Author's response to reviews

Title: Cardiopulmonary Bypass Has a Modest Association with Cancer Progression: A Retrospective Cohort Study

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BMC Cancer

To whom it may concern:

The following response to two sets of peer reviewer comments on our manuscript is attached.

All correspondence regarding the attached manuscript can be sent to cathy.pinto@merck.com. I can be reached directly at 914-552-1736.

Sincerely,

Cathy Anne Pinto, PhD, MS
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Attachments
REVIEWER 1:

- **Comment #1) TITLE:** This should be more concise

  Page 1: The authors revised the title to: *Cardiopulmonary Bypass Has a Modest Association with Cancer Progression: A Retrospective Cohort Study*

- **Comment #2) ABSTRACT:** Why was the retrospective data collection terminated in 2004 and why was the date of censorship on December 31, 2006?

  The authors used all available data at the time of the study, which included data through 2004 from the open heart surgery registry and through 2006 from the cancer registry.

- **Comment #3) BACKGROUND:** Important for both factors mentioned by the authors: IL-10 and TGF-beta activate T-helper cell type 2 and down-regulate cellular immunity. Some other factors deserve mentioning in the immunomodulation by cardiopulmonary bypass: IL-1beta, IL-2 and its soluble receptors, IL-6, IL-8, IL-12 and TNF-alpha. Most of these promote inflammation.

  Page 4. The observed impact of CPB on other immune-regulatory factors have been included in the background section of the manuscript.

- **Comment #4) BACKGROUND:** In might be useful to state that, according to cardiologists, in patients with both diseases, treatment of the heart disease has usually priority, since this is the more lethal disorder on short term.

  Page 4: This has been added to the background.

- **Comment #5) BACKGROUND:** The study of Vieira et al (Cancer-related deaths among different treatment options in chronic coronary artery disease: results of a 6-year follow-up of the MASS II study; Coronary Artery Disease 2012, 23:79-84) is also of interest for inclusion in the references. Their conclusion is worthwhile: "Different treatment options for multi-vessel coronary artery disease (CABG with cardiopulmonary bypass, PCI or medical treatment) have similar overall mortality (6-year follow-up): CABG patients had the lowest incidence of cardiac death, but the highest incidence of non-cardiac causes of death, and specifically a higher tendency toward cancer-related deaths".

  Page 4: The authors agree with the relevance of the findings reported in this recent publication, and have included this reference in the background section of the manuscript.
• **Comment #6** METHODS: The authors mention in the key secondary endpoints skin melanoma, NHL and kidney cancer which are susceptible to immune modulation. This is certainly true for chronic immune suppression after transplantation, but does this also apply for short alteration in the immune system such as with cardiopulmonary bypass? This should be commented in the section "discussion".

Pages 8, 13: The authors have clarified in the methods and discussion section that prior evidence suggests these cancers are susceptible to chronic immune suppression. The authors are speculating that, given prior evidence of these cancers being susceptible to chronic immune modulation, the same may hold true for short term immunosuppression.

• **Comment #7** RESULTS: Figure 3 should be figure 2 (last paragraph, page 11, second line from bottom)

The authors noted several changes that need to be made to correct table and figure titles, as reflected by revisions on pages 10, 12, 21, 22, 24, 25, and 27. Table and Figure title and legends have also been revised in compliance with journal guidelines pertaining to maximum word count. Figure short titles and legends have been appended to the end of the manuscript.

• **Comment #8** DISCUSSION The strengths and limitations are well presented. The "association between cardiopulmonary bypass and malignancy is modest at best" and needs confirmation. It seems useful to explain also some other advantages of OPCAB to non-cardiologists. Therefore, this discussion can be strengthened by giving some other reasons (technical issues, organ damage, etc.) why OPCAB should be preferred above ON-pump CABG

The authors respectfully disagree that this additional detail is germane to the study design or interpretation of results. If the results of the association between CPB and cancer progression were significant and likely to impact clinical practice guidelines, then further detail concerning the potential benefits of OPCAB would be warranted. However, as the results suggest a modest association at best, the authors believe this detail would not add important scientific perspective.

