*1. How about a sentence explaining the basic principle of estimating the contributions of detection and treatment?  It’s a black box up to hear, and the reader ought to get the basic idea in order to take seriously the basic claim in the paragraph.  How can they understand your objection to the Sun study without some background on how you distinguish the three potential drivers of the gain?  Additionally, what assumptions drove the variation in the CISNET models?*

We added to the Introduction a sentence that explains the basic principle of estimating the contribution of detection and treatment. “Quantifying these contributions requires the simultaneous assessment of three components: [1] changes in the distribution of stage at diagnosis over time because women diagnosed at earlier stages typically lived longer than women diagnosed at later stages, [2] improvements in breast cancer treatment that reduce fatality rates from breast cancer, and [3] improvements in the prevention and treatment of other diseases that are the leading causes of death among women diagnosed with early stage breast cancer (e.g., cardiovascular disease [CVD]). “

We then use this basic principle to explain the limitations of previous research.  The most important limitation of previous work is failing to account for improvements in fatality rates from other diseases.  We moved to the Discussion the specific limitation of the CISNET modeling approach, namely that the approach underestimates the gain in life expectancy because it effectively ignores changes in other cause fatality rates.

*2. This is a nice paragraph but its significance is largely lost because you don’t first explain the over-all analytic strategy.  In trying to explain why your study is a contribution, I imagine a table that shows the pieces of a model that gets you to the final result, what you did to obtain the data for each piece, what other previous workers did in their models, and why your method is superior.  This table might be an appendix in the article, but its main purpose would be to help you structure your article so that readers would understand why it is a contribution to a crowded field.*

We created Figure 1 to explain our overall analytic strategy.  This figure shows how we estimate the contribution of earlier detection, breast cancer treatment, and treatment of other diseases.

*3. I suggested in my comments on the earlier version that you outline your basic analytic strategy.  The material in the last paragraph of the introduction does not explain how you*

We rewrote the analytic methods and its accompanying Figure 1 to describe the overall analytic strategy and, specifically, how we start from input data, use life table methods, and estimate the contributions.

*4. What are these and why are they important to your method?*

We now write why incidence-based fatality rates are important to our method, “By allowing this 10-year time window between diagnosis and death, we mitigate the potential bias of ascertainment in cause of death and calculate incidence-based case fatality rates between 1975 and 2002 for 422,141 breast cancer patients.”

*5. Why is this important????  Did other authors use it?*

We now explain the importance of incidence-based case fatality rates -- the mitigation of potential ascertainment bias in cause of death.

*6. Strongly consider reversing the order of 2.1 and 2.2.  The analytic section gives some insight into how you can get the result, which explains why you obtained the input data and why certain characteristics of it are important.*

We reversed the order of the subsections in the Methods section.  We now begin with the analytic methods and its accompanying Figure 1.  We then provide greater detail of the specific data in section 2.2.

*7. Exposure to what?*

We deleted this sentence and now more succinctly describe the adjustment for overdiagnosis.  “We adjust case fatality rates for these smaller sized tumors (both all-cause and cause-specific) by removing the person-years overdiagnosed cases contributed to the denominator of the rates (eAppendix B).  We also adjust the annual share of smaller sized tumors by subtracting the overdiagnosed cases from the annual count of incident cancers and recalculating the distribution by tumor size.”

*8. All-cause?  I’m surprised.  What’s the reason?*

We now explain the method in the new Section 2.1 and accompanying Figure 1 that we utilize two steps.  In the first step, we use as input data all-cause case fatality rates and the annual share of tumor sizes.  Through Kitagawa decomposition, we then split the gain in life expectancy into the contribution from changes in the annual share of tumor sizes (our estimate for the contribution of earlier detection) and the contribution from changes in all-cause fatality rates.

In the second step, we further split the contribution from changes in all-cause fatality rates into the contribution from changes in fatality rates from breast cancer and changes in fatality rates from other diseases using Beltrán-Sánchez et al. decomposition.

