Jin-Lei Wang,
Director, Editorial Office
Baishideng Publishing Group Co., Limited

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Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 8264-revised.doc).

Title: Competing risks of death in younger and older postmenopausal breast cancer patients

Authors: Judy-Anne W Chapman, Kathleen I Pritchard, Paul E Goss, James N Ingle, Hyman B Muss, Susan F Dent, Ted A Vandenberg, Brian Findlay, Karen A Gelmon, Carolyn F Wilson, Lois E Shepherd, Michael N Pollak

Name of Journal: *World Journal of Clinical Oncology*

ESPS Manuscript NO: 8264

Thank you for the opportunity to revise the manuscript. Review comments were helpful in clarifying the presentations. Please find below interlaced responses to all the review questions, which include the text inserted into the manuscript.

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated per the Editor's directions.

2 Revision has been made according to the suggestions of the reviewers

(1) **Reviewer 1** had no requested changes.

(2) **Reviewer 2**

Patients >70 years of age are likely to die from OC have as these patients have associated comorbidity. Majority of these patients have low risk disease that is why minimum adjuvant treatment is given to them to avoid toxicity. Increasing BMI is also a manifestation of associated comorbidity and comorbidities increase with age.

1. The author has not justified the tittle "Review of competing risks of death" without pointing out the risk factors.
   Response: The title has been clarified with deletion of the words "Review of".

2. Postmenopausal or age >70 years: title is postmenopausal patients but then author sub grouped these patients are likely to die from OC.
   Response: The requested delineation of two classifications for postmenopausal women has been made in the title:

   "Competing risks of death in younger and older postmenopausal breast cancer patients"

   This increases the word count to 12, which we hope is alright as it answers a review request.

3. Age, tumour size, nodal status, number of positive nodes, and hormone receptor status are standard risk factors for patients with breast cancer. There is nothing new in it.
   Response: This investigation is a secondary use of a breast cancer trial database so the data collected were for factors which are thought to be standard prognostic risk factors for patients with breast cancer. However, we examine whether these factors may be relevant for both breast cancer and other cause mortality, and find that there is differential association of baseline factors and type of death. Age and higher BMI are associated with other cause mortality, while T status, nodal involvement and hormone receptor status are associated with breast cancer.

   The Discussion has been augmented in the Discussion Section on page 15 of the revised manuscript: "This study represents a secondary use of a breast cancer trial database. We examined whether prognostic risk factors similarly impacted both BrCa and OC, and found that there was differential association of baseline factors and type of death. Age and higher BMI were associated with OC mortality, while T status, nodal involvement and hormone receptor status were associated with BrCa mortality. Adjuvant chemotherapy was neither mandated nor prohibited;

33% of patients received adjuvant chemotherapy (Pritchard, et al[10]). However, in this trial, age was not associated with BrCa death, but OC mortality."

As well, the summary at the end of the last paragraph of the Discussion on page 17 of the revised manuscript has been augmented to emphasize the new elements: "In summary, the progress for earlier detection and improved management of breast cancer means that women with early breast cancer will increasingly face joint mortality risks of other chronic diseases. This situation raises the opportunity for a new paradigm of simultaneously targeting several chronic diseases, or at least assessing the joint risks of mortality, for a better understanding of predisposition of patients to mortality other than breast cancer. MA.14 was an early trial of the insulin pathway targeted therapy, OCT, which conceptually may have affected both BrCa and OC mortality, so was used here to demonstrate analyses that might be considered for the new assessment framework. The current work is offered as a proof of principle to demonstrate the relevance of collecting detailed cause-specific mortality data and factors which may be associated with non-breast cancer death."

The Editor's requested "Core tip" is provided on page 4 of the revised manuscript to emphasize the most innovative and important points. "With earlier detection and improved therapies, patients with early breast cancer simultaneously face multiple health risks; 54% of women >70 years at diagnosis died from other causes. Octreotide LAR, an early drug targeting the insulin pathway, might have affected both breast and other cause mortality. We demonstrated a method of jointly assessing the impact of therapy and baseline patient characteristics on multiple causes of death. Older patients with higher BMI experienced more other cause mortality, while women with smaller hormone receptor positive tumours and less lymph node involvement were less likely to die from breast cancer."

4. Older patients (p=0.002) and higher BMI (p=0.01) were associated with more OC mortality. The author should have highlighted the OC of mortality.
   Response: A limitation of using the MA.14 breast cancer trial data is that even with median 9.8 years follow-up, we do not have sufficient counts of other types of death to further refine investigations, delineate attributions. Twenty-four MA.14 patients experienced other malignancies and 31 other causes of death; these two classifications were combined. Prospective collection of death type in larger trial populations, over longer follow-up would be needed to improve interpretation. The current work is offered

as a proof of principle to demonstrate the relevance of collecting detailed cause-specific mortality data.
This limitation has been added to the discussion on page 16 of the revised manuscript:
"There is a limitation in ability to delineate comorbidity with MA.14 data. Eligibility criteria were that patients have no previous or concurrent other malignancy except for carcinoma of the skin, cervix, endometrium, colon, or thyroid adequately treated 5 or more years before study entry, and had no inter-current illness expected to reduce life expectancy to less than 5 years after surgery. The number of non-breast cancer deaths was too few to refine investigations since with a median 9.8 years follow-up, 24 patients experienced other malignancies and 31 other causes of death; the two classifications were combined. Prospective collection of death type in larger trial populations, over longer follow-up would be needed to improve disease-specific interpretation."

5. Associated comorbidity is not analysed.

   Response: As outlined in the response to point 4., there is a limitation in ability to delineate comorbidity with MA.14 data. Eligibility criteria were that patients were to have no previous or concurrent other malignancy except for carcinoma of the skin, cervix, endometrium, colon, or thyroid adequately treated 5 or more years before study entry and to have no inter-current illness expected to reduce life expectancy to less than 5 years from the date of surgery. The first eligibility restriction was provided on page 7 previously, at the end of the first paragraph of the Methods section. The second criteria has been added to the same paragraph (on page 7 of the revised manuscript) as it affects our ability to assess the effects of comorbidity: "Patients were….to have no inter-current illness expected to reduce life expectancy to less than 5 years from the date of surgery."

6. Older patients are usually under treated – many studies are reported in the literature.

   Response: Receipt of adjuvant chemotherapy was neither mandated nor prohibited; 33% of patients received adjuvant chemotherapy (Pritchard, et al[10]). However, in this trial, age was not associated with breast cancer death, but other cause mortality.

   This point has been added to the Discussion section (page 15 in revised manuscript): "Receipt of adjuvant chemotherapy was neither mandated

nor prohibited; 33% of patients received adjuvant chemotherapy (Pritchard, et al[10]). However, in this trial, age was not associated with breast cancer death, but other cause mortality."

7. The discussion is very superficial.
   Response: As indicated above, additional content suggested by the reviewer has been added to the Discussion.

8. What recommendation do author come out from the study?
   Response: With substantively more women now dying from causes other than breast cancer, we recommend that trials and treatment options consider the joint risks that a breast cancer patient faces. The recommendation has been delineated in more detail both in the Discussion Section, the summary, and in the "Core tip".

3 References and typesetting were corrected according to the Editor's directions. I used the suggested links to look for PubMed and DOI references for all articles, providing weblinks to articles which lacked these.

Sincerely yours,

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