

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Trends in the risk of cardiovascular disease in women with breast cancer in a Dutch nationwide cohort study
AUTHORS	Buddeke, Josefien; Gernaat, Sofie; Bots, Michael; van den Bongard, Desire; Grobbee, Diederick; Vaartjes, Ilonca; Verkooijen, Helena

VERSION 1 - REVIEW

REVIEWER	Tania Marin Flinders University, Australia
REVIEW RETURNED	24-Mar-2018

GENERAL COMMENTS	<p>This is a generally well written and informative manuscript that adds important empirical information to the field of cardiotoxicity. As such, I would recommend that you add cardiotoxicity to your keywords and your abstract.</p> <p>General comments</p> <p>Did you receive ethical approval to conduct the review of medical records?</p> <p>Do you have a CONSORT, STROBE or PRISMA checklist you can include as a figure?</p> <p>Tables - please report both n and % and keep constant number of decimal places even if 0.0</p> <p>In text reference citations should be outside (after) the punctuation mark,</p> <p>Line 24 pg 4 - I don't think this has been proven for all breast cancer treatments. Maybe limit this statement to the treatments identified in the papers cited.</p> <p>Line 30 pg 4 - the word 'many' is not a quantifiable amount,</p> <p>Line 33 pg 6 - first word should be 'ninety' not 90</p> <p>Line 38 pg 7 - please quantify 'most'</p> <p>Line 9 pg 11 - remove one of the words 'patients'</p> <p>Line 45 pg 11 - patients should be patient's</p> <p>Line 28 pg 13 - change 'percentage' to 'percent'</p> <p>Line 8 pg 14 - consider adding a word after the comma to complete the sentence</p> <p>Line 34 pg 14 - change 'undergo previously' to 'undergone previous'</p>
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REVIEWER	Na-Jin Park University of Pittsburgh, USA
REVIEW RETURNED	11-Apr-2018

GENERAL COMMENTS

1. The reviewer has found a major confusion on methods that needs to be addressed for better clarity of this manuscript: different follow-up years and data sources for mortality and hospitalization from cardiovascular disease (CVD). The different follow-up years were due to different data sources and availability (Dec. 2015 for CVD death by Cause of Death Registry and Dec. 2010 for CVD hospitalization by Hospital Discharge Register) than any specific theoretical reason. That needs to be clearly addressed from the beginning of the Methods section.

- For those who were admitted for BC in 2008-2010 (21.2% of BC cases in Table 1), there are only 2 or less years follow-up for CVD hospitalization vs. 7 years for CVD mortality, leading to lowest proportions of outcomes. With various timepoints for risks of CVD mortality and hospitalization, Table 1 alone is confusing and misleading. If authors intended to present cumulative risks over years of study period in Table 1, please say so.
- To fix misleading Table 1, authors may consider devising into two separate tables for CVD mortality (as well as breast cancer [BC] mortality) and CVD hospitalization. More detailed information such as timepoints would be very helpful.
- This may be the reason why different timepoints were used to calculate absolute risks for CVD mortality vs. CVD hospitalization (i.e., 5, 7, and 10 years vs. 1, 3, and 5 years), which was not clearly indicated in page 7 under Methods. Given that inconsistency in timepoints confusing, it will be better with two separate outcomes of CVD mortality and CVD hospitalization to compare time trends and between groups.

2. The Results section needs reorganization. Titles for tables and figures are confusing. Is Table 2 about 5-year CVD mortality risk? What did you find about CVD hospitalization by age? Older women with BC, as well as older female with no BC, would be much susceptible to CVD hospitalization. Why not include the comparison to general population for CVD hospitalization? CVD hospitalization is one of primary outcome, and the manuscript seems incomplete without those data. If possible, the reviewer would like to see detailed trends in detailed conditions (e.g., hypertension, pulmonary embolism) for hospitalization in BC patients and in the comparison to general population. That information is extremely important in guiding clinical BC survivorship care.

3. US readers may need further information on that admission for BC is the standard procedure for BC patients in the Netherlands. Or is that for surgical removal of BC? If so, operable BC is something to describe the study population?

4. Please revise the Abstract accordingly. Particularly, statements in the Conclusions are not clear (e.g., with patients having the lowest risk??). The reviewer did not think that a total CVD hospitalization over study period, 19.7%, in BC patients was a major finding by reading this manuscript body. Authors need to make a directional decision to make this paper consistent and logical.

5. The reviewer liked the Discussion. Additional data and cleaning/organization would make this paper more informative.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

This is a generally well written and informative manuscript that adds important empirical information to the field of cardiotoxicity. As such, I would recommend that you add cardiotoxicity to your keywords and your abstract.

