tumor size-specific fatality rates
115 served as input to demographic life tables that produced tumor size-specific life
116 expectancies in 1975 and 2002 (eAppendix C). We calculated overall life expectancy in
117 1975 and 2002 as the weighted average of tumor-size specific life expectancies, where
118 the weights corresponded to the annual distribution of incident breast cancers by tumor
119 size also adjusted for overdiagnosis (overdiagnosed cases artificially raise the observed
120 proportion of smaller sized tumors, eAppendix B). The gain in life expectancy was then
121 computed as the difference in overall life expectancy for cohorts formed in 1975 and
122 2002 and followed forward 10 years. Next, we utilized an established demographic
123 method (Kitagawa decomposition[16]) to estimate how much of this gain was due to
124 changes in the annual distribution of incident breast cancers by tumor size (i.e., more
125 small tumors over time) and improvements in adjusted all-cause fatality rates.
126 The second step estimates the contribution of advances in breast cancer
127 treatment (component [2]) and advances in the treatment of other diseases (component

[3]) on gains in life expectancy. We began with tumor size-specific fatality rates from 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 produced corresponding life-years in 1975 and 2002. We then utilized a related demographic method (Beltrán-Sánchez decomposition[17]) 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 from all other causes. The three components, all of which we derived from life tables, summed to the total gain in life expectancy. We did not report any sampling uncertainty in the gain in life expectancy or its three components because our calculations used registry data that fully captured the mortality experience of defined populations.[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. We analyzed 663,860 breast cancer cases diagnosed between 1975 and 2012 and included cases with both malignant and non-malignant (e.g., ductal carcinoma in situ) behavior. SEER classifies breast cancer as the cause of death based on the death certificate and identity of a primary tumor.[18] 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. A 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).[19,20] We calculated fatality rates for 422,141 breast cancer patients by 5-year age groups 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 all other causes). We also calculated the distribution of incident cancer cases by tumor size at diagnosis and year of diagnosis. We calculate fatality rates, rather than death certificate-based mortality rates, because the former enables us to separate the rates by tumor size at diagnosis.

**2.3 Adjustment for Overdiagnosis.** Overdiagnosis is the detection of asymptomatic breast cancers that are so slow-growing that they would never present symptomatically.[21] For our primary analysis, we assume an overdiagnosis prevalence of 10% for tumors ≤3cm based on the Malmö, Sweden trial.[22] We conducted two sensitivity analyses on the assumed prevalence of overdiagnosis: [1] varied it to 52% for tumors ≤3cm based on highest estimate from published literature[23–27] and [2] varied it to 97% for tumors <1cm (because 97% of SEER patients diagnosed with <1cm tumors survived at least 10 years and, thus, *could* have been overdiagnosed) and 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 person-years. In contrast, the incidence rates of 2-3cm, 3-5cm and ≥5cm increased from 1975, peaked around 1984, and decreased thereafter. The annual proportion of <1cm and 1-2cm tumors grew over time because their incidence rates increased more than those of larger sized tumors.

For patients diagnosed with <1cm, 1-2cm, 2-3cm, and 3-5cm tumors, fatality rates from other causes were higher than those from breast cancer (Figure 2, Panel C). Only for patients diagnosed with ≥5cm tumors were fatality rates from breast cancer larger than those from other causes. Overall, the decrease in fatality rates, both from breast cancer and other causes, led to an increase in tumor size-specific life expectancies; the growing proportion of smaller size tumors placed greater weight on these tumor-size specific life expectancies as drivers of overall life expectancy.

**3.2. Analysis of Gains in Life Expectancy.** 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%). Second, improvements in case fatality rates from breast cancer contributed 6.79 years to this gain (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 this gain (11%).

**3.3 Contribution of Earlier Detection to Overall Gain in Life Expectancy 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 2.92-year contribution of earlier detection: between 0.41 to 0.72 years of life (Table 1). In other words, earlier detection in these age groups each contributed to between 3.8% and 6.6% to the gain in life expectancy.

**3.4. Effect of Overdiagnosis.** In secondary analysis, we varied the assumed prevalence of overdiagnosis for tumors ≤3cm up to 52%, versus 10% in primary analysis (Figure 4). As the overdiagnosis prevalence increased, the absolute contribution from improvements in case fatality rates from breast cancer remained virtually identical while the contribution from earlier detection and gain in life expectancy both decreased. Thus, the proportionate contribution from improvements in case fatality rates from breast cancer increased while the proportionate contribution from earlier detection decreased. For example, at a 20% overdiagnosis prevalence, the gain in life expectancy equaled 10.31 years (compared to 10.94 years at a 10% overdiagnosis prevalence): 66% from reductions in case fatality rates from breast cancer, 22% 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 prevalence). We also independently varied the overdiagnosis prevalence 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 newly diagnosed breast cancer patients. 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%).

Based on our methods, which require fewer assumptions than previous work, we believe that our results provide a more accurate estimate of the contribution of earlier detection and advances in cancer treatment to the gain in life expectancy. For instance, CISNET estimates an age of death from all other causes and an age of death from breast cancer (among women with screen-detected breast cancer) in its simulation model.[28] CISNET then takes the smaller of these two ages of death as the realized age of death.[28] We prove mathematically and demonstrate empirically that the CISNET approach yields biased estimates of life expectancy and the gain in life expectancy (eAppendix I). Consider the gain in life expectancy for US women between 1975 and 2002. Under the CISNET approach, life expectancy at birth would have equaled 68.13 years in 1975 and 72.58 years in 2002. The gain in life expectancy at birth between

1975 and 2002 would have equaled 4.46 years. Yet, life expectancy at birth actually equaled 76.45 years in 1975 and 79.62 years in 2002, which corresponds to a gain of 3.17 years. Thus, the CISNET approach produces a bias of 1.50 years (4.46–3.17 years) for the gain in life expectancy. In contrast to the CISNET approach, we jointly model life expectancy from breast cancer and all other causes of death using a competing risk approach: overall survival equals the product of survival from breast cancer and survival from other causes of death. Our approach—by construction—yields an unbiased estimate of life expectancy and the gain in life expectancy.

Our study also reduces uncertainty over the contribution of earlier detection to the gain in life expectancy. 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 about rates of breast cancer progression from small non-invasive tumor to malignant cancer.[29] One CISNET model estimated the contribution of earlier detection to the decline in breast cancer mortality rates to be 28%, whereas another model estimated it to be 65% (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 used life tables based on the actual experience of breast cancer patients to estimate that earlier detection contributed 28% of the gain in life expectancy. Additionally, Sun et al. (2010) estimated that earlier detection contributed 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 not distinguishing between breast cancer and other diseases as causes of death. During the same time period (1988-2000), we used life tables to calculate that early detection contributed 24% of 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 susceptible 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.[3,30] 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 in 50-59 year olds (4.11%) and 60-69 year olds (3.75%) and slightly less than the corresponding contribution in 70-79 year olds (6.58%). Thus, our results suggest earlier detection among 40-49 year olds provided approximately equal benefit, measured in the contribution to the gain in life expectancy, as it did among 50-59 and 60-69 year olds. The similar contribution from earlier detection may be partly due to similar increases in mammography screening rates for these age groups across time.[31]

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: between 35 and 72% 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 estimate by Sun et al. 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,[32,33] made an increasing contribution to the gain in life expectancy among breast cancer patients from 1975 to 2002 partly 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.[34] 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 (as shown in Figure 2, Panel C).[34] 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 time. 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 breast cancer patients experience a set of fatality rates, which vary by age and time, based on their year of breast cancer diagnosis ('period life expectancy') rather than on their year of birth ('cohort life expectancy'). This assumption may produce a biased estimate of the gain in life expectancy. To evaluate this bias, we could calculate the difference in the gain in cohort life expectancies and the gain in period life expectancies. Yet, cohort life expectancy can only be computed retrospectively after all individuals in the cohort have died, which is not the case, for example, for patients diagnosed in 2002. To overcome this inherent constraint, we calculate period and cohort temporary life expectancy, which equals the total number of person-years lived between two ages in a life table based on a set of period and cohort fatality rates, respectively. Based on these temporary life expectancies, we estimated a small and conservative bias of 0.48 years in the gain in life expectancy when using period-based fatality rates rather than cohort-based fatality rates (eAppendix J). Thus, our use of period-based fatality rates largely captures the lived experience of breast cancer patients.

Second, we cannot quantify the contribution of individual types of treatment because patients typically received multiple modalities. Third, we cannot quantify the contribution of specific factors that produced the observed effectiveness of detection (e.g., improved standards in the interpretation of mammograms) because SEER does not capture screening information or the circumstances leading to diagnosis. Fourth, we do not quantify the contribution of earlier detection and advances in breast cancer treatment after the introduction of a specific innovation. The effect of specific

334 innovations is difficult to track because the diffusion of novel chemotherapy agents,
335 imaging modalities, and new clinical and surgical techniques occurs slowly over time
336 rather than immediately after introduction.[35,36] Finally, we required that breast cancer
337 death must have occurred within 10 years of diagnosis when calculating case fatality
338 rates to partially mitigate lead time bias. We vary the time interval between 8 years and
339 12 years and reach identical substantive conclusions (eAppendix K).
340 In conclusion, several factors contributed to the gain in life expectancy for breast
341 cancer patients. More widespread screening increased the proportion of small-sized
342 tumors among newly diagnosed breast cancer patients. At the same time, incremental
343 improvements in medical care reduced the risk of death among breast cancer patients
344 from breast cancer itself. As patients lived longer, they also benefited from advances in
345 treating other diseases, such as CVD, from which they otherwise have died. We apply
346 existing demographic methods to disentangle the precise contribution of earlier
347 detection and advances in breast cancer treatment on the gain in life expectancy,
348 accounting for concurrent advances in the treatment of other diseases. The value of
349 screening is based on the balance of potential benefits of earlier detection and potential
350 harms from overdiagnosis and overtreatment. Our study assessed the benefit of early
351 detection on its contribution to the gain in life expectancy. When it becomes possible to
352 measure the harms as losses in life expectancy, it will be possible to directly measure
353 the balance of benefits and harms. This common approach may clarify the controversy
354 about whether mammography confers net benefit.