*9. To be really concrete, you could show an excerpt from a life table.*

In eAppendix C, we now show an excerpt from a life table that begins with the fatality rates (the observed data), adjusts for overdiagnosis, transforms to probabilities of survival, and estimates life expectancy.

*10. And how do you get from probability of survival to life expectancy?*

In the new Figure 1, we show how we get from probability of survival to life expectancy.  In eAppendix C, we provide a detailed example of a life table that shows how we start from fatality rates, transform them to probabilities of survival, and estimate life expectancy.

*11. This is the heart of your approach to disaggregating the contribution of early detection.  As I noted in commenting on the earlier version, you need somewhat to persuade the reader that this is a valid method, which is partly explaining it so that people “get’ it and partly describing validation studies of the method.  Also, have other authors used the same technique?*

The new Figure 1 provides readers with an overview of the analytic method.  We now cite the methods to show they are published and validated.

*12. This is a pretty good explanation although it would be nice to know how you get from probabilities of survival (see the preceding paragraph) to the relative contribution of these two sources of life expectancy.   Now if you could just explain how the demographic method for tumor size and cancer –specific mortality gets you a life table and how the output of that table gets you to the relative contribution of tumor size and tumor mortality rate to overall survival.*

In the new section 2.1 and accompanying Figure 1, we describe the analytic flow of our method.  We describe the input data, as well as the specific demographic methods we utilize.  The first decomposition (Kitagawa) estimates the contribution of earlier detection.  The second decomposition (Beltrán-Sánchez et al.) estimates the contribution of advancements in breast cancer treatment and advancements in the treatment of other diseases.

*13. Why did you do this?*

We now explain how each demographic method accomplishes the goal of estimating the contribution of 1) earlier detection, 2) advancements in breast cancer treatment, and 3) advancements of the treatment of other diseases on the gain in life expectancy.  We specifically name the demographic methods that we utilize and trace the input and output of each method.

*14. In other words, other-cause death rates in people with breast cancer???*

We deleted the conceptual example paragraph and replaced it with a detailed explanation of the analytic method on which Figure 1 is based.  We now characterize fatality rates from breast cancer as the cause of death as, “In the second step, we also began with fatality rates by tumor size now separated by cause of death (breast cancer and all other causes).”

*15. That’s an easy case.  The harder and more important one is when size is decreasing and treatment is getting better.  How do the demographic methods disaggregate these two trends?*

We deleted the previous Figure 1 and replaced it with an overview of our analytic method that shows how we begin with input data and use demographic methods to estimate the three contributions.  Specifically, we show how we disaggregate the contribution from decreases in all-cause fatality rates into the contribution from decreases in fatality rates from breast cancer (our estimate for advancements in breast cancer treatment) and decreases in fatality rates from other diseases (our estimate for advancements in the treatment of other diseases).

*16. This explanation is helpful.  Think you need to emphasize how you get from the life table outputs to the proportion of effect over time due to screening and to treatment.*

In the new Figure 1, we describe how we use the input data (e.g., all-cause case fatality rates) and use two life-table methods to estimate the contribution of earlier detection and treatment.  In the new Section 2.1, we discuss each step of the method from input data to estimated contribution.

17. Probably need to say that the interaction between better screening and better treatment does not occur in the model but in the actual numbers in the life table.

In the new analytic methods and accompanying Figure 1, we explain how we separate the effect of better screening and better treatment using life table methods.

*18. Explain why 3% corresponds to a maximum over Dx rate of 97%.*

We now explain the reasoning for setting the upper bound of overdiagnosis at 97% for <1cm tumors.  “Second, we varied the level up to 97% for tumors <1cm (because 97% of patients diagnosed with <1cm tumors did not die of breast cancer within 10 years and, thus, could have been overdiagnosed) and up to 52% for 1-3cm tumors.”