Response: Thank you. We added cardiotoxicity as a keyword

General comments:

1. Did you receive ethical approval to conduct the review of medical records?

Response: For this study no approval of the ethical committee is necessary. The analyses are performed in a secured environment of Statistics Netherlands and are compliant with the privacy legislation in The Netherlands.

We added this information to the manuscript:

“Linkage of data from the different registries was performed in a secured environment of Statistics Netherlands and complies with the privacy legislation in The Netherlands and with the Declaration of Helsinki (Reitsma et al. 2003). For this type of study no approval of the ethics committee is necessary.”

2. Do you have a CONSORT, STROBE or PRISMA checklist you can include as a figure?

Response: We added the STROBE checklist as Supplement B to the manuscript as we already had 6 tables and figures in the main manuscript.

3. Tables - please report both n and % and keep constant number of decimal places even if 0.0

Response: We changed the numbers in the Tables accordingly.

4. In text reference citations should be outside (after) the punctuation mark.

Response: We moved the references to after the punctuation mark.

5. Line 24 pg 4 - I don't think this has been proven for all breast cancer treatments. Maybe limit this statement to the treatments identified in the papers cited.

Response: We rewrote this sentence into:

“Previous studies reported associations between some breast cancer treatments and the development of CVD, including anthracycline-based chemotherapy,⁶⁻⁷ trastuzumab,⁸ and radiotherapy treatments.^{9,10}”

6. Line 30 pg 4 - the word 'many' is not a quantifiable amount,

Response: We rewrote this sentence into:

“In the last decade, efforts have increasingly been made to reduce the risk of CVD induced by breast cancer treatments.”

7. Line 33 pg 6 - first word should be 'ninety' not 90

Response: We changed '90' to 'ninety'.

8. Line 38 pg 7 - please quantify 'most'

Response: We added the percentage between brackets.

9. Line 9 pg 11 - remove one of the words 'patients'

Response: We removed the second word 'patients'.

10. Line 45 pg 11 - patients should be patient's

Response: We rewrote this sentence.

"Breast cancer diagnosis was confirmed in all patients (Supplementary Table A)."

11. Line 28 pg 13 - change 'percentage' to 'percent'

Response: We changed 'percentage' to 'percent'.

12. Line 8 pg 14 - consider adding a word after the comma to complete the sentence.

Response: We added a word to complete the sentence and rewrote the following sentence:

"Pulmonary embolism explained 15% of the increased number of CVD hospitalizations and is often caused by venous thromboembolism.³⁸ This increase may be related to the thrombotic effect of the selective estrogen receptor modulator tamoxifen.^{39,40}

13. Line 34 pg 14 - change 'undergo previously' to 'undergone previous'

Response: We changed these words accordingly. We want to thank the reviewers for these instructive feedback.

Reviewer: 2

1. The reviewer has found a major confusion on methods that needs to be addressed for better clarity of this manuscript: different follow-up years and data sources for mortality and hospitalization from cardiovascular disease (CVD). The different follow-up years were due to different data sources and availability (Dec. 2015 for CVD death by Cause of Death Registry and Dec. 2010 for CVD hospitalization by Hospital Discharge Register) than any specific theoretical reason. That needs to be clearly addressed from the beginning of the Methods section.

Response: We relocated the sentence "HDR data was available from 1995 to 2010, and data from PR and Cause of Death Registry were available until 2015" to the beginning of the Method section.

2. For those who were admitted for BC in 2008-2010 (21.2% of BC cases in Table 1), there are only 2 or less years follow-up for CVD hospitalization vs. 7 years for CVD mortality, leading to lowest proportions of outcomes. With various timepoints for risks of CVD mortality and hospitalization, Table 1 alone is confusing and misleading. If authors intended to present cumulative risks over years of study period in Table 1, please say so.

3. To fix misleading Table 1, authors may consider devising into two separate tables for CVD mortality (as well as breast cancer [BC] mortality) and CVD hospitalization. More detailed information such as timepoints would be very helpful. This may be the reason why different timepoints were used to calculate absolute risks for CVD mortality vs. CVD hospitalization (i.e., 5, 7, and 10 years vs. 1, 3, and 5 years), which was not clearly indicated in page 7 under Methods. Given that inconsistency in

timepoints confusing, it will be better with two separate outcomes of CVD mortality and CVD hospitalization to compare time trends and between groups.

Response 2 and 3:

We added this explanation to Table 1:

“† Data on hospital admissions was available until 2010. Absolute risks of hospitalization for CVD decrease with more recent calendar period”

Thank you. We separated the information presented in Table 1 into two tables (Table 1 and Table 2).

Table 1 presents data on cardiovascular admission. In a footnote under Table 1 we added “Data on hospital admissions was available until 2010. Absolute risks of hospitalization for CVD decrease with more recent calendar period”

(new) Table 2 presents data on cardiovascular mortality. In a footnote under the Table we added “Data on cause of death was available until 2015. Absolute risks of death from CVD decrease with more recent calendar period”

We added this explanation in the Method section:

“Shorter time periods for CVD hospitalization were chosen because it was expected that possible cardiotoxic effects of breast cancer treatments may have a direct effect on CVD hospitalization but less on CVD mortality.”

