Reviewer’s report

Title: Hot flashes are not predictive for serum concentrations of tamoxifen and its metabolites

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Reviewer: Thomas E Mürdter

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In a retrospective study, Jager et al. investigated the correlation of vasomotor symptoms with plasma levels of tamoxifen and its metabolites in order to evaluate the usefulness of this common side effect of anti-hormone therapy as a surrogate for tamoxifen plasma levels and outcome.

This is an interesting, well planned study and excellently written manuscript. However, the major drawback of this study is its limited number of patients included. The authors need to address this issue; at least, they should discuss this in more detail.

Major Compulsory Revisions:

Abstract:
Page 2 lines 36f: As there are also reports missing significant correlations between hot flashes and outcome (see discussion) this sentence needs to be modified.

Background
Page 3 lines 65: ..., is also a potent inhibitor.... In contrast to norendoxifen with an IC50 in the nanomolar range, endoxifen is only a weak aromatase inhibitor with an IC50 of 10µM. Please correct.

Page 3 line 81f: This sentence does not adequately reflect the results of the referenced study. Cuzick et al. used a subset of the ATAC trial to analyze the correlation between treatment induced endocrine symptoms (hot flashes and arthralgia) and treatment outcome in a total of 1997 patients under tamoxifen treatment. Whereas vasomotor symptoms alone were not significantly correlated to survival (HR 0.82 (0.63–1.05), p=0.12) there was a significant correlation between joint pain and survival (0.55 (0.39–0.78) 0.001) which was also present in the subgroup of patients receiving anastrozole. Based on this, one may question why the authors did not include joint pain in their questionnaire. This should be addressed to in the discussion.

Patients and Methods
Page 4 line 96: Please state that both, pre- and postmenopausal patients were included in the study. This is of importance as estradiol plasma levels are included in the analysis.

Page 4 lines 98f: As this study is a retrospective study using a rather complex
system to evaluate subjective data, time lap between blood sampling and filing the questionnaire may influence the validity of data obtained. Therefore, please give more detailed information on the time schedule.

Are there any data available on reproducibility of the evaluation of vasomotor symptoms, e.g. repeated filing of the questionnaire?

Results
Page 7 line 181: As both, pre- and postmenopausal women were included in this study the high variability of E2 levels is not surprising. Moreover, correlation of E2 levels and hot flashes should be performed after stratification according to menopausal status (Table 3A and 3B). Results in tables S1a and 1b reflect this drop in E2 plasma levels during menopause.

Discussion
Page 8 lines 228f: Again, for this evaluation patients should be stratified according to menopausal status. Is there any difference in the two groups of patients (w and w/o hot flashes prior to tamoxifen)? According to Djorgoshoo et al (Menopause 2009) who investigated more than 5,000 breast cancer patients, frequency of hot flashes is highest for patients at the age 45-55 (the age of menopause).

Page 9 lines 237: Please add a short discussion on sample size.

Minor Essential Revisions:
Page 3 line 71: … by cytochrome P450 (CYP) enzyme. Please include abbreviation
Page 8 line 210: …Lorizio et al have suggested…
Page 16 Table 3: Please include (all patients) or (n=115) in the heading

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests