

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Cohort profile: Helping Ourselves, Helping Others - The Young Women's Breast Cancer Study (YWS): A multi-site prospective cohort study to advance the understanding of breast cancer diagnosed in women aged 40 and younger
<b>AUTHORS</b>	Rosenberg, Shoshana M.; Zheng, Yue; Ruddy, Kathryn; Poorvu, Philip D.; Snow, Craig; Kirkner, Gregory J.; Meyer, Meghan E.; Tamimi, Rulla M.; Schapira, Lidia; Peppercorn, Jeffrey; Come, Steven; Borges, Virginia; Warner, Ellen; Gelber, Shari; Collins, Laura; Winer, Eric P.; Partridge, Ann

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Qiu, Jiajia Fudan University Shanghai Cancer Center, Department of Nursing Administration
<b>REVIEW RETURNED</b>	13-Nov-2023

<b>GENERAL COMMENTS</b>	<p>Respected Editor:</p> <p>Thank you for inviting me to review the manuscript. The following are my comments.</p> <p>The topic of the article is really interesting and the focus is meaningful. As breast cancer has the highest incidence rate among malignant tumors around the world, and young women are a real concern and they are worth exploring. This study has a large sample size, a long follow-up time, and a wide range of research results. It was really a very difficult project.</p> <ol style="list-style-type: none"><li>1. The content of the article is more about the introduction of the process, and the introduction of the research tools is less. Since there are many outcome indicators, can you clearly sort out and introduce the research tools of each indicator? In particular, psychosocial research tools.</li><li>2. Since the study design is a longitudinal study, should longitudinal changes in each outcome measure be presented? So that you can explore the clinical significance of each index in the longitudinal changes and trends, and the implications for clinical practice.</li><li>3. More statistical methods for longitudinal data are recommended.</li><li>4. The outcome indicators of the study include objective indicators and subjective indicators. Can you discuss the relationship between them and the changing trend?</li></ol>
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	5. In Page 7, the part of Enrollment procedures, you presented that current median follow-up of the cohort is 10 years (range:0.4-16 years), I don't quite understand the data here. The enrolled population was from 2006 to 2016. Even for patients enrolled in 2016, the minimum follow-up time was more than 0.4 years.
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<b>REVIEWER</b>	Autier, Philippe International Prevention Research Institute
<b>REVIEW RETURNED</b>	23-Nov-2023

<b>GENERAL COMMENTS</b>	<p>Article of SM Rosenberg and colleagues describes the progress of a large cohort study of US women who were diagnosed with a breast cancer before 40 years of age. Authors are to be commended for the successful organisation of the YMS which gathers considerable amounts of data since its inception in 2006. Strengths and limitations of the study are well described.</p> <p>However, I didn't understand the objective of this long paper. The major part of the paper looks like a catalogue of data gathered since the study start, and of the many analyses to come. The paper is verbose, with many sentences or ideas repeated over and over. It's reading requires a sizeable effort.</p> <p>Authors should rather outline what they are aiming at with their paper, and offer more details on outputs susceptible to interest readers, for instance, on page 15, line 32, to tell more about the new lines of investigations? Or how did (or will) findings of the YMS change medical practice and patient management? What are the main hypotheses contemplated, even those that may appear speculative? Will there be an external control group? And so on.</p> <p>Lastly, some of arguments justifying a study specially centred on younger women with breast cancer are controversial. The greater proportion of overdiagnosed small breast cancers in women aged 50 or more than in women less than 40 years of age distorts comparisons of tumour size and of survival between age groups. There is ample literature on these issues (eg, CHO et al, JNCI 2014; Welsh, JAMA, 2007). Breast screening of young women is not an option, first because of the rarity of the condition in women less than 40 years, and second because the UK Age trial showed no reduction of the risk of breast cancer death when screening starts at 39-41 years (Moss et al, Lancet Oncology, 2015 and following articles). Authors seems to insists on increasing incidence rates among young women. However, in the cited article, the increase in breast cancer incidence rate among women 20-39 years of age is of 1.1 per 100,000 from 1999 to 2018, which is not that spectacular and probably does not deserve alarming messages. Hence, the description of breast cancer issues specific to young women and arguments laid for justifying the study should better reflect the variability of interpretations of epidemiological facts.</p>
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**VERSION 1 – AUTHOR RESPONSE**

