PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A systematic review of barriers to early presentation and diagnosis with cancer among Black women
AUTHORS	Jones, Claire; Maben, Jill; Jack, Ruth; Davies, Elizabeth; Forbes, Lindsay; Lucas, Grace; Ream, Emma

VERSION 1 - REVIEW

REVIEWER	Drake, Bettina Washington University School of Medicine
REVIEW RETURNED	12-Nov-2013

GENERAL COMMENTS	The topic of this review is very important to the literature. A few comments to strengthen the review include: The article title is "…diagnosis with cancer among Black women." It seems as though the review is focused mostly on breast cancer and many if not most of the articles presented discuss racial differences. Therefore it seems as though the unique contribution of this review to the literature is the focus on racial differences in breast cancer. In addition, breast cancer is much different in terms of screening and early presentation than other female cancers. The aim of the review on page 4 lines 53-54 state the aim of the review is "to early presentation with , …symptomatic cancer". Early presentation is typically not symptomatic. Please clarify. Page 5: it is not clear why studies reporting uptake o , or barriers to cancer screening were excluded. This seems like an important area and specific to the topic of the review. Under Results, lines 50-55: only 3 papers were non-breast cancer, why were they significant enough to include when the focus of the review can be improved by excluding and only focusing on breast cancer. Additionally, 1 study was not clearly on cancer. How did this study qualify to be included and what value does it add?

REVIEWER	Jillian Jacobellis PhD, MS also (CNM) certified nurse midwife University of Colorado, School of Public Health Colorado Department of Health & Environment
REVIEW RETURNED	14-Nov-2013

GENERAL COMMENTS	Study design is appropriate to answer question BECAUSE THE objective states you are "exploring" barriers however, there are many limitations to this study & these data that need to be underscored: lumping all ethic groups of black women, countries of residency and origin into one group. Although followed Cochrane approach to identify appropriate studies there was no proper control of SES, most importantly insurance status. Also, how were black

	Hispanic women treated in these data? Noteworthy: Dr Nancy Krieger has many papers on the treatment of race/ethnicity & SES & cancer staging differentials--it may be valuable for authors to review this literature. Perhaps in the abstract conclusion--need to hint at limitations. eg, further studies to ... or state: this study may over generalize conclusion need to replicated...

REVIEWER	Donald Lannin Yale University School of Medicine United States
REVIEW RETURNED	17-Nov-2013

GENERAL COMMENTS	This is a very nice review of a complicated topic and it should be published. The authors give an accurate overview of the literature on barriers to detection of symptomatic cancer, and the article fills a need as similar recent reviews are not available. Of course there is always some subjectivity and bias in a review of this type. The authors selected only 23 studies out of an initial 930 possibly relevant articles. I know of a number of articles that I believe address this topic that were not included, and presumably these were in the 907 that were excluded. Despite this, however, the included articles are fairly representative and the majority of the important concepts are addressed. A critical point that was not addressed in this review is our changing knowledge about the importance of tumor biology. Fifteen years ago we felt that most breast cancers were biologically similar and that differences in tumor size and prognosis depended heavily on how early the tumors were diagnosed. Today we realize that there is a tremendous variability in tumor biology; many small screen-detected cancers are so indolent that they represent “over-diagnosis” as they would never become clinically significant within a patient’s lifetime, whereas other cancers are so aggressive that they are systemic at the outset and can never be diagnosed at an early curable stage. This impacts racial differences, as we now know that many young Black women present with locally advanced tumors, not because they delayed seeking medical care, but because they have very aggressive “triple-negative” cancers. Studies are needed that compare delay in diagnosis among women of various races when stratified by tumor prognostic and biological factors. One of the problems with this review is that it is overly ambitious. Most of the studies addressed breast cancer but a couple addressed cervical cancer and two addressed all cancers; some studies used delay or tumor stage as outcome measures among patients with a cancer diagnosis, whereas other studies used hypothetical behavior in a general population of women without cancer; and most importantly the studies included Black women from the United States, the Caribbean, Great Britain, and from Africa. This heterogeneity clearly affects the conclusions. For example, the authors state that the impact of the financial burden of healthcare on delay in diagnosis is “unclear”. This may be true in some health systems or geographic areas, but most workers in the rural southern US or inner cities in the US would disagree. Clearly socioeconomic factors are important but may be more or less associated with race in different countries. In contrast, it is actually amazing that so many

