## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Ethnic differences in cardiovascular morbidity and mortality among breast cancer patients in The Netherlands: a register-based cohort study. |
| **AUTHORS** | Deen, Laura; Buddeke, Josefien; Vaartjes, Ilonca; Bots, Michiel; Nørredam, Marie; Agyemang, Charles |

## VERSION 1 – REVIEW

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| **REVIEWER** | Dr. Nadia Obi<br>Institute for Medical Biometry and Epidemiology, University Medical Center Hamburg-Eppendorf, Martinistr. 52, 20246 Hamburg, Germany |
| **REVIEW RETURNED** | 14-Feb-2018 |

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| **GENERAL COMMENTS** | **Reviewer - Comments to Deen et al. Ethnic differences in cardiovascular morbidity and mortality among breast cancer patients in the Netherlands…**<br><br>This register-based study by Deen et al. is a highly interesting contribution to the emerging fields of migrant health in Europe as well as cardiovascular morbidity in breast cancer survivors. The authors showed differences in CVD morbidity and mortality for various ethnic groups living in The Netherlands compared to the autochthone Dutch population.<br><br>The manuscript is well written, and the introduction and discussion are well developed. References are appropriate.<br><br>The main obstacle seems to be the lacking ability to explain differential findings by potential causing factors, such as stage, therapies, relapse, SES, and life-style including screening, which were not available. Thus, the paper remains a little superficial and clearly demonstrates the necessity of targeted epidemiological studies.<br><br>However, since this kind of data is scarce in Europe, I recommend the following revision.<br><br>**Major comments**<br><br>**Statistical methods:**<br>1. I suggest calculating competing risk models as state of the |

art, which account for death other than CVD. Death due to breast cancer is the major cause of death in the early years after diagnosis and seems to vary among the groups addressed (with 66% highest in Antilleans). In the figure by Bradshaw et al. (ref. 3, see next page), cause-specific HR and subdistribution HR did make a difference from statistically significant to non-significant HR.

**Discussion**

2. Interpretation of results: I do not fully agree with the authors' interpretation of non-significant results for Turkish and Antillean women (page 8, key findings). Because table 2 and 3 show almost no differences in adjusted estimates and CIs, I assume that the power is low for both the Antilleans and the Turkish. However, risk elevations are similarly evident in both groups.
3. Therefore, I suggest a modified text in line 186 – 188: "…,Surinamese and Turkish women had a higher …, though in Turkish women the HR for CVD admission was statistically non-significant.
4. In line 191, I suggest to distinguish between Moroccans and Antilleans and add a half-sentence for Antillean women: "For Moroccan women the risk of a cardiovascular event did not differ from Dutch women with breast cancer, whereas for Antillean women the risk of any cardiovascular event was non-significantly higher."
5. For Antilleans, the result should be modified accordingly in the Abstract.
6. It would be interesting whether the discussed surveys on risk factors and disease incidence (refs. 28-31) hold for the Antilleans as well, since they probably resemble the Surinamese women with African background and other Caribbean women in UK.
7. In lines 255-258 the sentence beginning with "In addition, a study from the US,…(32)" is about African Americans, who were not referred to in the paper. It seems therefore dispensable, unless the authors would state a specific link to the Antillean and Surinamese women.
8. Could the results for Indonesian women be due to censoring caused by a drift of breast cancer patients who re-migrated to the country of origin? Please, include a statement on this in the discussion.

**Minor comments:**

Page 6, line 132-133: ICD-codes on seem not to be ICD-10$^{th}$ revision. Please provide ICD-10 codes

Page 7, line 145:

Please, be more specific on type of breast cancer and adjustment of age. Did you use a continuous variable or categorized as in table 1? Age category 45-59 years would have been too rough, since it mixes pre-and postmenopausal women, who may have very different risk factor profiles and tumor characteristics.