Reviewer: 1

Thank you for inviting me to review the manuscript. The following are my comments. The topic of the article is really interesting and the focus is meaningful. As breast cancer has the highest incidence rate among malignant tumors around the world, and young women are a real concern and they are worth exploring. This study has a large sample size, a long follow-up time, and a wide range of research results. It was really a very difficult project.

**Response:** We thank the reviewer for acknowledging the importance of our work.

1. The content of the article is more about the introduction of the process, and the introduction of the research tools is less. Since there are many outcome indicators, can you clearly sort out and introduce the research tools of each indicator? In particular, psychosocial research tools.

**Response:** This manuscript was written to fit the guidelines of *BMJ Open's* Cohort Profile manuscript category. As such, per the journal guidelines for this type of manuscript, we have included extremely detailed information about the setting of the cohort, recruitment procedures, follow-up, and data collection. We understand that there is interest in the many outcomes we described; we have summarized the primary domains of interest, which include several psychosocial domains (e.g., fear of recurrence, coping, anxiety, depression, quality of life, social support) in Table 3.

2. Since the study design is a longitudinal study, should longitudinal changes in each outcome measure be presented? So that you can explore the clinical significance of each index in the longitudinal changes and trends, and the implications for clinical practice.

**Response:** As noted, the objective of this manuscript was to provide a detailed description of the YWS cohort, briefly describe findings to date (without presenting detailed results), comment on strengths and limitations, and share potential opportunities for collaboration. While we have summarized and cited selected key findings (please see pages 11-13), we have not extensively detailed results from each analysis, including analyses that examined longitudinal changes in psychosocial outcomes over time. Regarding implications for clinical practice, we have highlighted how findings from the YWS have informed clinical guidelines (pages 11-12), in reference to: 1) fertility/pregnancy data that has been referenced in international guideline as well as informed a practice changing international trial that evaluated the safety of pregnancy after breast cancer; 2) an analysis that supported the use of the Recurrence Score (RS) in younger women.

3. More statistical methods for longitudinal data are recommended.

**Response:** Per the journal editorial guidelines for a "Cohort profile," detailed statistical plans were not included in the manuscript.

4. The outcome indicators of the study include objective indicators and subjective indicators. Can you

discuss the relationship between them and the changing trend?

**Response:** As noted above, because the primary objective of this manuscript was to provide an overview of the YWS, beyond the key study findings which have been referenced, we have not provided specific details regarding how variables are treated as this is typically analysis dependent and beyond the scope of what is presented in this broad overview paper.

5. In Page 7, the part of Enrollment procedures, you presented that current median follow-up of the cohort is 10 years (range:0.4-16 years), I don't quite understand the data here. The enrolled population was from 2006 to 2016. Even for patients enrolled in 2016, the minimum follow-up time was more than 0.4 years.

**Response:** Thank you for the opportunity to clarify this point. Calculation of follow-up is based on individual patient data; the lower end of this range (e.g., 0.4 years) reflects the follow-up duration of patients who died soon after diagnosis and/or were lost to follow-up early on in the study.

Reviewer: 2

1) Article of SM Rosenberg and colleagues describes the progress of a large cohort study of US women who were diagnosed with a breast cancer before 40 years of age. Authors are to be commended for the successful organisation of the YMS which gathers considerable amounts of data since its inception in 2006. Strengths and limitations of the study are well described.

However, I didn't understand the objective of this long paper. The major part of the paper looks like a catalogue of data gathered since the study start, and of the many analyses to come. The paper is verbose, with many sentences or ideas repeated over and over. It's reading requires a sizeable effort.