**Additional Contributions**: 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, the American Lung Association, and the National Cancer Institute grant number R21CA197912. Dr. Beltrán-Sánchez was supported by the National Institute of Aging (R24HD047873 and P30AG017266).

**Role of the Funder/Sponsor**: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. □

**Conflict of Interest Disclosures**: None reported.

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

## References


1. Berry DA, Cronin KA, Plevritis SK, et al. Effect of Screening and Adjuvant Therapy on Mortality from Breast Cancer. *N Engl J Med*. 2005;353(17):1784-1792. doi:10.1056/NEJMoa050518.

2. Nelson HD, Tyne K, Naik A, Bougatsos C, Chan BK, Humphrey L. Screening for Breast Cancer: An Update for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2009;151(10):727-737. doi:10.7326/0003-4819-151-10-200911170-00009.

3. Kopans DB. The 2009 U.S. Preventive Services Task Force Guidelines Ignore Important Scientific Evidence and Should Be Revised or Withdrawn. *Radiology*. 2010;256(1):15-20. doi:10.1148/radiol.10100057.

4. Petitti DB, Calonge N, LeFevre ML, Melnyk BM, Wilt TJ, Schwartz JS. Breast Cancer Screening: From Science to Recommendation. *Radiology*. 2010;256(1):8-14. doi:10.1148/radiol.10100559.

5. Gotzsche PC MD, Heath I, Visco F. *Mammography Screening: Truth, Lies and Controversy*. 1 edition. London ; New York: Radcliffe Medical PR; 2012.

6. Berry D. Breast cancer screening: Controversy of impact. *Breast*. 2013;22(0 2):S73-S76. doi:10.1016/j.breast.2013.07.013.

7. Miller AB, Wall C, Baines CJ, Sun P, To T, Narod SA. Twenty five year follow-up for breast cancer incidence and mortality of the Canadian National Breast Screening Study: randomised screening trial. *BMJ*. 2014;348:g366. doi:10.1136/bmj.g366.

8. Harding C, Pompei F, Burmistrov D, Welch H, Abebe R, Wilson R. Breast cancer screening, incidence, and mortality across US counties. *JAMA Intern Med*. 2015;175(9):1483-1489. doi:10.1001/jamainternmed.2015.3043.

9. Myers ER, Moorman P, Gierisch JM, et al. Benefits and harms of breast cancer screening: A systematic review. *JAMA*. 2015;314(15):1615-1634. doi:10.1001/jama.2015.13183.

10. Myers ER, Moorman P, Gierisch JM, et al. Benefits and harms of breast cancer screening: A systematic review. *JAMA*. 2015;314(15):1615-1634. doi:10.1001/jama.2015.13183.

11. Sun E, Jena AB, Lakdawalla D, Reyes C, Philipson TJ, Goldman D. The Contributions of Improved Therapy and Earlier Detection to Cancer Survival Gains, 1988-2000. *Forum Health Econ Policy*. 2010;13(2).

12. Park J-H, Anderson WF, Gail MH. Improvements in US Breast Cancer Survival and Proportion Explained by Tumor Size and Estrogen-Receptor Status. *J Clin Oncol*. July 2015:JCO.2014.59.9191. doi:10.1200/JCO.2014.59.9191.

13. Helvie MA. Digital Mammography Imaging: Breast Tomosynthesis and Advanced Applications. *Radiol Clin North Am*. 2010;48(5):917-929. doi:10.1016/j.rcl.2010.06.009.

14. Consensus statement: treatment of early-stage breast cancer. National Institutes of Health Consensus Development Panel. *J Natl Cancer Inst Monogr*. 1992;(11):1-5.

15. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for Prevention of Breast Cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst*. 1998;90(18):1371-1388. doi:10.1093/jnci/90.18.1371.

16. Kitagawa EM. Components of a Difference Between Two Rates*. *J Am Stat Assoc*. 1955;50(272):1168-1194. doi:10.1080/01621459.1955.10501299.

17. Beltrán-Sánchez H, Preston SH, Canudas-Romo V. An integrated approach to cause-of-death analysis: cause-deleted life tables and decompositions of life expectancy. *Demogr Res*. 2008;19:1323-1350. doi:10.4054/DemRes.2008.19.35.

18. Lund JL, Harlan LC, Yabroff KR, Warren JL. Should cause of death from the death certificate be used to examine cancer-specific survival? A study of patients with distant stage disease. *Cancer Invest*. 2010;28(7):758-764. doi:10.3109/07357901003630959.

19. Chu KC, Miller BA, Feuer EJ, Hankey BF. A method for partitioning cancer mortality trends by factors associated with diagnosis: an application to female breast cancer. *J Clin Epidemiol*. 1994;47(12):1451-1461.

20. Chu KC, Tarone RE, Freeman HP. Trends in prostate cancer mortality among black men and white men in the United States. *Cancer*. 2003;97(6):1507-1516. doi:10.1002/cncr.11212.

21. Marcus PM, Prorok PC, Miller AB, DeVoto EJ, Kramer BS. Conceptualizing Overdiagnosis in Cancer Screening. *J Natl Cancer Inst*. 2015;107(4):djv014. doi:10.1093/jnci/djv014.

22. Zackrisson S, Andersson I, Janzon L, Manjer J, Garne JP. Rate of over-diagnosis of breast cancer 15 years after end of Malmö mammographic screening trial: follow-up study. *BMJ*. 2006;332(7543):689-692. doi:10.1136/bmj.38764.572569.7C.

23. Yen M-F, Tabár L, Vitak B, Smith RA, Chen H-H, Duffy SW. Quantifying the potential problem of overdiagnosis of ductal carcinoma in situ in breast cancer screening. *Eur J Cancer Oxf Engl 1990*. 2003;39(12):1746-1754.

24. Jørgensen KJ, Gøtzsche PC. Overdiagnosis in publicly organised mammography screening programmes: systematic review of incidence trends. *BMJ*. 2009;339:b2587.

25. Welch HG, Black WC. Overdiagnosis in Cancer. *J Natl Cancer Inst*. 2010;102(9):605-613. doi:10.1093/jnci/djq099.

26. Kalager M, Zelen M, Langmark F, Adami H-O. Effect of screening mammography on breast-cancer mortality in Norway. *N Engl J Med*. 2010;363(13):1203-1210. doi:10.1056/NEJMoa1000727.

27. Etzioni R, Xia J, Hubbard R, Weiss NS, Gulati R. A Reality Check for Overdiagnosis Estimates Associated With Breast Cancer Screening. *J Natl Cancer Inst*. 2014;106(12):dju315. doi:10.1093/jnci/dju315.

28. Cancer Intervention and Surveillance Modeling Network (CISNET) Collaborators. *Breast Cancer Model Profiles*.; 2015. http://cisnet.cancer.gov/breast/profiles.html.

29. Stout NK, Knudsen AB, Kong CY (Joey), McMahon PM, Gazelle GS. Calibration Methods Used in Cancer Simulation Models and Suggested Reporting Guidelines. *PharmacoEconomics*. 2009;27(7):533-545. doi:10.2165/11314830-000000000-00000.

30. Gøtzsche PC, Olsen O. Is screening for breast cancer with mammography justifiable? *Lancet*. 2000;355(9198):129-134. doi:10.1016/S0140-6736(99)06065-1.

31. Breen N, A. Cronin K, Meissner HI, et al. Reported drop in mammography: Is this cause for concern? *Cancer*. 2007;109(12):2405-2409. doi:10.1002/cncr.22723.

32. Hunink MM, Goldman L, Tosteson AA, et al. The recent decline in mortality from coronary heart disease, 1980-1990: The effect of secular trends in risk factors and treatment. *JAMA*. 1997;277(7):535-542. doi:10.1001/jama.1997.03540310033031.

33. Weisfeldt ML, Zieman SJ. Advances In The Prevention And Treatment Of Cardiovascular Disease. *Health Aff (Millwood)*. 2007;26(1):25-37. doi:10.1377/hlthaff.26.1.25.

34. Schairer C, Mink PJ, Carroll L, Devesa SS. Probabilities of Death From Breast Cancer and Other Causes Among Female Breast Cancer Patients. *J Natl Cancer Inst*. 2004;96(17):1311-1321. doi:10.1093/jnci/djh253.

35. Cutler DM, McClellan M. Is Technological Change In Medicine Worth It? *Health Aff (Millwood)*. 2001;20(5):11-29. doi:10.1377/hlthaff.20.5.11.

36. Ponce NA, Ko M, Liang S-Y, et al. Early Diffusion Of Gene Expression Profiling In Breast Cancer Patients Associated With Areas Of High Income Inequality. *Health Aff (Millwood)*. 2015;34(4):609-615. doi:10.1377/hlthaff.2014.1013.

## 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: [1] contribution from change in tumor-size distribution (earlier detection), [2] contribution from changes in case fatality rates from breast cancer (advances in breast cancer treatment), and [3] 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

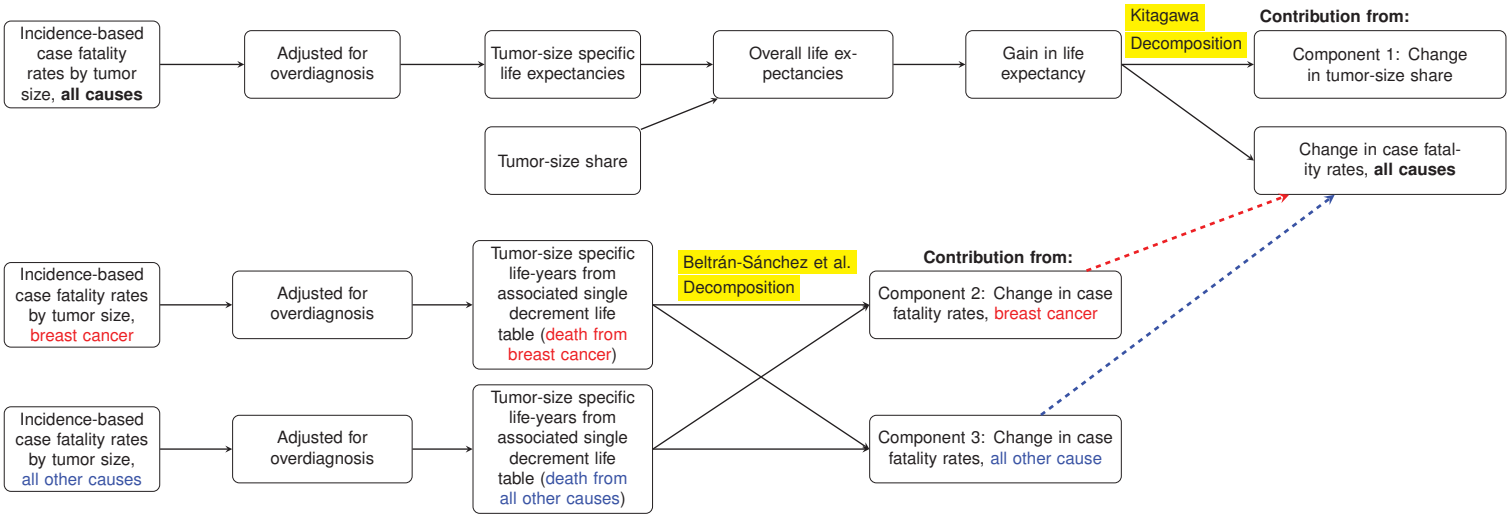
Overall gain in life expectancy and the contribution of the temporal shift in tumor size (by tumor size and net contribution) and reductions in case fatality rates from breast cancer and competing causes of death.

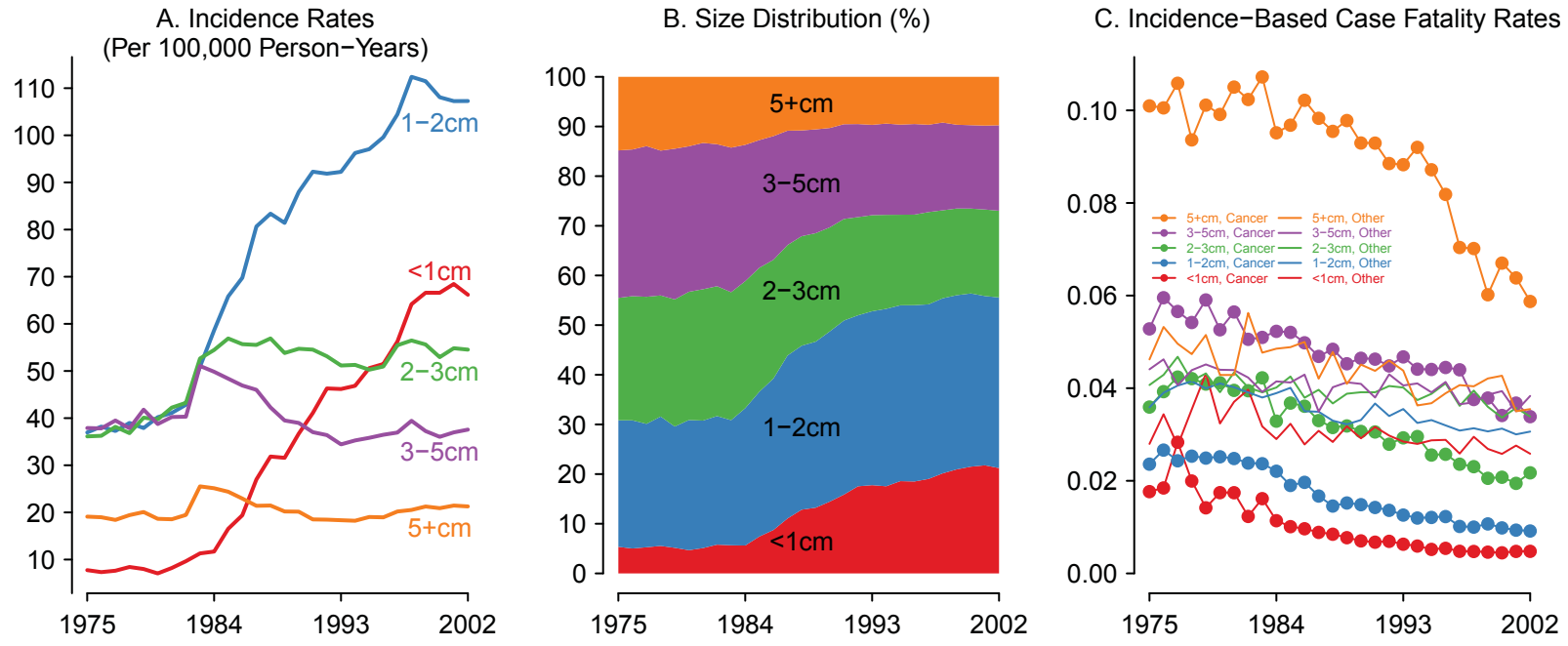
Figure 4. Contributions to Gain in Life Expectancy, Varying Assumed Prevalence of Overdiagnosis

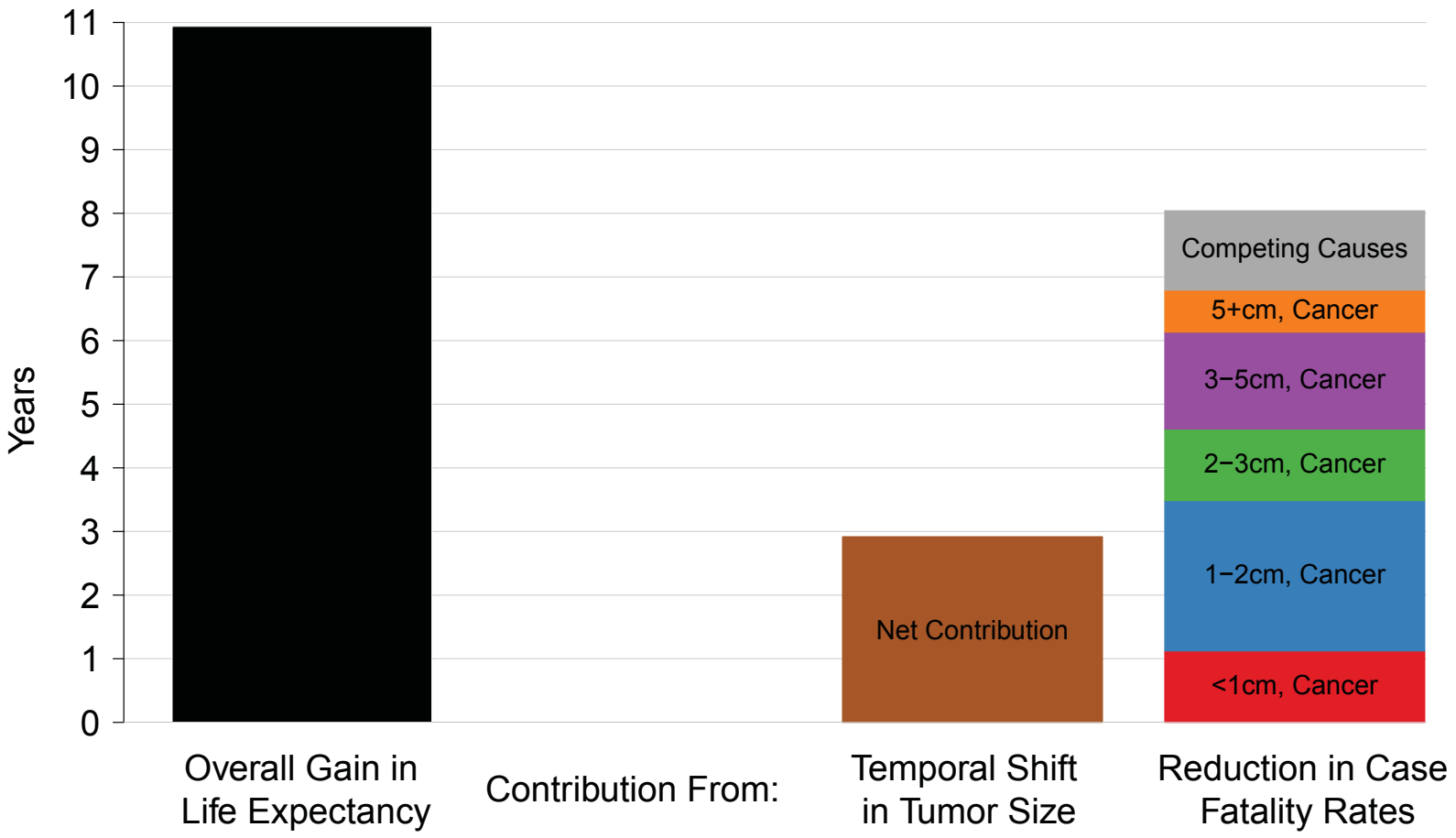
Overall gain in life expectancy and its constituent components (temporal shift in tumor size, reductions in case fatality rates from breast cancer, and reductions in case fatality rates from competing causes of death) varying the assumed prevalence of overdiagnosis for tumors ≤3cm from 0% to 52%.