4. The Results section needs reorganization. Titles for tables and figures are confusing.

Is Table 2 about 5-year CVD mortality risk?

Response: Thank you. Table 2 (in the revised manuscript Table 3) is indeed about 5-year CVD mortality. We changed the caption into:

“Table 3. Relative risk of death from cardiovascular disease and breast cancer within five years after breast cancer admission among 163,881 breast cancer patients”

In addition, the names of the columns were changes into “Five-year CVD mortality” and “Five-year breast cancer mortality”.

Titles of the figures are changed into:

Figure 1. Trends in age-standardized 5-, 7- and 10-year cardiovascular disease mortality per 1,000 patients with breast cancer and women from the general population. Relative reduction (%) shows the relative change in cardiovascular mortality compared to reference year 1996.

Figure 2. Trends in 5- and 10-year cardiovascular disease mortality rates in breast cancer patients per 10,000 person-years by age. Relative reduction (%) shows the relative decline in cardiovascular mortality rates compared to reference year 1996.

Figure 3. Trends in 1-, 3- and 5-year age-standardized number of cardiovascular disease hospitalizations per 1,000 breast cancer patients. Relative reduction (%) shows the relative decline in cardiovascular mortality rates compared to reference year 1996.

5. What did you find about CVD hospitalization by age? Older women with BC, as well as older female with no BC, would be much susceptible to CVD hospitalization.

Response: We added the sentence “Seventy percent of the breast cancer patients with a hospital admission for CVD during follow-up were 60 years or older at time of breast cancer treatment (Table 1).” to the first paragraph of the Results section. Indeed, older women are more susceptible to CVD hospitalization than younger women, irrespective of breast cancer status. We did not look into CVD hospitalization by age in detail but instead age-standardized the trends to account for the differences in age distribution over time.

6. Why not include the comparison to general population for CVD hospitalization? CVD hospitalization is one of primary outcome, and the manuscript seems incomplete without those data.

Response: We agree with the reviewer that it would be interesting to compare CVD hospitalization to the general population. However, unfortunately, those data were only available for CVD mortality and not for CVD hospitalization. We hope the reviewer still feels the results of the study are valuable and adds important empirical information to the research field.

7. If possible, the reviewer would like to see detailed trends in detailed conditions (e.g., hypertension, pulmonary embolism) for hospitalization in BC patients and in the comparison to general population. That information is extremely important in guiding clinical BC survivorship care.

Response: We agree with the reviewer that trends in specific conditions are important in guiding care for breast cancer survivors.

We included the next paragraph in the Results section:

“The absolute risk of hospitalization for CVD in the first year after breast cancer increased from 54 per 1,000 women in 1996 to 67 per 1,000 women in 2009 (increase of 13 hospital admissions per 1,000 breast cancer patients, Figure 3). The increase in hospitalization for CVD mainly due to an increase in hospitalizations for high blood pressure (from 6.7 in 1996 to 11.0 hospitalizations in 2009 per 1,000 breast cancer patients), pulmonary embolism (from 4.4 in 1996 to 6.6 hospitalizations in 2009 per 1,000 breast cancer patients), rheumatic heart disease/valve disease (from 1.4 in 1996 to 2.5 hospitalizations in 2009 per 1,000 breast cancer patients) and by admission for heart failure (from 4.7 in 1996 to 5.6 hospitalizations in 2009 per 1,000 breast cancer patients).”

As pointed out in 6) those data were, unfortunately, unavailable for the general population. However, we believe that these trends over time in breast cancer survivors only also represents valuable information and context for further study.

8. US readers may need further information on that admission for BC is the standard procedure for BC patients in the Netherlands. Or is that for surgical removal of BC? If so, operable BC is something to describe the study population?

Response: Thank you for pointing this out. Surgery is standard procedure in the Netherlands. Only a very small part of the patients will not have surgery and therefore may not have a hospital admission for breast cancer. A previous study showed that breast cancer patients under 80 years without metastatic breast cancer, 1.3% refused surgery (Verkooijen, 2005). Together with patients who refused surgery due to metastases at time of diagnosis and those who refused treatment due to many comorbid conditions, the authors estimate that we missed less than 5% percent of the patients with breast cancer.

We added next sentences to the ‘study population’ section:

“For the present study, women with a first hospital admission for in situ (ICD-9: 233, ICD-10: D05) and invasive breast cancer (ICD-9: 174, ICD-10: C50) between 1996 and 2010 were identified. Surgical removal is standard procedure for breast cancer treatment in the Netherlands. We estimate that less

than five percent of the patients with breast cancer were missed due to refusal of surgery (Verkooijen, 2005).”

9. Please revise the Abstract accordingly. Particularly, statements in the Conclusions are not clear (e.g., with patients having the lowest risk??).

10. The reviewer did not think that a total CVD hospitalization over study period, 19.7%, in BC patients was a major finding by reading this manuscript body. Authors need to make a directional decision to make this paper consistent and logical.

Response to comment 9) and 10):

We revised the abstract accordingly. We rewrote the Conclusion to clarify that breast cancer patients have a lower risk of CVD mortality compared to women of the general population. In addition, we removed the finding about 19.7% from the abstract but instead stated that the increase in CVD admission over time was largely explained by an increase in hospital admission for hypertension, pulmonary embolism, rheumatoid heart/valve disease and heart failure.

11. The reviewer liked the Discussion. Additional data and cleaning/organization would make this paper more informative.

Response: Thank you. We changed the manuscript according to reviewer’s comments and we hope the reviewers think the manuscript is informative and now structured in a more logical way. We want to thank the reviewers for their constructive feedback.

VERSION 2 – REVIEW

REVIEWER	Tania Marin Flinders University Australia
REVIEW RETURNED	04-Jul-2018

GENERAL COMMENTS	<p>I find this an interesting read and recognise that you have incorporated previous reviewer comments. This paper will add important information to the research on CVD risk in women with breast cancer and the outcome of CVDs in this cohort.</p> <p>1. You report the relative risk of CVD mortality for the breast cancer cohort between 1996 and 2010. I would be interested to know the relative risk of CVD mortality between the breast cancer cohort and the general population. Did it change from 1996 to 2010?</p> <p>2. What CVD risk factors did you include? In your limitations you only mention age; however, you have described others in your methods.</p> <p>3. Why do you propose "The absolute risk of death from CVD is lower in women with breast cancer compared to women from the general population"? I don't think you have stated this clearly.</p> <p>Page 4 line 36/37. There is no evidence to show that the guideline recommendations have been integrated into standard care. Unless you have some evidence of this I would rephrase this from "standard of care" to "recommended care" and reference the guidelines. Additionally, did you find any literature that spoke about</p>
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	<p>risk factor assessment or monitoring throughout chemotherapy? You could read up on this and incorporate into your discussion: DOI: https://doi.org/10.1016/j.hlc.2017.06.198 and https://doi.org/10.1186/s40959-017-0025-7</p> <p>Page 4 line 41 to 43 "to anti-tobacco programmes, and campaigns focusing on the importance of physical activity" these are non-pharmacological</p> <p>Page 6 line 13. I suggest changing "Patients and public were not involved in this study" to "Patients and public were not directly involved in this study."</p> <p>Page 7 line 38-40 trastuzumab is spelt wrong. I would suggest changing "radiation therapy" to "chest irradiation" and deleting "are associated with these outcomes"</p> <p>Page 16 line 38 remove the word 'it'</p>
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REVIEWER	Na-Jin Park University of Pittsburgh, USA
REVIEW RETURNED	10-Jul-2018

