PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	**Predictors of early death in female breast cancer patients in the UK: a cohort study. bmjopen-2011-000247**
AUTHORS	Stapelkamp, Ceilidh; Holmberg, Lars; Tataru, Daniela; Moller, Henrik; Robinson, David

VERSION 1 - REVIEW

REVIEWER	***Dr Anna Gavin*** Director, N. Ireland Cancer Registry, Centre for Public Health, Queen's University Belfast, Northern Ireland and Information and Analysis Lead, National Cancer Intelligence Network, England
REVIEW RETURNED	15-July-2011

REPORTING & ETHICS	This research paper is based on audit data which does not require ethics approval.
GENERAL COMMENTS	This is a well written article which contributes new information on the topic of what contributed to lower survival rates from cancer in the UK compared with other European countries. Information on biases as this is a sample of women audited should be included. Further exploration of early chemotherapy deaths is warranted. I feel this paper should have some additional details included. 1. Information on the number of women in the audit for each year/period compared with total breast cancer diagnosed and deaths of all breast cancers in 1 year and after 1 year for the population of North Thames. The women included in the audit were a sample of all the women who could have been entered. There is in the paper a reported variable number of Trust submitting (max 26 minimum 7). The more recent years saw fewer Trusts submitting data so the data is skewed to the earlier years rather than recent time and evidenced in the last rows of Table 3 – this possibly has implications for the applicability of the findings to recent times. It would be good to have an extra table comparing the age, etc. of the total population of women who had breast cancer with those included in the audit. 2. The increased risk of death within 1 year following chemotherapy might be due to sepsis or other chemotherapy side effects. If it is possible it would be good to examine specific cause of death in these patients. If cause of death could be linked with chemotherapy complication then that has implications for chemotherapy services. The skewed nature of the data with high numbers of patients from earlier years might mean this is a historic problem which has been corrected since. This deserves further exploration with data presented for earlier vs later years.

REVIEWER	***Lindsay Forbes, Professor*** Clinical Senior Lecturer in Health Services Research King's College London UK *I have no competing interests.*
REVIEW RETURNED	26-July-2011

THE STUDY	I think the paper would benefit from a little more detail in the methods on the data collection of some of the variables (in particular, spread at diagnosis, route to diagnosis (how was "incidental" defined?)). How do the trusts collate the data and is there any quality assurance of this? I can see that data on treatment received were checked against HES and registration data so are probably more reliable than, for example, data on route to diagnosis and spread at diagnosis. I recognise that this is addressed briefly in the discussion on page 10 – my view would be that this is very important and should have more prominence in the methods and discussion. I think the paper would also benefit from a bit more detail on how comorbidity was classified from HES data. This is important because it is so crucial to one of the conclusions i.e. that older women are more likely to die early, even after comorbidity and how advanced their cancer is is taken into account. How complete are HES data considered to be? It may be worth stating that the Charlson Morbidity Index only takes into account 22 specific serious conditions to ensure the general medical reader understands quickly that minor incidental conditions are not considered to constitute co-morbidity, for example. On this note, one of the key limitations of the study is the amount of missing data on comorbidity. It isn't entirely clear why this is. Is it because the record could not be linked to HES? It is because no comorbidities were listed on HES for that patient? Is this interpreted as "no comorbidity" or "missing comorbidity"? I think the paper might benefit from a little more detail on this. The authors may consider reducing the number of references slightly.
RESULTS & CONCLUSIONS	In view of the missing data (on comorbidity in particular) I think that the second line of the discussion that age and disease severity were INDEPENDENT predictors of early death may be a little strong. I think that the paper might benefit from slightly more clarity – in a pattern running through the introduction, results, summary of findings at the beginning of the discussion and the conclusions - about the key hypotheses tested. I agree that all the hypotheses that appear to be tested are valid; my request is simply that they are slightly more explicit. There are a lot of comparisons reported in the paper and because of this, at times, the "story" is slightly difficult to follow.
GENERAL COMMENTS	The data on ethnicity are limited because so many are missing, so the findings of the multivariable analysis of this are difficult to interpret – is it worth reporting this analysis, as it does not appear to form part of one of the main hypotheses?