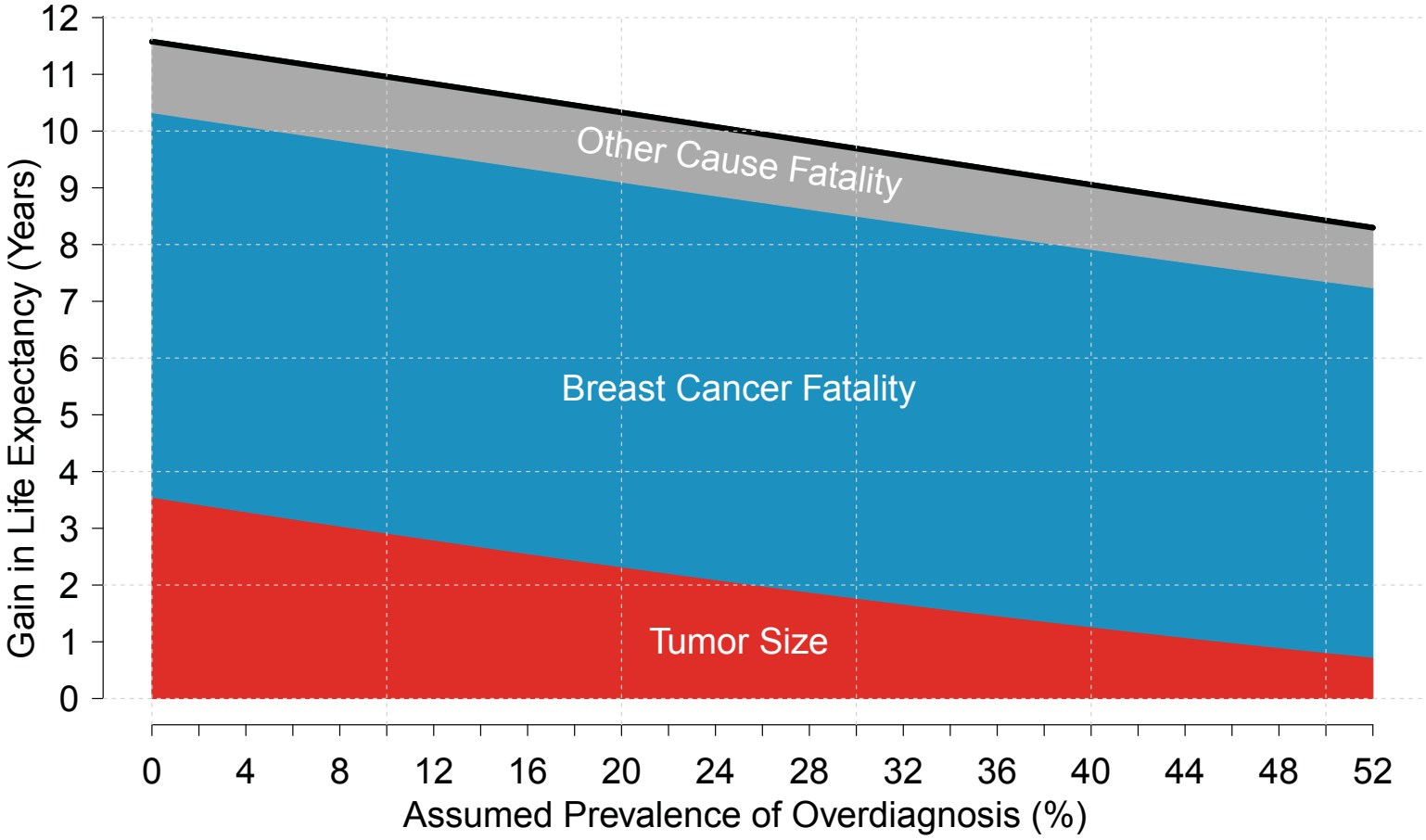
Table 1. Contribution of Earlier Detection on Gain in Life Expectancy

| | Contribution to Gain in Life Expectancy | |
|---|---|---|
| Age Group (Years Old) | 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 |


Incidence-based case fatality rates by tumor size, **all causes**
Adjusted for overdiagnosis
Tumor-size specific life expectancies
Overall life expectancies
Gain in life expectancy
Kitagawa Decomposition
Contribution from:
Component 1: Change in tumor-size share
Tumor-size share
Change in case fatality rates, **all causes**
Incidence-based case fatality rates by tumor size, breast cancer
Adjusted for overdiagnosis
Tumor-size specific life-years from associated single decrement life table (death from breast cancer)
Beltrán-Sánchez et al. Decomposition
Contribution from:
Component 2: Change in case fatality rates, breast cancer
Incidence-based case fatality rates by tumor size, all other causes
Adjusted for overdiagnosis
Tumor-size specific life-years from associated single decrement life table (death from all other causes)
Component 3: Change in case fatality rates, all other cause


A. Incidence Rates
(Per 100,000 Person−Years)
110
100
90
80
70
60
50
40
30
20
10
1−2cm
<1cm
2−3cm
3−5cm
5+cm
1975
1984
1993
2002
B. Size Distribution (%)
100
90
80
70
60
50
40
30
20
10
0
5+cm
3−5cm
2−3cm
1−2cm
<1cm
1975
1984
1993
2002
C. Incidence−Based Case Fatality Rates
0.10
0.08
0.06
0.04
0.02
0.00
5+cm, Cancer
5+cm, Other
3−5cm, Cancer
3−5cm, Other
2−3cm, Cancer
2−3cm, Other
1−2cm, Cancer
1−2cm, Other
<1cm, Cancer
<1cm, Other
1975
1984
1993
2002


11
10
9
8
7
6
5
4
3
2
1
0
Years
Competing Causes
5+cm, Cancer
3−5cm, Cancer
2−3cm, Cancer
1−2cm, Cancer
<1cm, Cancer
Net Contribution
Overall Gain in Life Expectancy
Contribution From:
Temporal Shift in Tumor Size
Reduction in Case Fatality Rates


Gain in Life Expectancy (Years)
12
11
10
9
8
7
6
5
4
3
2
1
0
Other Cause Fatality
Breast Cancer Fatality
Tumor Size
0
4
8
12
16
20
24
28
32
36
40
44
48
52
Assumed Prevalence of Overdiagnosis (%)

# eAppendix for "Quantifying the Contribution of Earlier Detection and Advancements in Treatment on Gains in Life Expectancy for US Breast Cancer Patients Since 1975"

Samir Soneji* Hiram Beltrán-Sánchez†

*Dartmouth Institute for Health Policy & Clinical Practice and Norris Cotton Cancer Center, Geisel School of Medicine at Dartmouth. Email: samir.soneji@dartmouth.edu

†Department of Community Health Sciences and California Center for Population Research, University of California, Los Angeles. Email: beltrans@ucla.edu

# A Computation of Incidence-Based Case Fatality Rates

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 <1 cm 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. Also, the proportion of women diagnosed with <1cm breast cancer in 2001 equaled 4,602 out of 19,029 newly diagnosed breast cancers (24.2%).

# B Adjustment for Overdiagnosis

Suppose 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 (22/5099.5) would become 22/[5099.5 - 0.10*5099.5]. Formally, let $\mathcal{A}$ be a set of starting ages for age intervals analyzed (e.g., 40, 45, ..., $\omega = 100$ years), $\mathcal{T}$ be a set of years (e.g., 1975, ...2002), and $\mathcal{S}$ be a set of tumor sizes at diagnosis (e.g., <1cm, 1-2cm, 2-3cm, 3-5cm, and ≥5cm). Let $\alpha_s$ represent the assumed level of overdiagnosis for tumor size $s \in \mathcal{S}$. Let $m_{a,t,s}$ represent the observed case fatality rate for age group $a \in \mathcal{A}$, year $t \in \mathcal{T}$, and tumor size $s \in \mathcal{S}$. Then, the case fatality rate adjusted for overdiagnosis equals:

$$m^*_{a,t,s} = \frac{1}{1-\alpha_s} \times m_{a,t,s}.$$

In 2001, the number of women diagnosed with breast cancer equaled: 4602 with <1cm tumors, 7208 with 1-2cm tumors, 3684 with 2-3cm tumors, and 1300 with ≥5cm tumors. These counts translate to the following distribution: 24%, 38% 19%, 12%, and 7%, respectively. Suppose 10% of <1cm breast cancers were overdiagnosed (460 of 4602 women). We subtract these 460 women from the count of breast cancers in 2001 and recalculate the distribution: 22% for <1cm, 39% for 1-2cm, 20% for 2-3cm, 12% for 3-5cm, and 7% for ≥5cm. Let $\alpha_s$ represent the assumed level of overdiagnosis for tumor size $s \in \mathcal{S}$. Let $n_{t,s}$ represent the observed count of breast cancer cases in year $t$ and for tumor size $s$. The observed distribution of incident breast cancer cases, $\pi_{t,s}$, equals

$\frac{n_{t,s}}{\sum_{s\in\mathcal{S}} n_{t,s}}$. The distribution of incident breast cancer cases adjusted for overdiagnosis equals:

$$\pi^*_{t,s} = \frac{(1-\alpha_s)\times n_{t,s}}{\sum_{s\in\mathcal{S}}(1-\alpha_s)\times n_{t,s}}.$$

# C Computation of Tumor Size-Specific Life Expectancy

The life expectancy of a breast cancer patient newly diagnosed at age $a^* \in \mathcal{A}$, at time $t$, and with tumor size $s$ equals:

$$e_s(a^*, t) = \int_{a^*}^{\omega} e^{\left(-\int_{a*}^{a} \mu_s(y,t)\,dy\right)} da \tag{1}$$

where $\mu_s(a,t)$ represent the hazard of mortality and $\omega$ is the starting age of the final and open-ended age interval.

## C.1 Calculation of Life Expectancy from a Period Life Table

Although the theoretical definition of life expectancy is given within the continuous-time framework, as shown in Equation (1), the data are typically recorded in a discrete form. A period life table is a common source of discrete data, and is often analyzed in order to approximate the continuous-time mortality process. Kitigawa and Beltrán-Sánchez decomposition methods both require the use of a period life table. A main purpose of a period life table is to calculate the life expectancy of a hypothetical cohort that experiences the currently observed cross-sectional mortality rates.

Let $\mathcal{A}$ be a set of the starting ages for the age intervals of a period life table. We use $\omega$ to denote the starting age of the oldest age interval. Let $n_x$ represent the width (years) of an age interval starting at age $x \in \mathcal{A}$. Typically, the width of age intervals is the same for all but the youngest and oldest age intervals $[\omega, \infty)$, e.g., $n_x = 5$ for all $x \in \mathcal{A} \setminus \{0, 1, \omega\}$ and $n_\omega = \infty$. When $n_x > 1$, a period life table is said to be abridged.

A period life table is created by first observing the mid-interval population, denoted by ${}_{n_x}P_x$, and the total number of deaths, denoted by ${}_{n_x}D_x$, for each interval $[x, x+n_x)$. Then, the observed mortality rate for each interval, denoted by ${}_{n_x}M_x$, is calculated as ${}_{n_x}D_x/{}_{n_x}P_x$. Keeping with the standard demographic notation, we use prescripts to indicate the width of the interval under consideration. A period life table relies on the following stationarity assumptions of the population (Chiang, 1983; Preston et al., 2000):

1. The age-specific hazard rate is constant over time, i.e., $\mu(x,t) = \mu(x)$ for all $t \in \mathcal{T}$;
2. The birth rate is constant over time; and
3. The net migration rates are zero at all ages.