GENERAL COMMENTS	<p>1. Abstract</p> <ul style="list-style-type: none"> • Please choose one or the other: A nationwide prospective observational study or A nationwide observational cohort study - Cohort (prospective or retrospective) studies are prospective regardless of types of cohort. • I guess that breast cancer women are also ≥ 40 years of age? Please clarify that in abstract and methods. • Combine primary and secondary outcomes. Avoid technical terms. For example, absolute vs. relative risks of CVD may be presented as CVD mortality rate or hazard ratio of CVD mortality. I would also suggest the trends of CVD mortality over 10 years and CVD hospitalization over 5 years after breast cancer as primary and secondary outcomes. Also include data sources and analyses (cox model; hazard ratios per xxx person-years with Confidential Intervals) under outcomes. • Article summary does not include the findings on CVD hospitalization which is a secondary (?) outcome. Or you may reformat that as "strengths and limitations of the study" focusing on methodology and uniqueness of this study. Please review the authors' guidelines. <p>2. Introduction</p> <ul style="list-style-type: none"> • "In 2012, there were over 3 million five-year breast cancer survivors worldwide": Although I understand that 2012 statistics is more relevant to this study, I would prefer most recent statistics. • Clearly describe what gaps in literature you are trying to fill up with this study at the end of third paragraph. – i.e., no trend data on this topic available..., thereby we have little understanding on xxx. • Please consider to revise the last statement of Introduction to: The purpose of this study was to investigate trends of risks in CVD mortality and CVD hospitalization following breast cancer diagnosis in 1996-2010 compared with those in women without breast cancer in the Netherlands. <p>3. Methods and Materials</p>
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	<ul style="list-style-type: none"> • Suggestion of revising the first paragraph of study population: Data for the present study were obtained from three Dutch national registries. The Dutch Population Register was used to obtain demographic characteristics, available from 1995 to 2015. Hospital Discharge Register was used to identify women admitted for breast cancer and CVD hospitalization, available until 2010. The Cause of Death Registry was available until 2015, providing data on causes of death (i.e., CVD, breast cancer or any cause). • Avoid to use abbreviation for these registries. • The last statement of 2nd paragraph in page 5: Consider to revise to – For this study using national registries, no approval of the ethics committee is required. • Data analysis <ul style="list-style-type: none"> - The newly added statement at the end of the first paragraph is confusing. Instead, provide different median (IQR) follow-up time in years for CVD death and CVD hospitalization. - This is based on survival analysis. Please clarify starting point and end point for each group; explain about how you censored early termination of follow-up; and provide rates based on person-time at risk. “Per 1,000 women” is incorrect and revise to person-years. - Please revise the statement in lines 34-40 in page 7. Currently I don’t understand what that means. - Include the basic analysis information: 2-sided? Alpha =? 4. Results <ul style="list-style-type: none"> • Place CVD mortality (primary) data table as Table 1 and Table 2 with CVD hospitalization (secondary). Revise body of results accordingly. • Table 1: Please correct numbers for CVD hospitalization within years after breast cancer. The caption needs to be changed (e.g., Interval years between breast cancer admission and CVD hospitalization). • Table 2: Correct numbers for death within years after breast cancer admission and caption (same way with Table 1). • Validation of breast cancer discharge codes: This section could be moved to “study outcomes” in Methods. Also clarify whether you excluded incorrect cases. 5. Discussion <ul style="list-style-type: none"> • In 3rd paragraph of page 14, when you describe higher or lower in comparison to other studies, provide some numbers to show that (e.g., 10% vs. 6%). • There are some statements unclear: Lines 28-32, 39-44 in page 15. • Did you look at whether CVD hospitalization at 1, 3, 5 years (or cumulative) is associated with CVD death at 5, 7, 10 years (or cumulative) in breast cancer patients? That relationship, if any, indicate significant clinical implications. 6. This requires full editing with keeping in mind followings: <ul style="list-style-type: none"> • “Absolute vs. relative risks”: technical terms may be appropriate in data analysis or results, but interpretations of these terms should be mainly used throughout the paper. e.g., death rate vs. hazard ratio; 58% lower instead of 0.58 times lower etc..... • CVD death is a primary outcome; and a secondary one is CVD hospitalization. Please follow the order in presenting throughout the paper.
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VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

I find this an interesting read and recognise that you have incorporated previous reviewer comments. This paper will add important information to the research on CVD risk in women with breast cancer and the outcome of CVDs in this cohort.

We thank reviewer 1 for reading the manuscript and for raising suggestions to improve the manuscript.

1. You report the relative risk of CVD mortality for the breast cancer cohort between 1996 and 2010. It would be interested to the know the relative risk of CVD mortality between the breast cancer cohort and the general population. Did it change from 1996 to 2010?

The relative risk for 5-, 7- and 10-year CVD mortality for breast cancer patients compared to the general population remained similar over time.

	1996	
5 year CVD mortality	0.76	0.80 in 2010
7 year CVD mortality	0.78	0.80 in 2008
10 year CVD mortality	0.77	0.73 in 2005

This information can (roughly) be derived from Figure 1. We added “The relative risk for 5-, 7- and 10-year CVD mortality for breast cancer patients compared to the general population remained similar over time.” to the result section.

2. What CVD risk factors did you include? In your limitations you only mention age; however, you have described others in your methods.

We only included age as a CVD risk factor in the model. No other CVD risk factor were available in the Hospital Discharge Register. We mentioned in the methods that chest irradiation, chemotherapy, trastuzumab and aromatase inhibitors are known to be associated with a higher risk of heart failure and coronary heart disease. However, our study did not have information on breast cancer treatments. We rewrote the methods about these therapies to avoid confusion.

3. Why do you propose "The absolute risk of death from CVD is lower in women with breast cancer compared to women from the general population"? I don't think you have stated this clearly.

Figure 1 shows that more women from the general population die from CVD than women with breast cancer. To make it more clear, we've changed the sentence into: “Overall, the absolute risk of death from CVD is lower in women with breast cancer compared to women from the general population”.

Page 4 line 36/37. There is no evidence to show that the guideline recommendations have been integrated into standard care. Unless you have some evidence of this I would rephrase this from "standard of care" to "recommended care" and reference the guidelines. Additionally, did you find any literature that spoke about risk factor assessment or monitoring throughout chemotherapy? You could read up on this and incorporate into your discussion:

DOI: <https://doi.org/10.1016/j.hlc.2017.06.198> and <https://doi.org/10.1186/s40959-017-0025-7>

Thank you for these suggestions. We have changed “standard of care” into “recommended care” and referred to the Dutch guideline Oncoline.

Although the suggested literature is very interesting, it is out of the scope of this manuscript. We were not able to show any association between breast cancer treatment such as chemotherapy and CVD outcomes, as we did not have information on breast cancer treatments.

Page 4 line 41 to 43 "to anti-tobacco programmes, and campaigns

focusing on the importance of physical activity" these are non-pharmacological

We changed this sentence into: "In parallel, breast cancer patients have also been exposed to improvements in pharmacological prevention of CVD with antihypertensive and statins and non-pharmacological prevention programs such as anti-tobacco programmes, and campaigns focusing on the importance of physical activity.^{15,16}"

Page 6 line 13. I suggest changing "Patients and public were not involved in this study" to "Patients and public were not directly involved in this study."

We revised this sentence according to the reviewers' suggestion.

Page 7 line 38-40 trastuzumab is spelt wrong. I would suggest changing "radiation therapy" to "chest irradiation" and deleting "are associated with these outcomes"

We revised the last statement according to the reviewers' suggestion.

Page 16 line 38 remove the word 'it'

We removed the word 'it' according to the reviewers' suggestion.

Reviewer 2

Abstract

- Please choose one or the other: A nationwide prospective observational study or A nationwide observational cohort study - Cohort (prospective or retrospective) studies are prospective regardless of types of cohort.

We now use the same description of the study design throughout the manuscript: a nationwide cohort study

To our knowledge, all cohort studies are observational regardless of the of type of cohort.

- I guess that breast cancer women are also ≥ 40 years of age? Please clarify that in abstract and methods.

We included breast cancer patients from all ages. Only for the comparison with the general population, we focused on women aged 40 years and older, because CVD mortality per year was too low in younger breast cancer patients to perform accurate standardization.

We included this explanation in the method section.

- Combine primary and secondary outcomes. Avoid technical terms. For example, absolute vs. relative risks of CVD may be presented as CVD mortality rate or hazard ratio of CVD mortality. I would also suggest the trends of CVD mortality over 10 years and CVD hospitalization over 5 years after breast cancer as primary and secondary outcomes. Also include data sources and analyses (cox model; hazard ratios per xxx person-years with Confidential Intervals) under outcomes.

Thank you. We combined the primary and secondary outcome section and rewrote the method and result section.

- Article summary does not include the findings on CVD hospitalization which is a secondary (?)

outcome. Or you may reformat that as “strengths and limitations of the study” focusing on methodology and uniqueness of this study. Please review the authors’ guidelines.

Thank you for pointing this out. The bullets indeed reflect on the strengths and limitations of the study. We changed the caption.

2. Introduction

- “In 2012, there were over 3 million five-year breast cancer survivors worldwide”: Although I understand that 2012 statistics is more relevant to this study, I would prefer most recent statistics.

These statistics are provided by Globocan, a project that estimates the incidence, mortality and prevalence from major cancer types for 184 countries of the world. The most recent statistics date from 2012.

- Clearly describe what gaps in literature you are trying to fill up with this study at the end of third paragraph. – i.e., no trend data on this topic available..., thereby we have little understanding on xxx.

Thank you. We included: “However, no recent trend data about CVD mortality and hospitalization after breast cancer is available. “ after paragraph 3.

- Please consider to revise the last statement of Introduction to: The purpose of this study was to investigate trends of risks in CVD mortality and CVD hospitalization following breast cancer diagnosis in 1996-2010 compared with those in women without breast cancer in the Netherlands.

We revised the last statement according to the reviewers' suggestion.

3. Methods and Materials

- Suggestion of revising the first paragraph of study population: Data for the present study were obtained from three Dutch national registries. The Dutch Population Register was used to obtain demographic characteristics, available from 1995 to 2015. Hospital Discharge Register was used to identify women admitted for breast cancer and CVD hospitalization, available until 2010. The Cause of Death Registry was available until 2015, providing data on causes of death (i.e., CVD, breast cancer or any cause).

We revised this paragraph according to the reviewers' suggestion.

- Avoid to use abbreviation for these registries.

We removed the abbreviation and replaced those by the full names of the registries.

- The last statement of 2nd paragraph in page 5: Consider to revise to – For this study using national registries, no approval of the ethics committee is required.

We revised this sentence according to the reviewers' suggestion.

• Data analysis

The newly added statement at the end of the first paragraph is confusing. Instead, provide different median (IQR) follow-up time in years for CVD death and CVD hospitalization. - This is based on survival analysis. Please clarify starting point and end point for each group; explain about how you censored early termination of follow-up; and provide rates based on person-time at risk. “Per 1,000 women” is incorrect and revise to personyears. - Please revise the statement in lines 34-40 in page 7. Currently I don’t understand what that means. - Include the basic analysis information: 2-sided? Alpha =?