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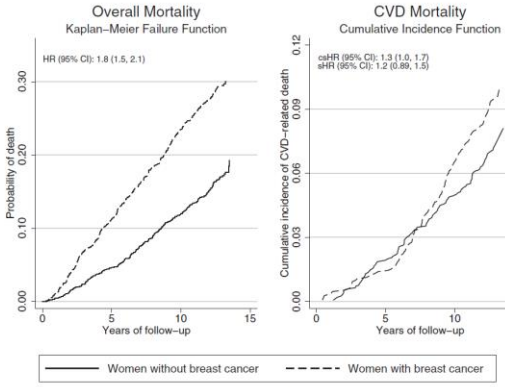
| | A concern is that models are largely unadjusted. In this context, why was marital status not included in the models?<br><br>Line 146: Please, indicate how Cox-PH assumptions were checked and for which covariates.<br><br>Table 1:<br><br>Follow-up time: please, give also min and max.<br><br>Median follow-up time varied, and was shortest in ethnic groups with more adverse outcomes. Can you explain or comment on this finding? |
| | Figure from Bradshaw et al. 2016 (see point 1)<br><br>  <br><br><br>**FIGURE.** Unadjusted Kaplan–Meier failure curves and adjusted HR for overall mortality (*first panel*) and cumulative incidence function, csHR and sHR for CVD-related mortality (*second panel*) among a population-based sample of breast cancer survivors and age-matched women without breast cancer. The Long Island Breast Cancer Study, 1996–2009. HRs adjusted for age at reference date (age at diagnosis for breast cancer survivors and date of identification for women without breast cancer), menopausal status, previous use of hormone replacement therapy, smoking history, average lifetime alcohol intake, body mass index the year before reference date, income, education, and history of the following cardiovascular disease risk factors: diabetes, myocardial infarction, hypertension, dyslipidemia, or stroke. Model for overall mortality included interaction between follow-up time and history of hypertension and myocardial infarction and models for CVD mortality included interaction between follow-up time and history of diabetes. csHR indicates cause-specific hazard ratio. |
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| **REVIEWER** | Michael S. Simon<br>Karmanos Cancer Institute, at Wayne State University, USA |
| **REVIEW RETURNED** | 26-Feb-2018 |

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| **GENERAL COMMENTS** | I am not sure why the authors included women with DCIS in the study sample. Given that cancer treatment may have an impact on post breast cancer cardio-toxicity, I feel that it is imperative to separate out women with DCIS in that the type of treatment for women with DCIS is vastly different (i.e. no radio-toxic chemotherapy). The other option is to do a sensitivity analysis excluding women with DCIS from the analysis to determine if it makes a difference in the results. |

**VERSION 1 – AUTHOR RESPONSE**

Dear editor,

Thank you for the invitation to submit a revised manuscript. We have carefully considered the feedback and we have made a number of revisions to the paper in light of the constructive comments from the reviewers. These revisions are summarised in the table below for your convenience.

| Editorial Requirements | **Our response/revisions** |
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| Please revise the Strengths and Limitations section (after the abstract) to focus on the methodological strengths and limitations of your study rather than summarizing the results | Thank you for pointing this out. We have revised the Strengths and Limitations section so it focusses more on the methodological strengths and limitation of the study. Please see page 3, lines 52-53. |
| Please provide more information about the data used in your study. For example, please state if the data was anonymised and if this is publicly available. | We have elaborated on the information regarding the data in the method section. Please see page 6, lines 118-123. |

| **Reviewer 1** | **Our response/revisions** |
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| This register-based study by Deen et al. is a highly interesting contribution to the emerging fields of migrant health in Europe as well as cardiovascular morbidity in breast cancer survivors. The authors showed differences in CVD morbidity and mortality for various ethnic groups living in The Netherlands compared to the autochthone Dutch population.<br>The manuscript is well written, and the introduction and discussion are well developed. References are appropriate.<br>The main obstacle seems to be the lacking ability to explain differential findings by potential causing factors, such as stage, therapies, relapse, SES, and life-style including screening, which were not available. Thus, the paper remains a little superficial and clearly demonstrates the necessity of targeted epidemiological studies.<br>However, since this kind of data is scarce in Europe, I recommend the following revision. | Thank you for your positive and constructive feedback.<br>We have taking your suggested revisions into account. Please see below the responses to each comment. |
| **Major Comments** | |
| 1. I suggest calculating competing risk models as state of the art, which account for death other than CVD. Death due to breast cancer is the major cause of death in the early years after diagnosis and seems to vary among the groups addressed (with 66% highest in Antilleans). In the figure by Bradshaw et al. (ref. 3, see next page), cause-specific HR and subdistribution HR did make a difference from statistically significant to non-significant HR. | Thank you for this interesting comment.<br><br>Taking into account your suggestion we have looked further into competing risk from death other than CVD. For most causes the numbers were too low (please see table 1 in the article). For breast cancer mortality the results showed that Turkish women had a lower breast cancer mortality, but since this was not the case for Surinamese and Antillean women, and Indonesian women also had a relative low breast |

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| | cancer mortality but not a higher CVD risk, we do not think this can explain the higher CVD risk among the Turkish and the Surinamese women in our study.<br><br>Regarding death due to cancers other than breast cancer Indonesians had a slightly lower risk and Surinamese women had a lower risk. However, this is still no full explanation as the Surinamese are much younger than the Dutch (and we corrected for age in the Cox proportional hazard analyses), but numbers were too low to stratify for age. Numbers for the Turks, Moroccans and Antilleans were too low to do analyses on death due to cancers other than breast cancer. |
| 2. Interpretation of results: I do not fully agree with the authors' interpretation of nonsignificant results for Turkish and Antillean women (page 8, key findings). Because table 2 and 3 show almost no differences in adjusted estimates and CIs, I assume that the power is low for both the Antilleans and the Turkish. However, risk elevations are similarly evident in both groups.<br><br>3. Therefore, I suggest a modified text in line 186 – 188: "…,Surinamese and Turkish women had a higher …, though in Turkish women the HR for CVD admission was statistically nonsignificant. | Thank you for this helpful comment and for pointing this out.<br><br>We agree that table 2 and 3 show almost no differences in risk elevations and that the non-significant results might be due to low power and we have therefore clarified this in the section with the key findings according to your suggestions. Please see page 9, lines 198-200. |
| 4. In line 191, I suggest to distinguish between Moroccans and Antilleans and add a half sentence for Antillean women: "For Moroccan women the risk of a cardiovascular event did not differ from Dutch women with breast cancer, whereas for Antillean women the risk of any cardiovascular event was non-significantly higher." | We have revised the section with the key findings according to your suggestions and in the result section. Please see page 9, line 203-205 and page 8, line 174-176. |
| 5. For Antilleans, the result should be modified accordingly in the Abstract. | We have modified this in the Abstract. Please see page 2, line 43-45. |
| 6. It would be interesting whether the discussed surveys on risk factors and disease incidence (refs. 28-31) hold for the Antilleans as well, since they probably resemble the Surinamese women with African background and other Caribbean women in UK. | Thank you for this helpful suggestion. We have included a short discussion regarding CVD risk factors and Antilleans.<br><br>Please see page 12, line 268-273. |
| 7. In lines 255-258 the sentence beginning with "In addition, a study from the US,…(32)" is about African Americans, who were not referred to in the paper. It seems therefore dispensable, unless the authors would state a specific link to the | We have now included a statement that links it to the Surinamese women. Please see page 12, line 276-278. |