*19. The Methods section should explain how you got from the life table to this number.*

We now explain in the methods section how we estimated the contribution of the three constituent components to the gain in life expectancy.  “We used the first estimate as a measure of the contribution of earlier detection to gains in life expectancy (component [1])”.  “We used the first estimate as a measure of advancements in breast cancer treatment (component [2]) and the second estimate as a measure of advancements in the treatment of other diseases (component [3]).”

*20. How do you know your estimate is accurate?*

We added a new paragraph that argues why our method yields a more accurate estimate of the contribution of earlier detection to the gain in life expectancy than CISNET.

“Our results provide a more accurate estimate of the contribution of earlier detection and cancer treatment on the gain in life expectancy than previous work. For instance, CISNET estimates two separate life expectancies assuming breast cancer as the only cause of death and all other causes as the only cause of death.24  CISNET then takes the smaller of these two values as the actual life expectancy.  Thus, gains in overall life expectancy over time become increasingly dominated by the cause with higher fatality rates and, hence, lower life expectancy.  Empirically, mortality rates from breast cancer exceeded those from all other causes and, therefore, the life expectancy from breast cancer was lower than life expectancy from all other causes.  Thus, although CISNET ostensibly considers mortality rates from other causes of death, it effectively relies only on breast cancer mortality rates when estimating the gain in life expectancy.  In doing so, the CISNET approach underestimates the gain in life expectancy over time.  This underestimation results in biased estimates of the contributions of breast cancer treatment and earlier detection on the gain in life expectancy.  In contrast, we jointly model life expectancy using a competing risk approach; overall survival equals the product of survival from breast cancer and survival from all other diseases. In other words, breast cancer patients only live if they do not die of breast cancer and do not die of other causes.”

*21. Which ones were the most important drivers and  were there reasons why the values for those drivers might have been so diverse?  What direction should these bias the results in?  What modeling technique did CISNET use and what role might the differing modeling techniques have played in the diverse results. Did CISNET use incidence-base mortality or methods that are  more bias-prone?*

In the new paragraph about why our method yields more accurate estimates, we discuss the CISNET method that produces biased estimates of the gain in life expectancy.  The CISNET method underestimates the gain in life expectancy by relying mostly on population-level breast cancer mortality rates and discounting the corresponding mortality rates from other causes.

*22. Your result could mean that you were too high.  Did your methods and Sun’s differ in ways that might explain the discrepancy?*

We now focus on the main difference between our method and Sun et al—distinguishing between breast cancer and other diseases as causes of death.  By failing to distinguish between these two causes, Sun et al. overestimated the contribution of breast cancer treatment and underestimated the contribution of earlier detection.  Our method, which does distinguish between these two causes, estimates a higher contribution of earlier detection that supports the assertion Sun et al. underestimated this contribution.

*23. In what direction might this bias Sun’s results?  And why do incidence-based case fatality rates avoid this problem and are less prone to bias?*

We removed discussion of the use of survival time data by Sun et al. and instead focus on the study not distinguishing between breast cancer and other diseases as causes of death.  By failing to distinguish between these two causes of death, Sun et al. overestimate the contribution of breast cancer treatment and, consequently, underestimate the contribution of earlier detection.

*24. This might or might not be something to comment on, but it doesn’t seem to belong in this paragraph.  What is your bottom line about the relative contributions, taking into account all 3 studies?*

We now contrast our study with the three studies cited (CISNET, Sun et al., and Bleyer and Welch).  We end the paragraph with the following summary sentence, “Overall, our calculation of the contribution of earlier detection is broadly similar to many of the CISNET models and Sun et al., although we arrive at this conclusion using methods with less assumptions and data with less biases.”

*25. Need to make this paragraph more relevant to your study or delete it.  You could use the extra words to amplify your description of your methods and make even more accessible to readers like me.*

We deleted the paragraph about the incidence rate of 3-5cm and ≥5cm tumors remaining relatively stationary since 1990.