Authors should rather outline what they are aiming at with their paper, and offer more details on outputs susceptible to interest readers, for instance, on page 15, line 32, to tell more about the new lines of investigations? Or how did (or will) findings of the YMS change medical practice and patient management? What are the main hypotheses contemplated, even those that may appear speculative? Will there be an external control group? And so on.

**Response:** We appreciate the reviewer's time spent reviewing our manuscript. As noted above, the paper was written to fit the guidelines of *BMJ Open's* Cohort Profile manuscript category. As such, per the journal guidelines, we have included extremely detailed information about the setting of the cohort, recruitment procedures, follow-up, and data collection to align with the purpose of a cohort profile, "to provide information on a cohort's establishment that goes beyond what can reasonably be described in the methods section of a research paper and to advise other researchers of existing datasets and opportunities for collaboration." In line with the journal's guidelines, we did not provide detailed results or provide extensive information about emerging research but summarized key research findings to date, included references to these publications, as well as provided an overview of how the cohort will be used in the future.

Regarding the clinical impact of the YWS, we refer the reviewer to “Findings to Date” (pages 11-12), where we have specified how findings from the YWS have impacted patient management: 1) findings related to fertility/pregnancy have been referenced in international guidelines as well as informed a practice changing international trial that evaluated the safety of pregnancy after breast cancer; 2) an analysis that supported the use of the Recurrence Score (RS) in younger women with hormone-receptor positive breast cancer.

There are currently no plans for an external control group, as this was not in the original study design. We have now added this as a limitation (page 16).

2) Lastly, some of arguments justifying a study specially centred on younger women with breast cancer are controversial. The greater proportion of overdiagnosed small breast cancers in women aged 50 or more than in women less than 40 years of age distorts comparisons of tumour size and of survival between age groups. There is ample literature on these issues (eg, CHO et al, JNCI 2014; Welsh, JAMA, 2007). Breast screening of young women is not an option, first because of the rarity of the condition in women less than 40 years, and second because the UK Age trial showed no reduction of the risk of breast cancer death when screening starts at 39-41 years (Moss et al, Lancet Oncology, 2015 and following articles). Authors seems to insists on increasing incidence rates among young women. However, in the cited article, the increase in breast cancer incidence rate among women 20-39 years of age is of 1.1 per 100,000 from 1999 to 2018, which is not that spectacular and probably does not deserve alarming messages. Hence, the description of breast cancer issues specific to young women and arguments laid for justifying the study should better reflect the variability of interpretations of epidemiological facts.

**Response:** We appreciate the reviewer bringing up these important points. Regarding trends in incidence, multiple studies have documented small increases in rates over time. While these increases may be viewed as incremental, the absolute number of breast cancer diagnoses is also increasing in younger women (Rosenberg et al. JAMA Oncology 2015; Koh et al, JAMA Network Open 2023), reflecting population-level demographic shifts (e.g., more women aged ≤40 younger at risk in the general population) which has clinical implications, as providers will see greater numbers of younger women in their clinical practice. Our intent was not to be alarming but rather highlight trends that have been widely documented for the most commonly diagnosed cancer in this age demographic. As cited, our group and others have shown that younger women tend to develop cancers with unfavorable pathologic features and aggressive subtypes that are associated with inferior survival compared to older women with breast cancer (see recent publication, Keegan et al. JCO 2023). We agree with the reviewer that the data do not currently support routine screening of average-risk younger women. Our intention in citing “lack of screening” was to note one contributor to later-stage diagnoses in younger women (i.e., these cancers are often self-detected and likely to be larger in size). Importantly, this may necessitate more intensive treatment, with quality of life implications.

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Autier, Philippe International Prevention Research Institute
<b>REVIEW RETURNED</b>	05-Jan-2024

<b>GENERAL COMMENTS</b>	Authors have adequately answered comments.
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