	It would be useful for the authors to justify why they chose to use death at one year from any cause as the independent variable, rather than death at one year from breast cancer. Tables The tables might be improved by grouping the reporting of the patient characteristics (age, ethnicity, spread at diagnosis, tumour size, node status, comorbidity, date of diagnosis, route to diagnosis) and grouping the treatment characteristics after this. So that they are free-standing, I think the tables reporting the multivariable analyses would benefit from explaining in a footnote that all other variables were included in the model. In table 2 – 5, the title “Cancer Plan” for the row is not very clear (I would suggest “date of diagnosis in relation to the Cancer Plan” or equivalent). Minor points The authors have chosen to see off the Beral and Peto argument (that international survival differences are due to differences in cancer registration) in the first paragraph. While this is very important, and I can see why they have done this, it comes across as slightly defensive. The authors might consider putting this slightly later in the introduction or even in the discussion. I understand the North Thames Prospective Audit of Breast Cancer is called this but I note that all the participating networks are not in the old North Thames area as described in page 4 line 44 i.e. South West London is in the old South Thames area. Page 9 2nd Paragraph – I understood what the authors meant on second reading i.e. that the fact that five year survival in the cohort was similar to ONS estimates meant that the cohort sample was reasonably representative of the UK population of women with breast cancer, but I think that the wording could be a bit clearer. Page 9. line 51-2 the sentence starting “a failure to record…” I think needs a bit of unpacking. I assume the authors are implying that people whose records are incomplete may be those who received worse care. Page 10 – first line of conclusions – “more” than what?

VERSION 1 – AUTHOR RESPONSE

Reviewer 1: Dr Anna Gavin
1. We have inserted a new table (Table 6) which compares women in the breast audit dataset with those registered with the TCR during the same period and some discussion around this.
2. We take on board the point relating to chemotherapy and the potential association between sepsis or other side effects and death. Informal analyses of cause of death data in relation to the time period in which patients were diagnosed did not reveal any differences that might warrant further investigation of this issue. Therefore we do not discuss this further in our article.

Reviewer 2: Lindsay Forbes
1. We have added further detail about how variables were defined and how they were collected.
2. We have included more detail on how comorbidity was classified from HES.
3. We agree that one of the study limitations is missing data. We have included more detail about missing comorbidity data and describe clearly that these data were only available for the 60% of our sample who could be linked to the HES dataset.
4. We have reordered the discussion which now flows better and better follows the aims of the study.
5. We retain the ethnicity analysis but are clearer about the limitations of this analysis due to missing data.
6. We have made explicit the rationale for our independent variable and explain the results of analyses of deaths due to breast cancer.
7. We have re-ordered the rows in the tables as suggested.
8. We have included the table footnote as suggested.
9. We have amended the 'Cancer Plan' heading as suggested.
10. We have moved the paragraph discussing Beral and Peto a little later in the introduction.
11. We have reworded our comments on the relative survival estimate from the ONS to make it clearer that we were reflecting here on the generalisability of our sample.
12. We have reworded our thoughts on the possible association between missing data and worse care.
13. We have deleted the word 'more' as it added nothing.

VERSION 2 - REVIEW

REVIEWER	***Anna Gavin, Dr*** Queen's University Belfast, NI Cancer Registry
REVIEW RETURNED	23-Aug-2011

GENERAL COMMENTS	I have reviewed the changed article and am satisfied with the changes

REVIEWER	***Lindsay Forbes, Professor*** Clinical Senior Lecturer in Health Services Research King's College London UK *No competing interests*
REVIEW RETURNED	25-Aug-2011

GENERAL COMMENTS	This paper is really improved. I have two very minor points. 'Incidental' cancers. These are referred to in the results as comprising interval caners and non-symptomatic cancers. How did the women with interval cancers present if not by symptomatic presentation, screening or non-symptomatic discovery in the course of other management? Please clarify. Page 10 line 36. I did not understand the sentence starting 'Furthermore..' How does presentation to health services depend on access to treatment? I think you mean access to services.