The assumptions imply that the survival function is also constant over time, i.e., $l(x, y) = l(x)$, and that the crude death rate, i.e., $\sum_{x \in \mathcal{A}} {}_{n_x}D_x / \sum_{x \in \mathcal{A}} {}_{n_x}P_x$, equals the crude birth rate, i.e., $B / \sum_{x \in \mathcal{A}} {}_{n_x}P_x$, where $B$ is the total number of births to members of the population in the period. Therefore, the total size of the hypothetical cohort is assumed to remain constant over time. Another important consequence of stationarity assumptions is that the age distribution of the hypothetical cohort in any given interval, $[x, x + n_x)$, is constant over time and is proportional to the survival function. Formally, for all $s \in [x, x + n_x)$, the age distribution is defined by the following density function,

$$\frac{l(s)}{\int_x^{x+n_x} l(t)\, dt}, \tag{2}$$

A common departure from stationarity occurs in many developing countries today, where annual births have been growing relative to deaths. A violation of the stationarity assumptions is also possible in developed countries where the death rates are declining due to the advance of medical technologies.

Since ${}_{n_x}P_x$ and ${}_{n_x}D_x$ are directly obtained from the Census data and vital statistics, they are typically large and represent the total deaths and population of the country. Thus, in the literature, the sampling variability about the mortality rate of the hypothetical cohort, denoted by ${}_{n_x}m_x$, is considered to be small and hence typically ignored. That is, ${}_{n_x}M_x$ is assumed to equal ${}_{n_x}m_x$, which is given by,

$$ {}_{n_x}m_x \quad = \quad \frac{\int_x^{x+n_x} l(t)\mu(t)\, dt}{\int_x^{x+n_x} l(t)\, dt}, \tag{3}$$

for all $x \in \mathcal{A}$.

Furthermore, it can be shown that the conditional probability of death within an interval $[x, x + n_x)$ given that an individual of the hypothetical cohort survived up to age $x$, which is denoted by ${}_{n_x}q_x$, is equal to $n_x \, {}_{n_x}m_x / [1 + (n_x - {}_{n_x}a_x) \, {}_{n_x}m_x]$, where ${}_{n_x}a_x$ represents the average person-years lived in a given interval $[x, x + n)$ among those who are alive at age $x$ but die within the interval. The values of ${}_{n_x}a_x$ are obtained from complete life tables and used in subsequent calculations as a known quantity (Preston et al., 2000).

Within this framework, the total number of person-years lived in an interval, $[x, x + n_x)$, is given by,

$$ {}_{n_x}L_x \quad = \quad n_x \, l_{x+n_x} \, + \, l_x \, {}_{n_x}q_x \, {}_{n_x}a_x, \tag{4}$$

where the members of the $l_{x+n_x}$ proportion who survive the entire interval each contribute $n_x$ years, and the members of the $l_x \; {}_{n_x}q_x$ proportion who die in the interval contribute ${}_{n_x}a_x$ years, on average. Finally, life expectancy at age $x$ is equal to the total number of person-years for subsequent age intervals,

$$e_x \;\; = \;\; \frac{1}{l_x} \sum_{i \in \mathcal{A}_x} {}_{n_i}L_i, \tag{5}$$

where $\mathcal{A}_x = \{i \in \mathcal{A} : \; x \leq i\}$. Under stationarity assumptions for the unbounded last age interval $[\omega, \infty)$, life expectancy at age $\omega$ is equal to the inverse of the death rate, i.e., $e_\omega = {}_\infty m_\omega^{-1}$. The equality follows from the fact that all those alive at age $\omega$ must die in the interval, i.e., ${}_\infty q_\omega = 1$.

We now show that under stationarity assumptions discussed above, $e_x$, which is the life expectancy calculated from a period life table in Equation (5), equals $e(x)$, which is the theoretical definition of life expectancy given in Equation (1). Although in common demographic notation, $l(x)$ is used in continuous notation and $l_x$ in discrete, both refer to the proportion alive at exact age $x$ and hence are numerically identical. Given the hazard function, $\mu(x)$, the conditional probability of death for an age interval, $[x, x + n_x)$, is equal to the number of deaths in an age interval divided by the proportion alive at the beginning of the age interval,

$${}_{n_x}q_x \;\; = \;\; \frac{\int_x^{x+n_x} l(t)\, \mu(t)\, dt}{l(x)}. \tag{6}$$

Next, the average number of years lived in an interval among those who die in the interval is equal to the total number of person-years lived among those who will die divided by the proportion who will die in the interval,

$${}_{n_x}a_x \;\; = \;\; \frac{\int_x^{x+n_x} l(t)\, \mu(t)\, (t - x)\, dt}{\int_x^{x+n_x} l(t)\, \mu(t)\, dt}. \tag{7}$$

Substituting Equations (6) and (7) into Equation (4) and integrating it by parts yield,

$${}_{n_x}L_x \;\; = \;\; \int_x^{x+n_x} l(t)\, dt. \tag{8}$$

Therefore, it follows that $e_x$ equals $e(x)$.

Table 1 shows the 1975 U.S. female abridged period life table. The radix, $l_0$, is set at 1 so that $l_x$ represents the survival probability. From age 0 to $\omega$, the cohort will live $\sum_{i=0}^{\omega} {}_n L_i = 76.45$ person-years. Hence, a 0 year-old member of the hypothetical cohort will live, on average, 76.45 years given she experiences these prevailing period age-specific conditional probabilities of death. For the last age group, ${}_\infty a_{100} = e_{100}$ because everyone who is alive at age $\omega = 100$ dies within the last interval.

| Age $x$ | $n_x$ | ${}_nm_x$ | ${}_nq_x$ | ${}_na_x$ | $l_x$ | ${}_nd_x$ | ${}_nL_x$ | $T_x$ | $e_x$ |
|---|---|---|---|---|---|---|---|---|---|
| 0 | 1 | 0.014 | 0.014 | 0.090 | 1.000 | 0.014 | 0.987 | 76.453 | 76.450 |
| 1 | 4 | 0.001 | 0.003 | 1.630 | 0.986 | 0.003 | 3.938 | 75.466 | 76.540 |
| 5 | 5 | 0.000 | 0.001 | 2.300 | 0.983 | 0.001 | 4.913 | 71.528 | 72.730 |
| 10 | 5 | 0.000 | 0.001 | 2.680 | 0.982 | 0.001 | 4.907 | 66.615 | 67.830 |
| 15 | 5 | 0.001 | 0.003 | 2.710 | 0.981 | 0.003 | 4.898 | 61.708 | 62.920 |
| 20 | 5 | 0.001 | 0.003 | 2.530 | 0.978 | 0.003 | 4.883 | 56.810 | 58.080 |
| 25 | 5 | 0.001 | 0.004 | 2.580 | 0.975 | 0.004 | 4.866 | 51.927 | 53.260 |
| 30 | 5 | 0.001 | 0.005 | 2.600 | 0.971 | 0.005 | 4.846 | 47.061 | 48.450 |
| 35 | 5 | 0.001 | 0.007 | 2.680 | 0.967 | 0.007 | 4.817 | 42.215 | 43.670 |
| 40 | 5 | 0.002 | 0.012 | 2.660 | 0.960 | 0.011 | 4.772 | 37.398 | 38.970 |
| 45 | 5 | 0.004 | 0.018 | 2.670 | 0.948 | 0.017 | 4.701 | 32.627 | 34.410 |
| 50 | 5 | 0.005 | 0.027 | 2.640 | 0.931 | 0.025 | 4.597 | 27.925 | 29.990 |
| 55 | 5 | 0.008 | 0.040 | 2.650 | 0.906 | 0.036 | 4.446 | 23.328 | 25.740 |
| 60 | 5 | 0.012 | 0.058 | 2.610 | 0.870 | 0.051 | 4.229 | 18.882 | 21.700 |
| 65 | 5 | 0.017 | 0.083 | 2.650 | 0.819 | 0.068 | 3.936 | 14.653 | 17.880 |
| 70 | 5 | 0.029 | 0.138 | 2.640 | 0.751 | 0.103 | 3.511 | 10.717 | 14.270 |
| 75 | 5 | 0.046 | 0.207 | 2.600 | 0.648 | 0.134 | 2.916 | 7.206 | 11.130 |
| 80 | 5 | 0.077 | 0.323 | 2.550 | 0.514 | 0.166 | 2.162 | 4.290 | 8.350 |
| 85 | 5 | 0.125 | 0.473 | 2.430 | 0.348 | 0.165 | 1.316 | 2.128 | 6.120 |
| 90 | 5 | 0.196 | 0.638 | 2.270 | 0.183 | 0.117 | 0.597 | 0.812 | 4.430 |
| 95 | 5 | 0.287 | 0.780 | 2.070 | 0.066 | 0.052 | 0.180 | 0.215 | 3.250 |
| $\geq 100$ | $\infty$ | 0.403 | 1.000 | 2.482 | 0.016 | 0.015 | 0.035 | 0.035 | 2.482 |

Supplemental Table 1: The 1975 U.S. Female Period Life Table and Life Expectancy. The period life table is created from the conditional probability of death, ${}_nq_x$, and the average person-years lived in the age interval by those dying in the interval, ${}_na_x$. $l_x$ is the proportion of survivors at age $x$, whereas $L_x$ represents the total number of person-years lived within the age interval $[x, x + n_x)$ for those who were alive at age $x$. The last age interval is $[100, \infty)$. The final column gives the life expectancy $e_x$ at each age.

## D Schematic Representation of the Methodology

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 remained constant between times 1 and 2 (Supplemental Figure 1, Panel A), tumor size-specific case fatality rates from breast cancer decreased between times 1 and 2 (Supplemental Figure 1, Panel B), and tumor size-specific case fatality rates from competing causes of death remained constant between times 1 and 2 (Supplemental Figure 1, Panel B). Tumor size-specific life expectancy increased between times 1 and 2 because tumor size-specific case fatality rates from breast cancer decreased over the time period (Supplemental 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 (Supplemental Figure 1, Panel D). In actuality, all three aforementioned factors change over time and contribute to the gain 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 in Section F.

