Abstract

1. We changed “precise contribution” to “relative contribution” in the Abstract, Background.
2. We deleted the sentence in the Abstract, Methods describing the assumed level of overdiagnosis.
3. We deleted the sentence about reaching nearly identical substantive conclusions varying the level of overdiagnosis.
4. We edited the sentence about the life-table methods to emphasize its strengths over simulation-based studies, “We used life-table methods, which require fewer assumptions than simulation-based studies, to calculate the gain in life expectancy and quantified the three constituent components of this gain:…”

Introduction

1. We clarified that previous research only estimated the contribution of screening and attributed the remainder to the contribution of breast cancer treatment.
2. We split discussion of limitations of previous work into [1] research that were vulnerable to overestimating the contribution of breast cancer treatment and [2] research that only focused on the reduction in breast cancer mortality rates and inherently ignored improvements in other cause mortality rates.

“Other studies only focus on the reduction in breast cancer mortality rates rather than reductions in overall mortality rates and, thus, inherently ignored the substantial improvements in the prevention and treatment of other diseases.1,12  Thus, these studies could not quantify the contribution of screening on the increase in overall survival of breast cancer patients over time.”

1. Throughout the paper, we now write “distribution of tumor sizes”.
2. We now write about the sensitivity analysis varying the overdiagnosis level, “Finally, we vary the level of overdiagnosis and re-quantify contributions to the gain in life expectancy.”

Methods

1. We now begin the description of the first step with a sentence of what this step will produce, “The first step estimates the contribution of earlier detection to gains in life expectancy (component [1]).”
2. To maintain the focus of Section 2.1 on the analytic methods, we now refer to the full description of incidence-based case fatality rates in Section 2.2. “We began with all-cause incidence-based case fatality rates (hereafter “fatality rates”) by tumor size, as described in Section 2.2.”

We also clarify the assumption regarding incidence-based case fatality rates in the Limitations paragraph of the Discussion. See point number 32 for more details.

1. We now include an appendix that provides an example of a life table and refer readers to it, “The adjusted tumor size-specific fatality rates served as the input to demographic life tables that produced tumor size-specific life expectancies in 1975 and 2002 (see eAppendix C for example of life table calculations).”
2. As with the first step, we now begin the description of the second step with a sentence of what this step will produce, “The second step estimates the contribution of advances in breast cancer treatment (component [2]) and advances in the treatment of other diseases (component [3]) on gains in life expectancy.”
3. We edited the sentence to active voice, “We then adjusted these rates for overdiagnosis.”
4. We clarify that there are separate life tables for breast cancer death and other cause death, “The adjusted tumor size- and cause-specific fatality rates served as the input to demographic life tables (one for breast cancer and the other for all other causes) that produce corresponding life-years in 1975 and 2002.”
5. We now explain what the 10-year window accomplishes, “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.”

Sun et al. (2010) used survival time, rather than incidence-based case fatality rates. Rather than this difference in data, we focused on the lack of consideration of other cause mortality as the chief limitation of Sun et al.

1. We separated the sentence about the 10-year window for the incidence-based case fatality rate and the number of patients for whom we calculated incidence-based case fatality rates.
2. We clarify that tumor size is based on clinical and operative/pathological assessment, “…), tumor size determined by clinical and operative/pathological assessment (<1cm, 1-2cm, 2-3cm, 3-5cm, ≥5cm),…”.
3. We now define overdiagnosis, “Overdiagnosis is the detection of asymptomatic breast cancers that are non-growing or so slow-growing that they would never present symptomatically during a women’s lifetime.20”.
4. We now refer to annual share as annual proportion.

Results

1. We clarify the unit of the case fatality rate: per 100,000 person-years among patients diagnosed with a specific size of breast cancer: “For example, the rate decreased from 101 to 59 deaths per 100,000 person-years among patients diagnosed with ≥5cm tumors and from 18 to 5 deaths per 100,000 person-years among patients diagnosed with <1cm tumors.”
2. We changed changed the focus the discussion of other cause mortality rates to highlight the importance of accounting for both causes of death. We now write that other cause fatality rates for <1cm to 3-5cm tumors are higher than the corresponding breast cancer fatality rates for these sizes.

“For patients diagnosed with <1cm, 1-2cm, 2-3cm, and 3-5cm tumors, case fatality rates from other causes were higher than those from breast cancer.  Only for patients diagnosed with ≥5cm tumors were case fatality rates from breast cancer larger than those from other causes.  This result highlights the importance of accounting for both causes of death (breast cancer and other causes) when assessing the gain in life expectancy for breast cancer patients.”