• **Comment #9** TABLES: The terms urgent, emergent and salvage should be defined. These can differ between authors, especially in cardio- surgical journals.

Page 22: Definitions have been included as footer in Table 1.
Authors designed a clinical study to clarify the hypothesis that the use of cardiopulmonary bypass (CPB) may cause a transient immunosuppression with the potential to promote the spread and growth of coexisting cancer cells. A retrospective cohort study of cancer risk, stage, and mortality in 43,347 patients who underwent coronary artery bypass graft (CABG) surgery with and without CPB in New Jersey between 1998-2004 was conducted. The study revealed that an increased risk for overall cancer incidence and cancerspecific mortality did not reach statistical significance. An increased risk of skin melanoma and lung cancer was only observed for patients with pump versus off-pump open-heart surgery. Authors concluded that these results suggest that there may be a relationship between CPB and cancer progression, however, the effect is likely modest at most. This clinical study is a retrospective but large scale study. I think this study may contribute higher evidence level about the effect of cardiopulmonary bypass on the cancer prognosis. But I think this study design has serious faults. Objects of this study are patients who were diagnosed cancer after CABG surgery. Patient with prior cancer diagnosis were excluded in this study. This study design may clarify the effect of cardiopulmonary bypass to increase of cancer incidence after CABG surgery. But the effect of cardiopulmonary bypass on patients who have cancer on CABG surgery is not observed. I think Journal readers want to know the effect of cardiopulmonary bypass to cancer prognosis on patients with any cancer.

• Comment #1. Patients who were diagnosed cancer within 1 year prior to CABG surgery should be added and be analyzed statistically.

The research objectives were to assess whether short term transient immunosuppression by CPB may lead to progression of co-existing cancer cells. This study examined whether CPB may have an impact on subclinical disease and conducted a separate study using the same linked databases and analytical methods which examined the impact on patients (n=6, 603) with prior cancer diagnoses including cancers diagnosed prior to or on the same day as their initial open-heart surgery. The analyses of this separate study were stratified by duration (1-, 2-, 4 years) between prior cancer diagnosis and subsequent open-heart surgery. No significant difference in the relative risk for patients with CPB compared to those with off-pump procedures was observed at any given time point, nor was there any qualitative difference in the hazard ratio for patients with a cancer diagnosis within shorter timeframes prior to surgery. A total of 917 patients (659 pump, 258 of pump) had a cancer diagnosis within 1 year prior to surgery. The adjusted hazard ratio was 1.05 (95% CI, 0.85-1.30: p=0.67), compared with 1.10 (95% CI, 0.87-1.42: p=0.41) and 1.07 (95% CI, 0.84-1.36: p=0.57) patients with diagnoses within 2-years and 4-years of surgery, respectively. The authors have included a reference to this study and findings on page 12 of the current version of the manuscript.
• **Comment #2.** Patients who were diagnosed cancer simultaneously to CABG surgery should be added and be analyzed statistically.
  As referenced above, patients with cancers diagnosed prior to and on the day of surgery were include in a separate study.

• **Comment #3.** Patients who were diagnosed cancer more than 1 year after CABG surgery are no meaning to this study. They should be deleted.

The authors respectfully disagree with the reviewer’s assertion that cancers diagnosed more than 1 year after CABG surgery should be deleted from the manuscript. The point in the natural history of disease where an immunosuppressive event may have an impact on outcome or progression is unknown. As stated in the discussion, the authors do agree that evidence of progression for cancers diagnosed within a shorter timeframe of surgery would serve as a more compelling argument supporting the thesis. However, as there are too few events to draw any definitive conclusions regarding the observed temporal association and where in the natural disease process this occurs, the authors believe it is important to present all outcomes data.

**OTHER MINOR REVISIONS:**
Other minor revisions have been made on pages