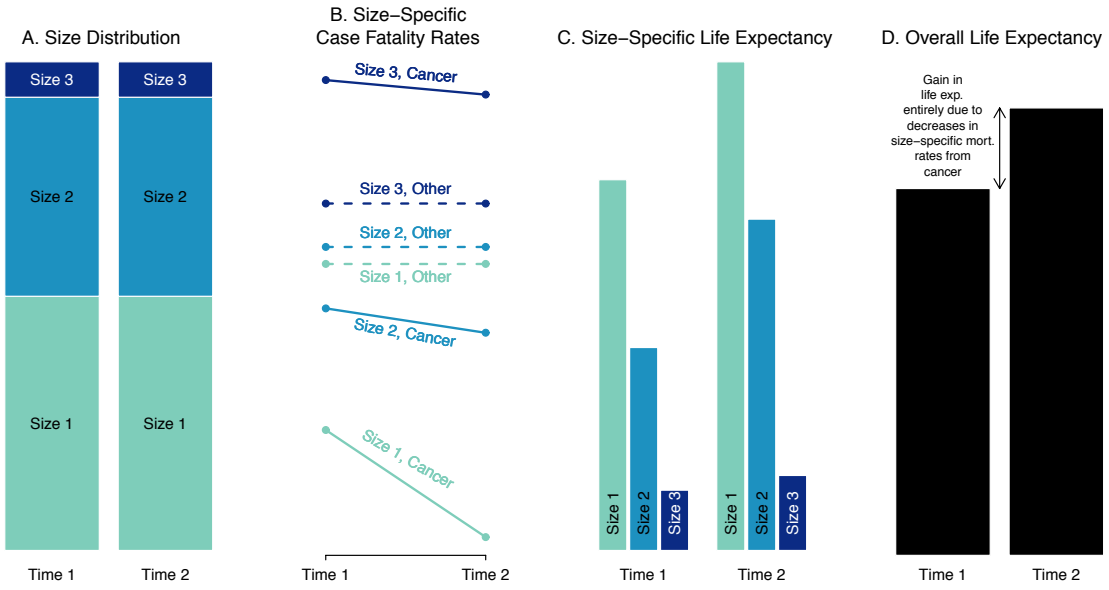
## E Decomposition by Tumor Size and Case Fatality Rates from Breast Cancer and Other Causes of Death

Let $\pi_s(t)$ equal the proportion of breast cancer patients diagnosed with tumor size $s$ in year $t$. Let $e_s(a,t)$ equal the tumor size-specific life expectancy at age $a$. The overall life expectancy at age $a$ and time $t$, $e(a,t)$, equals:

$$e(a,t) = \sum_{s \in \mathcal{S}} \pi_s(t)\, e_s(a,t),$$

where $\sum_{s \in \mathcal{S}} \pi_s = 1$.

The change in life expectancy at age $a$ between times $t_1$ and $t_2$ can be decomposed using the




Supplemental Figure 1: The gain in life expectancy depends on three factors: (A) changes in the tumor size distribution at cancer diagnosis, (B) changes in tumor size-specific case fatality rates from breast cancer, and (C) changes in tumor size-specific case fatality rates from competing causes of death.

methodology of (Kitagawa, 1955):

$$
\begin{aligned}
e(a,t_2) - e(a,t_1) &= \sum_{s\in\mathcal{S}} \left[\, \pi_s(t_2)\, e_s(a,t_2) - \pi_s(t_1)\, e_s(a,t_1)\right] \\
&= \sum_{s\in\mathcal{S}} \left[\pi_s(t_2) - \pi_s(t_1)\right] \left[\frac{e_s(a,t_1) + e_s(a,t_2)}{2}\right] + \\
&\quad \sum_{s\in\mathcal{S}} \left[e_s(a,t_2) - e_s(a,t_1)\right] \left[\frac{\pi_s(t_1) + \pi_s(t_2)}{2}\right]. \qquad (9)
\end{aligned}
$$

Equation (9) quantifies how much of the change in life expectancy at age $a$ between times $t_1$ and $t_2$ is due to: [a] shifts in the share of cancer tumor size (first term) and [b] changes in tumor-size-specific life expectancy (second term).

We can further decompose the second term of equation 9 by cause of death. In doing so, we can quantify how much of this change in tumor-size-specific cancer life expectancy, $e_s(a,t_2) - e_s(a,t_1)$, is due to improvements in case fatality rates from breast cancer and improvements in case fatality rates from competing causes of death. Let $\mathcal{C}$ be a set of mutually exclusive and exhaustive causes of death (e.g., breast cancer and all other causes). Let $L_{a,s,c}(t)$ represent the person-years lived in the life table based on the case fatality rate at age $a$, for tumor size $s$, from cause $c \in \mathcal{C}$, and at time $t$. Similarly, let $L_{a,s,-c}(t)$ represent the person-years lived in the life table based on the case

fatality rate at age $a$, for tumor size $s$, and from causes other than $c$ ($-c$), and at time $t$. Let $a^*$ be the first starting age of $\mathcal{A}$. Then, following the approach developed by (Beltrán-Sánchez et al., 2008),

$$e_s(a^*, t_2) - e_s(a^*, t_1) = \sum_{c \in \mathcal{C}} \sum_{a=a^*}^{\omega} \left[ L_{a,s,c}(t_2) - L_{a,s,c}(t_1) \right] \left[ \frac{L_{a,s,-c}(t_2) + L_{a,s,-c}(t_1)}{2n} \right], \tag{10}$$

where $n$ is the width of the age interval and $\omega$ is the starting age of the final and open-ended age interval.

We perform the decomposition starting at age 40; the final decomposition equation equals:

$$\begin{aligned} e(40, t_2) - e(40, t_1) &= \sum_{s \in \mathcal{S}} \left[ \pi_s(t_2)\, e_s(40, t_2) - \pi_s(t_1)\, e_s(40, t_1) \right] \\ &= \sum_{s \in \mathcal{S}} \left[ \pi_s(t_2) - \pi_s(t_1) \right] \left[ \frac{e_s(40, t_1) + e_s(40, t_2)}{2} \right] + \sum_{s \in \mathcal{S}} \left[ \texttt{Diff}_\texttt{e} \right] \left[ \frac{\pi_s(t_1) + \pi_s(t_2)}{2} \right], \end{aligned}$$

where $\texttt{Diff}_\texttt{e}$ is given by equation (10) evaluated at $a^* = 40$.

# F Decomposition by Tumor Size, Case Fatality Rates from Breast Cancer and Other Causes of Death, and Age Group

As previously defined $\pi_s(t)$ equals the proportion of cancer patients with tumor size $s$ in year $t$. This proportion can also be computed by age group such that $\pi_s(t) = \sum_{a \in \mathcal{A}} \pi_{s,a}(t)$ and $\sum_{s \in \mathcal{S}} \pi_s = 1$. Then, the change in life expectancy at age $a$ between times $t_1$ and $t_2$ can be estimated as:

$$\begin{aligned} e(40, t_2) - e(40, t_1) &= \sum_{s \in \mathcal{S}} \left[ \pi_s(t_2)\, e_s(40, t_2) - \pi_s(t_1)\, e_s(40, t_1) \right] \\ &= \sum_{s \in \mathcal{S}} \left[ \sum_{a \in \mathcal{A}} \pi_{s,a}(t_2)\, e_s(40, t_2) - \sum_{a \in \mathcal{A}} \pi_{s,a}(t_1)\, e_s(40, t_1) \right] \\ &= \sum_{s \in \mathcal{S}} \left[ \pi_{s,40}(t_2)\, e_s(40, t_2) - \pi_{s,40}(t_1)\, e_s(40, t_1) \right] + \\ &\quad \sum_{s \in \mathcal{S}} \left[ \pi_{s,45}(t_2)\, e_s(40, t_2) - \pi_{s,45}(t_1)\, e_s(40, t_1) \right] + \\ &\quad \vdots \\ &\quad \sum_{s \in \mathcal{S}} \left[ \pi_{s,\omega}(t_2)\, e_s(40, t_\omega) - \pi_{s,\omega}(t_1)\, e_s(40, t_1) \right]. \end{aligned}$$

Each summation in the above equation can be written as follows based on equation (9):

$$
\begin{aligned}
&e(40,t_2)-e(40,t_1)= \\
&\sum_{s\in\mathcal{S}}\left[\pi_{s,40}(t_2)-\pi_{s,40}(t_1)\right]\left[\frac{e_s(40,t_1)+e_s(40,t_2)}{2}\right]+\sum_{s\in\mathcal{S}}\left[e_s(40,t_2)-e_s(40,t_1)\right]\left[\frac{\pi_{s,40}(t_1)+\pi_{s,40}(t_2)}{2}\right]+ \\
&\sum_{s\in\mathcal{S}}\left[\pi_{s,45}(t_2)-\pi_{s,45}(t_1)\right]\left[\frac{e_s(40,t_1)+e_s(40,t_2)}{2}\right]+\sum_{s\in\mathcal{S}}\left[e_s(40,t_2)-e_s(40,t_1)\right]\left[\frac{\pi_{s,45}(t_1)+\pi_{s,45}(t_2)}{2}\right]+ \\
&\qquad\qquad\vdots \\
&\sum_{s\in\mathcal{S}}\left[\pi_{s,\omega}(t_2)-\pi_{s,\omega}(t_1)\right]\left[\frac{e_s(40,t_1)+e_s(40,t_2)}{2}\right]+\sum_{s\in\mathcal{S}}\left[e_s(40,t_2)-e_s(40,t_1)\right]\left[\frac{\pi_{s,\omega}(t_1)+\pi_{s,\omega}(t_2)}{2}\right]= \\
&\sum_{s\in\mathcal{S}}\left[\mathtt{Diff}_{\pi,40}\right]\bar{\mathtt{e}}_{\mathtt{s}}+\sum_{s\in\mathcal{S}}\left[\mathtt{Diff}_{\pi,45}\right]\bar{\mathtt{e}}_{\mathtt{s}}+\cdots+\sum_{s\in\mathcal{S}}\left[\mathtt{Diff}_{\pi,\omega}\right]\bar{\mathtt{e}}_{\mathtt{s}}+\sum_{s\in\mathcal{S}}\left[e_s(40,t_2)-e_s(40,t_1)\right]\left[\frac{\pi_s(t_1)+\pi_s(t_2)}{2}\right]
\end{aligned}
\tag{11}
$$

where $\mathtt{Diff}_{\pi,\mathtt{a}}=\pi_{s,a}(t_2)-\pi_{s,a}(t_1)$ and $\bar{\mathtt{e}}_{\mathtt{i}}=\frac{e_s(40,t_1)+e_s(40,t_2)}{2}$.

