Title: The reversal of recurrence hazard rate between ER positive and negative breast cancer patients with axillary lymph node dissection (pathological stage I-III) 3 years after surgery

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Author's response to reviews: see over
Dear the editor:

Thank you for your kind review of our manuscript “Prognostic factors for breast cancer patients with axillary lymph node dissection (pathological stage I-III) and the reversal of recurrence hazard rate between ER positive and negative breast cancer patients after long term survival”.

Regarding ETHICS, this study is a retrospective observational study, and not a trial at all. A retrospective analysis is a study involving data that have already been collected and databased, such as a review of medical records from the past for a specific medical treatment. Therefore, we have understood that this present research was not required the approval of an approximate ethics comities by the Helsinki Declaration (http://www.wma.net/e/policy/b3.htm). However, in the present study, all treatments for breast cancer were undertaken with informed consent and consents were also taken to confirm cancer diagnosis. We have inserted this matter in the Patients and Methods section of the revised manuscript (lines 1-3 in page 5).

As suggested we are hereby sending a revised manuscript that has been altered in response to your comments.

To reviewer 1
Thank you very much for your comment. Regarding to the issues that you pointed, we have resubmitted the revised manuscript that has been altered in response to your comments.

1) We agreed your opinion that the best way to assess the effect of any individual variable on the outcome of breast cancer patients was to divide the patient cohort into different subgroups based on the time points. However, consistent with this, we have already reported this matter recently (Eur J Surg Oncol 2007; 33: 696).

2) In the survival, we did not treat death from any cause as a censoring in overall and
disease free survival. Also, we have changed our emphasis regarding the outcomes from “overall survival” to “disease free survival and annual hazard of recurrence”.

3) As suggested by you, we have deleted the unknown data of ER status. Consequently, we have investigated 742 breast cancer patients.

4) In the present study, we did not include histologic grade in the analysis. Histologic grade is not included in the recent revision of the TNM staging system of breast cancer. One of the main reasons for omitting grade in the staging criteria includes the interaction between tumor size and histologic grade and lack of clear evidence for the role of grade in small tumors (TNM stage pT1 and pT2) as a result of difficulties in comparisons among previous studies because of the variety of follow-up times, grading systems, patient sample, and measured outcomes (JCO 2002; 20: 3628). Moreover, studies that looked only at the smallest tumors (pT1a, pT1b) tended to show somewhat smaller outcome differences between grade 1 and grade 3 than studies that included larger tumors (Eur J Cancer 1999; 35: 908; Cancer 1991; 68:1482). Therefore, we did not include histologic grade in the analysis.

5) As suggested by you, in the revised manuscript, we did not state that the prognosis for ER positive patients was worse than that for ER negative patients 10 years after surgery, in neither curve at 10 years was the ER positive survival lying below that of the ER negative group. According to the two waves (ER negative tumors versus ER positive tumors) of relapse pattern of breast cancer, we have discussed this matter, by looking at the data by Saphner et al. (JCO 1996; 14: 2738), as suggested by reviewer 3.

To reviewer 2
Thank you very much for your valuable comments. Regarding to the issues that you pointed, we have resubmitted the revised manuscript that has been altered in response to your comments.

1) As suggested by you, we have described the prognostic value of hormonal receptors on disease free survival in the revised manuscript. Moreover, we have deleted the unknown data of ER status. Moreover, we could not add the data of PgR status, because we did not have data base large enough to analyze.

2) We have selected the patient series, which of ER status could be investigated. Consequently, we have investigated 742 breast cancer patients. We have stated this matter in the Patients and Methods section. In addition, we have added the information regarding adjuvant hormone therapy, because the data have
demonstrated the importance for understanding the annual hazard of recurrence by estrogen receptor status. In the present study, a special pathological review was not done. Therefore, to avoid confusion, we have changed the sentence to “Number of lymph node metastasis and ER status of the primary tumors were analyzed by staff members of the Department of Pathology at Kyoto University Hospital”.

3) In the Method section, we have described the evaluation of ER in more detail.