We rewrote this paragraph and included a statement about censoring. We did not add median (IQR) follow-up time in years for CVD mortality and CVD hospitalization, because this information can be found in the result section (Table 1 and Table 2).

We rewrote the statement in lines 34-40 into:

“Previous studies showed an association between heart failure and coronary heart disease and prior exposure to chest irradiation,^{9,10} chemotherapy,^{20,21} trastuzumab,^{22,23} and aromatase inhibitors²⁴. Therefore, we investigated whether hospitalizations for heart failure and coronary heart disease and other CVD diagnoses changed over the years.”

CVD mortality rate in breast cancer patients was expressed per 1,000 women per year and per 10,000 person years. Survival analysis is used to investigate the change in the risk of dying from CVD and breast cancer from 1996 to 2010.

We provided basic analysis information.

4. Results

- Place CVD mortality (primary) data table as Table 1 and Table 2 with CVD hospitalization (secondary). Revise body of results accordingly.

Thank you. We changed the tables and the results accordingly.

- Table 1: Please correct numbers for CVD hospitalization within years after breast cancer. The caption needs to be changed (e.g., Interval years between breast cancer admission and CVD hospitalization).
- Table 2: Correct numbers for death within years after breast cancer admission and caption (same way with Table 1).

Thank you. We changed table 1 and 2 accordingly.

- Validation of breast cancer discharge codes: This section could be moved to “study outcomes” in Methods. Also clarify whether you excluded incorrect cases.

We relocated this section. We didn't exclude the slightly incorrect cases as we could only check the correct dates from patients hospitalized in the UMC Utrecht. In the limitations section in de Discussion we added:

“Lastly, our validation study showed that in 3 out of 90 patients (3.3%) the date of discharge in the registry was incorrect by two or more months which in some cases may have led to a wrong classification of time between breast cancer admission and CVD mortality/hospitalization.”

5. Discussion

- In 3rd paragraph of page 14, when you describe higher or lower in comparison to other studies, provide some numbers to show that (e.g., 10% vs. 6%).

We have changed the sentence into: “Similar to our study, Riihimäki et al. (2011) showed that the absolute risk of death from CVD, after a maximum follow-up of 19 years, is lower in breast cancer patients (27.1%) than in women from the general population (44.0%).²⁸”

- There are some statements unclear: Lines 28-32, 39-44 in page 15. We made corrections to these statements.

- Did you look at whether CVD hospitalization at 1, 3, 5 years (or cumulative) is associated with CVD death at 5, 7, 10 years (or cumulative) in breast cancer patients? That relationship, if any, indicate significant clinical implications.

We did not look into this association, because we feel this is out of the scope of our manuscript. Our data is rather descriptive of nature than causal. We feel that to study such associations, more information about CVD risk factors and breast cancer treatments is necessary.

6. This requires full editing with keeping in mind followings:

- “Absolute vs. relative risks”: technical terms may be appropriate in data analysis or results, but interpretations of these terms should be mainly used throughout the paper. e.g., death rate vs. hazard ratio; 58% lower instead of 0.58 times lower etc.....
- CVD death is a primary outcome; and a secondary one is CVD hospitalization. Please follow the order in presenting throughout the paper. We thank the reviewer for this suggestion. We have changed the manuscript accordingly.

VERSION 3 – REVIEW

REVIEWER	Na-Jin Park University of Pittsburgh, USA
REVIEW RETURNED	04-Jan-2019

GENERAL COMMENTS	<p>Trends in the risk of cardiovascular disease in women with breast cancer in a Dutch nationwide cohort study</p> <ul style="list-style-type: none"> • The revision reads better with some errors, including tables. • Page 4 line 12 provides incorrect statistics. It is 6.2 million, not 3 million, women in 2012 worldwide who had survived breast cancer after being diagnosed within the preceding five years. • Page 4 line 17: Revise to “in women of the general population” & “in women with breast cancer” instead of breast cancer patients. It is recommended to use like this throughout the paper, particularly with the statement of comparison between two groups. • Page 6 line 6: Revise to “women without breast cancer from the general population”. • Page 6 line 53: Revise HDR to Hospital Discharge Register. • Page 7 line 46: Replace “CVD” for cardiovascular. • Page 8 lines 38 – 43: Here is my suggestion for clarity: Breast cancer patients admitted in 2010 had 42% lower (HR..., 95% CI...) age-adjusted 5-year risk of death from CVD compared to those in 1996 (Table 3). Similar revision is recommended for the next statement (lines 43 – 45). • Figure 2 and results described in pages 8 – 9: The reviewer notices a smaller reduction in both 5- and 10-year relative risks of CVD death in women of 65 years or older age group compared to younger age groups. Despite the worldwide improvement in CVD management in the last decades, the elderly, particularly older women, have shown the least improvement, which may be an important message with the growing aging populations worldwide. It would be beneficial to include this message in discussion. • Page 14 line 22: Would delete “such as secondary prevention”. • Page 15 line 6: Please define “good prognosis” by adding (e.g., early-stage or low grade disease). • The paragraph starting at page 15 line 23 to page 16: The numbers of percentage (7% for heart failure, 29% for high blood pressure, 34% for ?, 15% for venous thromboembolism) were not included in the results or tables. Please provide the source for these numbers and then discuss the relevant issues in discussion. The reviewer was not able to come up with the numbers with the information provided. • Table 1: Please check out all numbers under “interval years between breast cancer admission and death n (%)”. The total numbers of each category (total, BC with CVD death, BC with BC death) are inconsistent with 163,881, 9,115, and 37,187 presented in the top row of table.
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	<ul style="list-style-type: none"> • Table 2: Please check out all numbers under “interval years between breast cancer admission and CVD hospitalization n (%)”. They should be match with the total breast cancer population and breast cancer patients with CVD hospitalization, 163,881 and 32,276, respectively.
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VERSION 3 – AUTHOR RESPONSE