	of the beliefs, taboos, and fears are similar among Black women, irrespective of their current area of residence. Since clearly these factors are not genetic, this says a lot about how durable cultural factors are over even many generations. The authors make some conclusions about which I would either disagree or at least urge caution. They note that the fear of partner abandonment was found in earlier studies but has not been reported in recent studies. This does not mean, however, that it is not a current problem; it clearly needs to be addressed in a single study over time. Furthermore, there are conflicting results about the significance of religiosity and fatalism. This may be a methodological issue. Some studies included just Black patients, whereas others included both Blacks and other races. If only Black patients are included, they are found as a group to be highly religious, but within the group there is no difference in stage by religiosity. In contrast, in studies that included all races, there was a much larger range of religiosity and this was highly correlated with advanced stage, with Blacks scoring highly on both religiosity and advanced stage. My major disagreement with this review is that, for unclear reasons, our 1998 JAMA paper was rated as “low quality”. With 540 breast cancer patients and 414 matched community controls, this is still the largest study to compare essentially all the variables encompassed in this review to carefully measured tumor stage. The study documented differences in beliefs between cancer patients and community controls, making it clearly more relevant than many of the subsequent larger studies that only inferred hypothetical behavior from general populations. Furthermore, the study provided a frame of reference by comparing socioeconomic variables, as a group, with cultural variables as a group. Although the study only involved participants in rural North Carolina, this framework could be very helpful if applied to Black populations in other settings, where it is likely that there may be changes in one or the other or both.

VERSION 1 – AUTHOR RESPONSE

Response to reviewers’ comments

We would like to thank the reviewers for their feedback which has been very helpful. Revisions are highlighted in yellow in the main document. We have included our responses to the reviewers comments below and cited the page number, paragraph and section of the revisions we have made to address each point (we have also submitted our responses to the comments in a table which is submitted as a supplementary file for the editor).

Comments and Responses

The article title is “…diagnosis with cancer among Black women.” It seems as though the review is focused mostly on breast cancer and many if not most of the articles presented discuss racial differences. Therefore it seems as though the unique contribution of this review to the literature is the focus on racial differences in breast cancer. In addition, breast cancer is much different in terms of screening and early presentation than other female cancers.

The authors agree with this point and so have amended the review to focus only on breast cancer. They have amended the title, content and have included articles to reflect this.

The aim of the review on page 4 lines 53-54 state the aim of the review is “to early presentation with , …symptomatic cancer”. Early presentation is typically not symptomatic. Please clarify.

The authors have addressed this point by explaining that although the UK has a national screening programme, many women present to their doctor with self-detected breast changes or symptoms. It is this presentation which is the focus of the review. We have clarified this on:
Page 4, 1st paragraph, aim of the review.

Page 5: it is not clear why studies reporting uptake of, or barriers to cancer screening were excluded. This seems like an important area and specific to the topic of the review.

As above, there are other studies looking at breast screening programmes specifically; but this study focuses on presentation outside of that screening programme (which in the UK only focuses on women age 50-70 and takes places only once every three years). We have focused the review on women who present to their doctor with self-detected breast changes or symptoms because we wanted to know and understand what women did or do not do once they had discovered breast changes (which may not be the same for women diagnosed through screening).

Under Results, lines 50-55: only 3 papers were non-breast cancer, why were they significant enough to include when the focus of the review can be improved by excluding and only focusing on breast cancer.

These papers have now been excluded and review tightened to focus on breast cancer only. Two further studies have also been excluded as they did not report findings for breast cancer separately.