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| Antillean and Surinamese women. | |
| 8. Could the results for Indonesian women be due to censoring caused by a drift of breast cancer patients who re-migrated to the country of origin? Please, include a statement on this in the discussion. | Thank you for this comment. Evidence from Denmark does not support the hypothesis of remigration bias (*European Journal of Public Health*, 2015 Feb;25(1):84-9), and therefore we do not consider remigration of women with breast cancer as a potential explanation for the findings for Indonesian women. |
| **Minor comments** | |
| Page 6, line 132-133: ICD-codes on seem not to be ICD-10th revision. Please provide ICD-10 codes. | Thank you for this point. The ICD-codes is ICD-9$^{th}$ revisions. This has been corrected accordingly. Please see page 6, line 135. |
| Page 7, line 145:<br><br>Please, be more specific on type of breast cancer and adjustment of age. Did you use a continuous variable or categorized as in table 1? Age category 45-59 years would have been too rough, since it mixes pre-and postmenopausal women, who may have very different risk factor profiles and tumor characteristics.<br><br>A concern is that models are largely unadjusted. In this context, why was marital status not included in the models? | The only information we have about breast cancer is breast cancer type; *in situ (ICD-9; 223)* and *invasive* (ICD-9: 174). This is described in the method section page 5, line 112-113. As discussed in the strength and limitation section, this is a limitation of the study as it would be very informative to have information about type of treatment.<br><br>Adjustments are made with the continuous age variable. This is clarified in the method section, page 7, line 149.<br><br>We did not include marital stage since it was not a confounder in forward (or backward) selection. Marital stage was not significant and the HRs did not change (<1%) when adding marital stage. |
| Line 146: Please, indicate how Cox-PH assumptions were checked and for which covariates. | We tested the assumption of proportionality of the functional hazards by plotting the log minus log functions. This is now added to the method section. Please see 7, line 150-151. |
| Table 1:<br><br>Follow-up time: please, give also min and max.<br><br>Median follow-up time varied, and was shortest in ethnic groups with more adverse outcomes. Can you explain or comment on this finding? | Thank you for this comment.<br><br>We consider the IQR to be a better measure to describe the distribution, and we have therefore kept this instead of providing the min and max. The follow up time was based on follow-up time until death (2012). However, we think it is more precise to provide follow-up time based on the composite endpoint. Therefore the follow-up provided in table 1 in the revised manuscript is the follow up time based on the composite |

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| | endpoint.<br><br>Regarding the varying median follow-up times, we have modified the description of follow up time in the result section. Please see page 7, line 160-161. |

| **Reviewer 2** | **Our response/revisions** |
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| I am not sure why the authors included women with DCIS in the study sample. Given that cancer treatment may have an impact on post breast cancer cardio-toxicity, I feel that it is imperative to separate out women with DCIS in that the type of treatment for women with DCIS is vastly different (i.e. no radio-toxic chemotherapy). The other option is to do a sensitivity analysis excluding women with DCIS from the analysis to determine if it makes a difference in the results. | Thank you for pointing this out.<br><br>We have considered your comment and run additional analyses without patients with *in situ* breast cancer and this did not change the interpretation of the results. HRs in Table 2-4 shifted with 2-5 hundredths. Based on this and that the numbers are not that large and leaving them out will decrease our sample size even more, we have decided to keep them in the analyses.<br><br>We have added a line regarding results of the sensitivity analysis in the result section. Please see page 8, line 187-191. |

**VERSION 2 – REVIEW**

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| **REVIEWER** | Nadia Obi<br>Institute for Medical Biometry and Epidemiology, University Medical Center Hamburg-Eppendorf, Martinistr. 52, 20246 Hamburg, Germany |
| **REVIEW RETURNED** | 26-Apr-2018 |

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| **GENERAL COMMENTS** | All issues were satisfiably addressed in the revision. Only, in Table 1 medians for follow-up time were reduced, and IQR is now missing for Surinamese. |

**VERSION 2 – AUTHOR RESPONSE**

Thank you very much for the opportunity to submit a revised manuscript. According to the reviewer comment we have made a minor revision to the paper. Please see below.

Reviewer: 1

All issues were satisfiably addressed in the revision. Only, in Table 1 medians for follow-up time were reduced, and IQR is now missing for Surinamese.

Our respons

Thank you for pointing this out. We have added the IQR for the Surinamese in table 1. Please see page 22.

The follow-up times were reduced as we changed them from follow-up time to death to follow-up time to composite endpoint (i.e. admission for CVD or death) since we think this is more precise.