4) In the present study, the median follow up time was 5.7 years and conclusions were drawn at 10 and 20 years. As suggested by you, this is a big difference. Therefore, we have not described the 20-year survival rates after operation in the revised manuscript.

5) To establish the interesting point, according to the two waves (ER negative tumors versus ER positive tumors) of relapse pattern of breast cancer, we have discussed this matter, by looking at the data by Saphner et al. (JCO 1996; 14: 2738), as suggested by reviewer 3.

To reviewer 3
Thank you very much for your kind and valuable comments. Regarding to the issues that you pointed, we have resubmitted the revised manuscript that has been altered in response to your comments.

1) As suggested by you, in the revised manuscript, we did not state that the prognosis for ER positive patients was worse than that for ER negative patients 10 years after surgery, in neither curve at 10 years was the ER positive survival lying below that of the ER negative group. Consequently, we have changed the title “The reversal of recurrence hazard rate between ER positive and negative breast cancer patients with axillary lymph node dissection (pathological stage I-III) 3 years after surgery”.

2) As suggested by you, we have reassessed this paper, looking at the data by Saphner et al (JCO 1996; 14: 2738). Saphner et al. showed the annual rate of events in patients with ER positive and negative cancers. Because beyond 10 years hazard had increased statistical errors, we investigated the annual hazard of recurrence until 10 years after operation. Hortobagyi et al. (Proc Am Soc Clin Oncol 1994; 23: 585A) previously reported that the disease-free survival in estrogen receptor (ER) positive and/or progesterone receptor (PgR) positive patients was higher than that in ER/PgR negative patients until 5 years after administration of the state-of-the-art adjuvant therapy, however, the disease-free survivals between these groups was reversed after 5 years. Saphner et al. (JCO 1996; 14: 2738) reported that compared with ER-positive patients, ER negative patients had higher annual hazard of recurrence
until around 3.5 years after surgery, but thereafter lower. In the present study, Figure 3 shows that a positive ER status was associated with a lower hazard of recurrence in the first 2 years after surgery, but a higher hazard of recurrence from years 3 to 10. Moreover, the EBCTCG performed a meta-analysis of systemic treatment of early breast cancer by hormone, cytotoxic, or biologic therapy methods in randomized trials involving 144,939 women (Lancet 2005; 365: 1687). Results from the EBCTCG meta-analysis show a highly significant advantage of 5 years versus 1 to 2 years of tamoxifen with respect to the risk of recurrence (Lancet 2005; 365: 1687). In the present study, in ER-positive cases, between 2 and 4 years after surgery, the hazard of recurrence of patients without adjuvant hormone therapy was higher than the patients with adjuvant hormone therapy. Moreover, the overall survival in ER-positive patients who received adjuvant hormone therapy between 1991 and 2005 was significantly increased significantly compared with that in ER-positive patients who did not receive adjuvant hormone therapy between 1981 and 1989. It is noteworthy that these facts emphasize the importance of adjuvant hormone therapy for ER positive cancer patients beyond 3 years after operation. In addition, the disease-free survival at 10 years after surgery between ER positive and negative patients was reversed. This may be related to the fact that the percentage of number of patients who received adjuvant hormone therapy in ER positive patients between 1980 and 1991 (11/84: 13%) was smaller that between 1991 and 2005 (170/368: 46%), because of reasons including poor understanding of modern treatment for adjuvant chemotherapy, the cost for drugs, and so on. On the other hand, the current recommendation is that adjuvant tamoxifen be discontinued after 5 years in all patients as current standard therapy, because there was a trend toward a worse outcome associated with a longer duration of treatment (J Natl Cancer Inst 1996; 88: 1510). Further analyses may be needed to clarify the optimal duration of adjuvant hormone therapy in operated breast cancer patients. We have discussed this matter in the Discussion section of the revised manuscript.

Thank you very much for your consideration. I am looking forward to your reply, hopefully saying this manuscript is accepted in your journal, BMC cancer.

Sincerely yours,

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