Additionally, 1 study was not clearly on cancer. How did this study qualify to be included and what value does it add?

We are unclear which study is being referred to in this instance and have re-checked all the studies which now all focus on breast cancer.

There are many limitations to this study & these data that need to be underscored: lumping all ethnic groups of black women, countries of residency and origin into one group.

We agree entirely with the reviewer on this point, which we address in the Discussion. It is also highlighted by us in the 'strengths and limitations' section. The studies included in the review are indeed limited in that they often do not distinguish between different ethnic groups of black women; which is something the authors of the review aim to address in their own forthcoming research. We have addressed this on:
Page 3, 4th bullet point, strengths and limitations
Page 16, 3rd and 4th paragraphs, discussion

Although followed Cochrane approach to identify appropriate studies there was no proper control of SES, most importantly insurance status.

The authors have now acknowledged this point in the discussion. From the studies conducted so far it is clear that we cannot unpick the effects of poverty and ethnicity clearly.

Also, how were black Hispanic women treated in these data?

No papers were found which reported separately on Black Hispanic women

Noteworthy: Dr Nancy Krieger has many papers on the treatment of race/ethnicity & SES & cancer staging differentials--it may be valuable for authors to review this literature.

Thank you for this reference. These papers have been considered and a point has been added in to acknowledge the wider issues around SES/race/ethnicity.
See Page 16, 2nd paragraph, discussion.

Perhaps in the abstract conclusion--need to hint at limitations. eg, further studies to ... or state: this study may over generalize conclusion need to replicated...

Thank you, we have now added a sentence in the conclusion of the abstract as suggested as follows: "The review is limited by the paucity of studies conducted outside the US and the limited detail reported by published studies preventing comparison between ethnic groups."
See Page 2, abstract.

A critical point that was not addressed in this review is our changing knowledge about the importance of tumor biology. Fifteen years ago we felt that most breast cancers were biologically similar and that differences in tumor size and prognosis depended heavily on how early the tumors were diagnosed. Today we realize that there is a tremendous variability in tumor biology; many small screen-detected cancers are so indolent that they represent "over-diagnosis" as they would never become clinically significant within a patient's lifetime, whereas other cancers are so aggressive that they are systemic at the outset and can never be diagnosed at an early curable stage. This impacts racial differences, as we now know that many young Black women present with locally advanced tumors, not because they delayed seeking medical care, but because they have very aggressive "triple-negative" cancers. Studies are needed that compare delay in diagnosis among women of various races when stratified by tumor prognostic and biological factors.

This point has now been covered in the background literature where the authors write, "This may reflect the higher proportion of Black women than White women developing triple negative breast cancer - an aggressive from of the disease associated with poorer outcomes. " Two papers are cited to support this point. Page 3, background 1st paragraph.

It is also addressed in the Discussion section 'Researchers need to compare stage at diagnosis and cancer survival between ethnic groups after stratifying for tumour prognostic and biological factors. This would allow the relative influence of cancer biology, women's delay and system delay on outcomes to be determined.'
Page 17, 1st paragraph, discussion

One of the problems with this review is that it is overly ambitious. Most of the studies addressed breast cancer but a couple addressed cervical cancer and two addressed all cancers;

This has now been amended and the review only focuses on breast cancer.

Some studies used delay or tumor stage as outcome measures among patients with a cancer diagnosis, whereas other studies used hypothetical behavior in a general population of women without cancer;This is a limitation of the study – that some studies reported on women with cancer and others from a general population.

This has now been addressed in the strengths and limitations list and the discussion: 'There was also some evidence of differences between women with and without cancer, suggesting a distinction between what women say they would do if they discovered a symptom, versus what they do with the onset of symptoms'
See Page 3, 2nd bullet point strengths and limitations
And Page 16, 5th paragraph discussion

Most importantly the studies included Black women from the United States, the Caribbean, Great Britain, and from Africa. This heterogeneity clearly affects the conclusions

Again, the authors have addressed this point, and agree it is a limitation of the studies available.
See Page 3, 3rd bullet point, strengths and limitations

For example, the authors state that the impact of the financial burden of healthcare on delay in diagnosis is “unclear”. This may be true in some health systems or geographic areas, but most workers in the rural southern US or inner cities in the US would disagree. Clearly socioeconomic factors are important but may be more or less associated with race in different countries.