The terms of equation(11) that include $\mathtt{Diff}_{\pi,40}\ldots\mathtt{Diff}_{\pi,\omega}$ correspond to the contribution of changes in the share of tumor size by age group to the change in cancer life expectancy between times $t_1$ and $t_2$. We can additionally estimate the contribution of changes in case fatality rates from breast cancer and competing causes of death to changes in tumor-size-specific life expectancy by age. The last term of equation (11) can be written as follows, based on equation (10):

$$
e_s(40,t_2)-e_s(40,t_1)=\sum_{c\in\mathcal{C}}\sum_{a=40}^{\omega}\left[L_{a,s,c}(t_2)-L_{a,s,c}(t_1)\right]\left[\frac{L_{a,s,-c}(t_2)+L_{a,s,-c}(t_1)}{2n}\right]. \tag{12}
$$

# G Assuming Constant Mortality Within Age Intervals

Let $M_{a,a+n}$ represent the mortality rate between ages $a$ and $a+n$ and let $\mu(a)$ represent the hazard of mortality at age $a$. The number (or proportion) of survivors at age $a+n$ in the life table, $l_{a+n}$, equals (Preston et al., 2000):

$$
l_{a+n}=l_a\,e^{-\int_a^{a+n}\mu(x)\,dx}=l_a\,e^{-n\,M_{a,a+n}}.
$$

Then, the number of person-years lived between ages $a$ and $a+n$ equals:

$$
{}_nL_a=l_a\int_a^{a+n}e^{-M_{a,a+n}(s-a)}ds=l_a\left(\frac{-1}{M_{a,a+n}}(e^{-n\,M_{a,a+n}}-1)\right). \tag{13}
$$

Suppose the age interval is $n=5$ years wide, then equation (13) equals:

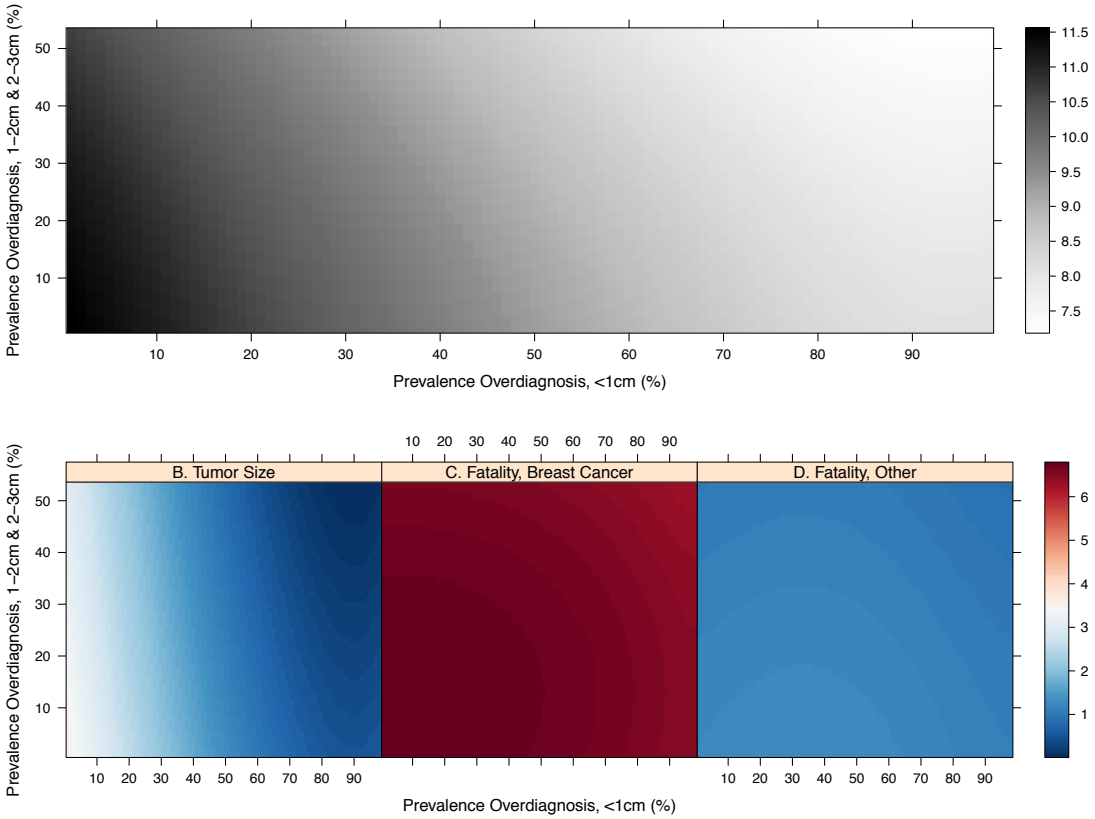
$$
{}_5L_a=l_a\left(\frac{-1}{M_{a,a+5}}(e^{-5\,M_{a,a+5}}-1)\right).
$$

For the last and open-ended age group (e.g., ≥100 years), we can assume there are no person-years lived beyond a certain time (say no more than 10 years) to compute ${}_{\infty}L_{100}$ as:

$$ {}_{\infty}L_{100} = l_{100}\left(\frac{-1}{M_{100+}}(e^{-10\,M_{100+}} - 1)\right). $$

# H Varying Assumed Prevalence of Overdiagnosis for <1cm and 1 − 3cm Tumors

We individually varied the assumed prevalence of overdiagnosis 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 SEER patients diagnosed with <1cm tumors who subsequently died of breast cancer within 10 years (3%). At conservative assumed prevalences of overdiagnosis: 97% for <1cm tumors and 35% for 1-3cm tumors, the contribution to the 7.58-year gain in life expectancy were: 6.40 years from reductions in case fatality rates from breast cancer (84%), 0.22 years from the temporal shift to smaller sized tumors (3%), and 0.98 years from reductions in case fatality rates from competing causes of death (13%).




Supplemental Figure 2: Gain in life expectancy (top panel) and contributions of the temporal shift to smaller sized tumors (bottom left), temporal reductions in case fatality rates from breast cancer (bottom center), and temporal reductions in case fatality rates from competing causes of death (bottom right) varying the assumed prevalence of overdiagnosis level for <1cm tumors (0% to 97%) and 1-3cm tumors (0% to 52%). The color scale for the top (bottom) panel indicates the number of years of the gain in life expectancy (contribution to the gain).

# I Bias in Life Expectancy and Gain in Life Expectancy Under CISNET Approach

CISNET first estimates age- and time-specific mortality rates from all other causes by subtracting breast cancer mortality rates from all-cause mortality rates. CISNET then generates an age of death from all other causes by randomly drawing from the the age of death distribution based on a set of the estimated mortality rates from all other causes of death. Second, CISNET generates an age of death from breast cancer following screen detection based on the patient's age and stage of detection. Finally, CISNET sets the overall age of death as the minimum of the age of death from all other causes and the age of death from breast cancer. We show below that the CISNET approach yields biased estimates of life expectancy and the gain in life expectancy.

## I.1 Mathematical Proof of Bias

In this section, we prove mathematically that the CISNET approach yields biased estimates of life expectancy and the gain in life expectancy. Let $X$ be a continuous random variable that represents the age of death when the only cause of death is breast cancer. Let $Y$ be a continuous random variable that represents the age of death when the only cause of death is all other causes. And let $Z$ be a continuous random variable that represents the age of death for all causes of death.

First, $\min(X, Y) \leq X$. By the linearity of expectation, $E[\min(X, Y)] \leq E(X)$, Similarly, $\min(X, Y) \leq Y$ and $E[\min(X, Y)] \leq E(Y)$. Then,

$$E[\min(X, Y)] \leq \min[E(X), E(Y)]. \tag{14}$$

The left term of equation (14) represents the estimate of life expectancy under the CISNET approach.

Consider $E(Z)$, which equals life expectancy for all causes of death. Suppose there is no mortality from all other causes. Then E(Z)=E(X). Now suppose there is no mortality from breast cancer. Then E(Z)=E(Y). In other words, E(X) and E(Y) bound E(Z): $E(Z) \in [E(X), E(Y)]$. Of course, a cause of death is only an actual cause if at least one person dies of this cause in the population. Thus, $E(Z) \in (E(X), E(Y))$ or, equivalently,

$$\min[E(X), E(Y)] < E(Z). \tag{15}$$

Combining equations (14) and (15),

$$E[\min(X, Y)] \leq \min[E(X), E(Y)] < E(Z). \tag{16}$$

Thus, the CISNET approach yields a biased estimate of life expectancy, $E[\min(X, Y)] - E(Z) < 0$.

Equivalently, we can define another set of continuous random variables for the *gain* in life expectancy when breast cancer is the only cause of death, $A$, when all other causes is the only cause of death, $B$, and for all causes, $C$. For example, $A$ represents the gain in life expectancy when breast cancer is the only cause of death between times $t_2$ and $t_1$, $t_2 > t_1$. Equation (16) applies to these set of random variables. The CISNET approach also yields a biased estimate of the gain in life expectancy: $E[\min(A, B)] - E(C) < 0$.

### I.2 Empirical Example of Bias

In this section, we provide an empirical example of the bias inherent in the CISNET approach to estimating life expectancy and the gain in life expectancy. Consider life expectancy in 1975 and 2002 and the gain in life expectancy between these two years. Rather than model survival following screen detection, we utilized breast cancer mortality rates. Breast cancer patients only contribute to the numerator of the breast cancer mortality rate if the patient dies of breast cancer. Thus, breast cancer mortality rates are not subject to the well-known biases of survival time such as lead-time bias.

We began with individual-level US death certificate data in 1975. We categorized the underlying cause of death as: death from breast cancer (ICD 8th edition code 174) and death from all other causes. We divided each of these age- (single year of age) and cause-specific death counts by the age-specific population counts of females in 1975 to estimate the age- and cause-specific mortality rates. Next we estimated the age of death distribution from the life table that inputted all other cause mortality rates. Formally, the age of death distribution equals the probability distribution function for the random variable age at death from all other causes (life table radix set at 1). We randomly drew from this age of death distribution N=2,000,000 times to yield $N$ ages of death from all other causes. The mean of these draws equals, in expectation, life expectancy.