In Section 2.1, we now write, “The three components, all of which we derive from life tables, sums to the total gain in life expectancy.”

We added a new sentence about similar increases in mammography screening rates by age group over time to support our main conclusion of nearly equal contributions of earlier detection by age group over time. “This comparable level of contribution from earlier detection may be due, in part, because of similar increases in mammography screening rates for these age groups across time.30”

We repeat the gain in life expectancy and contributions under the baseline 10% overdiagnosis level. “For example, at a 20% overdiagnosis level, the gain in life expectancy equaled 10.31 years (compared to 10.94 years at a 10% overdiagnosis level): 66% from reductions in case fatality rates from breast cancer, 23% from the temporal shift to smaller sized tumors, and 12% from reductions in case fatality rates from competing causes of death (compared to 62%, 27%, and 11%, respectively, at a 10% overdiagnosis level).”

Discussion

We estimate the gain in life expectancy for all age groups, not just for 40-year olds. We deleted “40-year old” and now write, “Our study quantifies the contribution of earlier detection and advances in breast cancer treatment on gains in life expectancy for a newly diagnosed breast cancer patient.”

We now include a citation to the CISNET *Breast Cancer Model Profiles* for the sentence about CISNET’s estimation of life expectancy as the smaller of two separate life expectancies (breast cancer as the only cause of death and other causes as the only cause of death).

We edited the sentence describing the implication for our joint modeling of life expectancy, “In other words, our approach equally relies on case fatality rates from both causes of death (breast cancer and other disease) when estimating the gain in life expectancy.”

We now describe the progression as “…some of which rely on untestable assumptions of breast cancer progression from small non-invasive tumor to malignant cancer.28”

We deleted the paragraph about the county-level analysis of mammography and breast cancer mortality to save words and because its focus was not as relevant to our paper as Berry et al. (2005), Sun et al. (2010), and Park et al. (2015).

We edited the conclusion of the age-specific analysis to be more concise – the contribution of earlier detection was fairly similar across age groups. We now write, “Thus, our results suggest earlier detection among 40-49 year olds provided approximately equal benefit, measure in the contribution to the gain in life expectancy, as it did among 50-59 and 60-69 year olds.”

We deleted the detailed discussion about different age groups capturing relatively smaller or larger shares of contributions of the proportion of smaller sized tumors. The main conclusion is that the contribution of earlier detection was approximately equal across age groups.

We now clarify the first limitation about the case fatality rates used to calculate life expectancy. We do not hold the case fatality rates constant across ages. Rather, we allow the case fatality rates to vary across age (as they do empirically). The set of age-specific case fatality rates come from 40-44, 45-49, 50-54, …, 100+ year old women all diagnosed in a given year. In other words, we calculate ‘period’ life expectancy rather than ‘cohort’ life expectancy. We conduct a sensitivity analysis in which we vary the period-based case fatality rates by the largest observed difference between period and cohort case fatality rates and report the effect on the gain in life expectancy and its constituent components.

“First, our life table methods and the resulting estimates of life expectancy assume that women experience a set of fatality rates, which vary by age, based on their year of breast cancer diagnosis rather than on their year of birth.  For example, the life expectancy of a 40-year-old woman diagnosed with 1-2cm breast cancer in 1990 is based on the case fatality rates of 40-44-year-old, 45-49-year-old, …, ≥100-year-old women diagnosed with similarly sized tumors also in 1990 (‘period life expectancy’).  In reality, the life expectancy of this 40-44-year-old woman diagnosed in 1990 would be based on the survival times from diagnosis to death of her birth cohort (‘cohort life expectancy’ equals the area under this survival curve).  The limitation of period life expectancy notwithstanding, it is commonly reported summary of a population’s mortality because cohort life expectancy can be computed only after all individuals have died.  Empirically, case fatality rates for cohort life expectancy were at most 20% smaller than the case fatality rates for period life (eAppendix J).  This difference between period- and cohort-based case fatality rates corresponds to a gain in life expectancy of 10.88 years between 1975 and 2002 (compared to 10.94 years in our primary analysis) with the following contributions: 62% from advances in breast cancer treatment, 28% from earlier detection, and 11% from advances in the treatment of other diseases (compared to 61%, 27%, and 11% in our primary analysis).”

We now begin the concluding paragraph, “In conclusion, several factors contributed to the gain in life expectancy for breast cancer patients.”

We now end the concluding paragraph, “Our study assessed the benefit of early detection on its contribution to the gain in life expectancy.  When the harms are also measured in gains in life expectancy, it will be possible to directly measure the balance of benefits and harms. This common approach may clarify the controversy about whether mammography confers net benefit.”