This point has now been addressed in the Discussion where the authors write: ‘Papers incorporated into the review did not unequivocally support an association in the US between financial barriers and late presentation with breast cancer in Black and African American women. It is likely that this finding reflects sampling issues; Black women sampled in these studies appeared relatively affluent, 58-92% had health insurance. Work of others, including Schneider, demonstrates clearly both the coexistence of socioeconomic factors and ethnicity and their impact on cancer staging and outcomes [43]. However, it is important to note that outside the US socioeconomic factors may be more or less associated with ethnicity. They may also impact differently on time to presentation with breast cancer in differing healthcare systems.’
See Page 16, 2nd paragraph, discussion.

In contrast, it is actually amazing that so many of the beliefs, taboos, and fears are similar among Black women, irrespective of their current area of residence. Since clearly these factors are not genetic, this says a lot about how durable cultural factors are over even many generations.

We agree and have commented on this: 'However, it is striking that so many of the beliefs, taboos, and fears were similar among Black women, irrespective of their country of residence. These factors are clearly not genetic which suggests cultural factors are durable over many generations.'
See page 16, paragraph 4, discussion.

The authors make some conclusions about which I would either disagree or at least urge caution. They note that the fear of partner abandonment was found in earlier studies but has not been reported in recent studies. This does not mean, however, that it is not a current problem; it clearly needs to be addressed in a single study over time.

We acknowledge this point and hope to have made it clearer that it does not mean partner abandonment is not a current issue.
See Page 14, 5th paragraph, factors which may explain the findings.

Furthermore, there are conflicting results about the significance of religiosity and fatalism. This may be a methodological issue. Some studies included just Black patients, whereas others included both Blacks and other races. If only Black patients are included, they are found as a group to be highly religious, but within the group there is no difference in stage by religiosity. In contrast, in studies that included all races, there was a much larger range of religiosity and this was highly correlated with advanced stage, with Blacks scoring highly on both religiosity and advanced stage.

This point has been addressed in the Discussion: ‘Religiosity might influence help-seeking behaviour but this will depend on how people perceive their own role and that of a higher influence in managing their health [42]. The highly individual nature of religious beliefs may explain why the influence of religiosity on delay was unclear in this review. Further, it may reflect the nature of the samples

recruited to the reviewed studies.'
See Page 15, last paragraph, discussion.

My major disagreement with this review is that, for unclear reasons, our 1998 JAMA paper was rated as "low quality". With 540 breast cancer patients and 414 matched community controls, this is still the largest study to compare essentially all the variables encompassed in this review to carefully measured tumor stage. The study documented differences in beliefs between cancer patients and community controls, making it clearly more relevant than many of the subsequent larger studies that only inferred hypothetical behavior from general populations. Furthermore, the study provided a frame of reference by comparing socioeconomic variables, as a group, with cultural variables as a group. Although the study only involved participants in rural North Carolina, this framework could be very helpful if applied to Black populations in other settings, where it is likely that there may be changes in one or the other or both.

Thanks you for alerting us to this. It was an error which arose when data extraction forms were grouped by quality. The data extraction form was not saved in the correct folder. The original form has been checked and the paper was found to be high quality. With apologies. We also checked the original data extraction forms of all other included studies to ensure they were graded appropriately and found no other errors.

VERSION 2 – REVIEW

REVIEWER	Donald Lannin Yale University School of Medicine USA
REVIEW RETURNED	31-Dec-2013

GENERAL COMMENTS	The authors have satisfactorily addressed the concerns of the reviewers. It is a very nice review, and I would recommend it be published.