Trends in the risk of cardiovascular disease in women with breast cancer in a Dutch nationwide cohort study

The revision reads better with some errors, including tables.

Page 4 line 12 provides incorrect statistics. It is 6.2 million, not 3 million, women in 2012 worldwide who had survived breast cancer after being diagnosed within the preceding five years.

We changed this sentence according to the more recent information from Globocan 2018, as follows: In 2018, the estimated number of women who have survived breast cancer after being diagnosed within the preceding five years is 6.87 million worldwide.

Page 4 line 17: Revise to “in women of the general population” & “in women with breast cancer” instead of breast cancer patients. It is recommended to use like this throughout the paper, particularly with the statement of comparison between two groups.

We changed this throughout the manuscript.

Page 6 line 6: Revise to “women without breast cancer from the general population”.

We revised this accordingly.

Page 6 line 53: Revise HDR to Hospital Discharge Register.

We revised this accordingly.

Page 7 line 46: Replace “CVD” for cardiovascular.

We revised this accordingly.

Page 8 lines 38 – 43: Here is my suggestion for clarity: Breast cancer patients admitted in 2010 had 42% lower (HR..., 95% CI...) age-adjusted 5-year risk of death from CVD compared to those in 1996 (Table 3). Similar revision is recommended for the next statement (lines 43 – 45).

We revised this accordingly.

Figure 2 and results described in pages 8 – 9: The reviewer notices a smaller reduction in both 5- and 10-year relative risks of CVD death in women of 65 years or older age group compared to younger age groups. Despite the worldwide improvement in CVD management in the last decades, the elderly, particularly older women, have shown the least improvement, which may be an important message with the growing aging populations worldwide. It would be beneficial to include this message in discussion.

We included the following sentence: Moreover, in the current study we showed that older women with breast cancer had the least improvement in CVD mortality over time compared to younger women with breast cancer. It seems that older women with breast cancer do not benefit as much younger women from the worldwide improvements in CVD risk management and CVD treatments.

Page 14 line 22: Would delete “such as secondary prevention”.

We revised this accordingly.

Page 15 line 6: Please define “good prognosis” by adding (e.g., early-stage or low grade disease).

We defined patients with good prognosis as ‘patients with early stage breast cancer’.

The paragraph starting at page 15 line 23 to page 16: The numbers of percentage (7% for heart failure, 29% for high blood pressure, 34% for ?, 15% for venous thromboembolism) were not included in the results or tables. Please provide the source for these numbers and then discuss the relevant issues in discussion. The reviewer was not able to come up with the numbers with the information provided.

Thank you for pointing this out. We added these percentages to the last paragraph on page 9 in the Results section. The percentages depict the proportion of the 1-year hospitalization increase explained by the respective cardiovascular diseases.

Table 1: Please check out all numbers under “interval years between breast cancer admission and death n (%)”. The total numbers of each category (total, BC with CVD death, BC with BC death) are inconsistent with 163,881, 9,115, and 37,187 presented in the top row of table.

We changed the categories ‘<7’ and ‘<10’ into 5-9 and >9 in order to make the numbers consistent with the numbers at the top of the row. That does not apply to the first column, because this depicts total women with breast cancer who did not all die during the study period.

Table 2: Please check out all numbers under “interval years between breast cancer admission and CVD hospitalization n (%)”. They should be match with the total breast cancer population and breast cancer patients with CVD hospitalization, 163,881 and 32,276, respectively.

The numbers do not match with the numbers on the top, because the categories ‘<1’, ‘<3’ and ‘<5’ have overlap. We decided not to change into exclusive categories because we think that the current categories are more relevant to women with breast cancer and are more consistent with the rest of the manuscript.