Similarly, we estimated the age of death distribution from the life table that inputted breast cancer mortality rates. We randomly drew from this age of death distribution $N$ times to yield $N$ ages of death from breast cancer. We also estimated the age of death distribution from the life table that inputted all-cause mortality rates and randomly drew from this distribution to yield $N$ ages of death from all causes.

For each individual $i$ in the simulation ($i = 1, \ldots, N$), we set the realized age of death as the minimum of the age of death from all other causes and the age of death from breast cancer. For example, Supplementary Table 2 shows the results of the simulation for a selection of individuals.

The mean age of death equals 76.46 years for all-cause mortality, 78.25 years for all other cause mortality, 77.00 for breast cancer mortality, and 68.53 for the CISNET approach.

| $i$ | Age of Death, All-Cause | Age of Death, All Other Causes | Age of Death, Breast Cancer | Age of Death, Realized |
|---|---|---|---|---|
| 1 | 81.50 | 70.50 | 60.50 | 60.50 |
| 2 | 82.50 | 87.50 | 87.50 | 87.50 |
| 3 | 91.50 | 72.50 | 79.50 | 72.50 |
| ... | | | | |
| 1,999,998 | 80.50 | 92.50 | 33.50 | 33.50 |
| 1,999,999 | 1.50 | 97.50 | 82.50 | 82.50 |
| 2,000,000 | 68.50 | 85.50 | 83.50 | 83.50 |
| Mean | 76.46 | 78.25 | 77.00 | 68.53 |

Supplemental Table 2: Age of Death Simulation: CISNET Approach. The realized age of death equals the minimum of the age of death from all other causes and age of death from breast cancer.

We follow the same procedure for 2002 and generate $N$ ages of death from all causes, all other causes, breast cancer, and the minimum of all other causes and breast cancer. Supplementary Table 3 summarizes the results for 1975, 2002, and the difference between these two years.

| Year | Age of Death, All-Cause | Age of Death, All Other Causes | Age of Death, Breast Cancer | Age of Death, Realized |
|---|---|---|---|---|
| 1975 | 76.46 | 78.25 | 77.00 | 68.53 |
| 2002 | 79.62 | 82.69 | 80.11 | 73.19 |
| Difference | 3.16 | 4.44 | 3.11 | 4.66 |

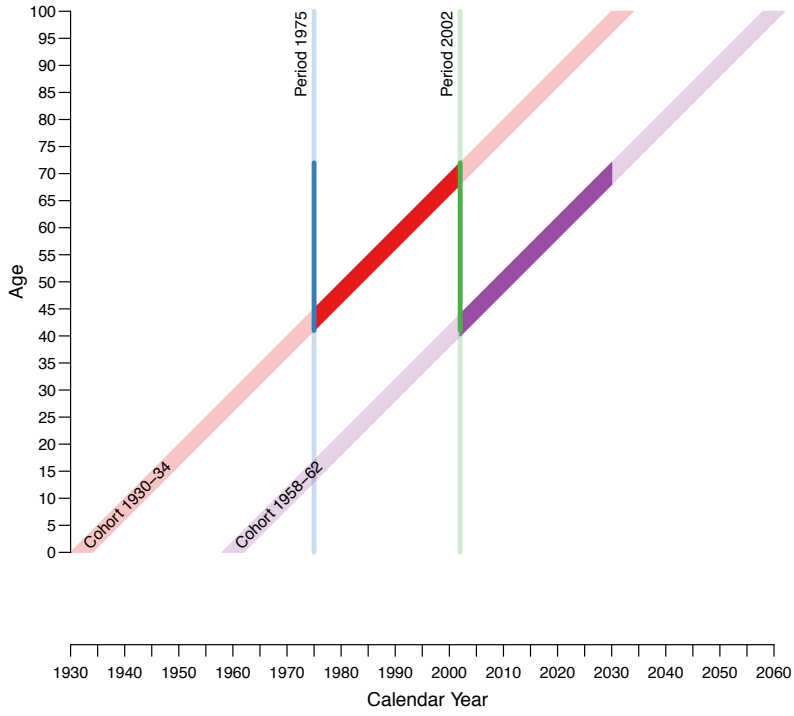
Supplemental Table 3: Gain in Life Expectancy, 1975 and 2002.

The CISNET approach (i.e., taking the minimum of the age of death from all other causes and age of death from breast cancer) is meant to recreate the experience of the population under all cause mortality. Yet, the gain in life expectancy under the CISNET approach equaled 4.66 years between 1975 and 2002 while the actual gain in life expectancy equaled 3.16 years. Thus, the CISNET approach over estimates the gain in life expectancy.

## J Cohort vs. Period Years of Life

We quantify the bias in estimating the average number of years lived by newly diagnosed breast cancer patients using period-based fatality rates, rather than by using cohort-based fatality rates. The bias equals the difference in cohort life expectancy and period life expectancy. Period life expectancy summarizes the mortality experience of a hypothetical cohort subjected−over its entire life−to the fatality rates of a specific year (period). Unlike period life expectancy, cohort life expectancy can only be calculated retrospectively once the entire cohort has died.

Consider the birth cohort of 1931-1935, which aged over time along the red-colored diagonal line shown in Figure 3. The birth cohort was 40-44 years old in 1975, 50-54 years old in 1985, 60-64 years old in 1995, and so forth. Suppose $\omega = 100$ equals the oldest age lived in this birth cohort. This birth cohort would only begin to reach age $\omega$ in 2030, which is the first year cohort life expectancy could actually be calculated.

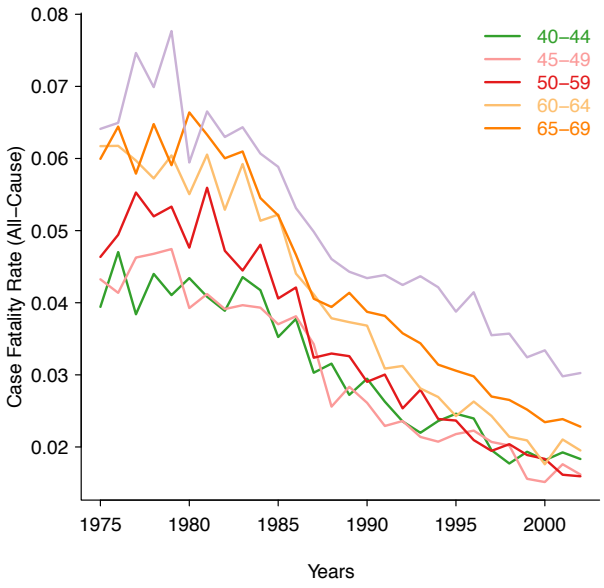



Supplemental Figure 3: Lexis diagram of 1975 (blue) and 2002 (green) period fatality rates and 1931-1935 (red) and 1958-1962 (purple) cohort fatality rates. The dark regions in each line represent years with incidence-based case fatality rate data.

Since we cannot estimate cohort life expectancy because not all individuals have died, we instead

compute *temporary life expectancy*, which equals the total number of person-years lived between ages $a_1$ and $a_2$ in the life table. We calculate temporary life expectancy between ages 40 and 69 using both the period (years 1975 and 2002) and cohort (birth cohort 1931-1935 and 1958-1962) fatality rates. Temporary life expectancy equaled 16.32 years based on 1975 period fatality rates, 23.16 years based on 2002 period fatality rates, and 17.77 years based on 1931-1935 birth cohort fatality rates.

To calculate temporary life expectancy for the 1958-1962 birth cohort (which was 40-44 years old in 2002), we assumed that this cohort will experience mortality improvements similar to that of the 1931-1935 cohort between 1975 and 2000. Specifically, we multiply the 2002 period fatality rates by the proportionate reductions by age group between the 1975 period fatality rates and 1931-1935 birth cohort. We assume the reductions observed in the earlier period and birth cohort apply to the later period and birth cohort because age-group-specific fatality rates have declined approximately linearly since about 1980 (Supplemental Figure 4).




Supplemental Figure 4: Time trends in Period Case Fatality Rates by Age.

Under these assumptions, temporary life expectancy equaled 24.12 years based on 1958-1962 estimated birth cohort fatality rates. Then, the gain in cohort-based temporary life expectancy between the 1931-1935 and 1958-1962 birth cohorts equaled 6.35 years, and the gain in period-based temporary life expectancy between 1975 and 2002 equaled 6.83 years. Thus, our use of period-based fatality rates likely provides an upper bound to the true, or cohort-based, gain in life

expectancy.

# K Varying Time Intervals Between Diagnosis and Death

| Time Interval | Gain in Life Expectancy | Tumor Size | Reductions in Case Fatality Rates from Breast Cancer | Reductions in Case Fatality Rates from Competing Causes |
|---|---|---|---|---|
| 8 | 11.23 | 3.15 (28%) | 7.07 (63%) | 1.03 (9%) |
| 9 | 10.93 | 3.09 (28%) | 6.76 (62%) | 1.09 (10%) |
| 10 | 10.69 | 2.99 (28%) | 6.57 (61%) | 1.15 (11%) |
| 11 | 10.38 | 2.78 (27%) | 6.27 (60%) | 1.35 (13%) |
| 12 | 10.28 | 2.65 (26%) | 6.05 (59%) | 1.59 (15%) |

Supplemental Table 4: Gain in life expectancy and contribution of the temporal shift to smaller sized tumors, temporal reductions in case fatality rates from breast cancer, and temporal reductions in case fatality rates from competing causes of death, 1975-2000, varying time interval between breast cancer diagnosis and death. Note: Yrs=years.

## References

Beltrán-Sánchez, H., Preston, S. H., and Canudas-Romo, V. (2008). An integrated approach to cause-of-death analysis: Cause-deleted life tables and decompositions of life expectancy. *Demographic Research*, 19(35):1323–1350.

Chiang, C. L. (1983). *Life Table and Its Applications*. Krieger Pub Co, Malabar, FL.

Kitagawa, E. (1955). Components of a difference between two rates. *Journal of the American Statistical Association*, 50(272):1168–1194.

Preston, S. H., Heuveline, P., and Guillot, M. (2000). *Demography: Measuring and Modeling Population Processes*. Blackwell, Oxford, UK.