*26. Surprising it wasn’t larger since younger cures gain many more life-years than older ones.*

We now explain in greater detail why earlier detection among 40-49 and 70-79 year olds contributed more to the gain in life expectancy than earlier detection among 50-59 and 60-69 year olds.  In the Discussion, we now write, “The net contribution of earlier detection results from offsetting trends in the share of incident breast cancer by tumor size and age of diagnosis.  Fifty to fifty-nine and 60-69 year olds captured a larger amount of the increasing contribution from the growing share of smaller sized tumors than 40-49 and 70-79 year olds.”

*The 10.94 years was specific to this age group wasn’t it?*

Yes, the 10.94 year gain in life expectancy was the gain in life expectancy between 1975 and 2002 for a newly diagnosed 40-year old breast cancer patient.  We added a limitation that explains we assume women experience over their entire life the incidence-based case fatality rates of her year of cancer diagnosis.

*27. I don’t see the logic of this statement.  Please explain it.*

We deleted the sentence about the UK-based Age Trial since the trial assessed efficacy in a trial setting whereas we estimate the benefit of screening at the population level.

*28. Explain this.  Do you mean that Sun did not distinguish between cancer and other diseases as a cause of death?  Be clear here.*

We now clarify that Sun et al. did not distinguish between cancer and other diseases as causes of death.  We write, “Our calculation of the contribution of advancements in breast cancer treatment in this time period, 64%, suggests the previous estimate may be too high because the study failed to distinguish between breast cancer and other diseases as causes of death.”

*Also the next paragraph appears to enlarge on this point.  Why not combine the last sentence of this paragraph with the next paragraph?*

We connect the final sentence (the failure to distinguish between breast cancer and other diseases) and the first sentence of the next paragraph (advancements in the prevention and treatment of competing causes of death) by writing, “Yet, advancements in the prevention and treatment of competing causes of death, such as CVD,26,27 also contributed to the gain in life expectancy among breast cancer patients.”

*29. Aren’t there any potentially vulnerable basic assumptions of your method?  Think you need to  at least address this point.*

We now discuss the assumptions of our method as the first limitation, “First, we base cohorts on year of breast cancer diagnosis, rather than on year of birth.  Thus, our life table methods and the resulting estimates of life expectancy assume women experience over their entire life the incidence-based case fatality rates of their year of breast cancer diagnosis.  This assumption may lead to a conservative estimate of the gain in life expectancy between 1975 and 2002 because age-specific fatality rates declined over this time period.”

*30. Explain this point.*

We corrected the bias to ascertainment bias in cause of death classification.  “Second, we required that breast cancer death must have occurred within 10 years of diagnosis when calculating case fatality rates to partially mitigate the effect of mitigate the ascertainment bias in cause of death.”

*31. Are they really new or just newly applied to cancer epidemiology/demography?  If they are really new, who has validated them?  Our statisticians wouldn’t let us publish a paper in Annals if it relied on a method that hadn’t been validated.*

The methods we utilize are existing demographic methods that we apply to cancer epidemiology.  In the methods, we now name and cite the methods.  In the concluding paragraph in the Discussion, we now write, “We apply existing demographic methodologies to disentangle the precise contribution of earlier detection and advancements in breast cancer treatment on the gain in life expectancy, accounting for concurrent advancements in the treatment of other diseases.”

*32. Think you need to acknowledge that your results are in the ball-park of previous studies but avoid the potential biases in some of the data and methods of earlier work.  That’s your case for publication.*

We now acknowledge our results are within the range of CISNET and Sun et al., although we use methods with less assumptions and data with less biases.  In the Discussion, we now write, “Overall, our calculation of the contribution of earlier detection is broadly similar to many of the CISNET models and Sun et al., although we arrive at this conclusion using methods with less assumptions and data with less biases.”