

Article details: 2018-0028	
Title	<b>Breast cancer risk and breast screening for trans people: an integration of three systematic reviews</b>
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Reviewer 1	A. Narayan
General comments (author response in bold)	<p>1. The authors have provided a tremendously valuable contribution to the literature on breast cancer related to transgender patients. My biggest issue with the manuscript is its sheer ambition in conducting three separate systematic reviews. I would revise the manuscript to focus just one of the reviews and rewrite the introduction to focus on one hypothesis (perhaps the first one or the third one). I would also be more explicit for each question about the purpose and hypothesis.</p> <p>• <b>We thank reviewer 1 for their careful review of our manuscript and their positive feedback. During the conceptualization of this manuscript we considered submitting three separate manuscripts, one for each review, for publication. After much thought, given the limited evidence identified in each review, we decided to not submit separate manuscripts and instead we integrated the findings of our three reviews into a single manuscript. We believe that the integration of these three reviews into a single manuscript provides the reader with a more complete picture of the evidence that should be considered by organized screening programs when developing breast screening recommendations and policies for trans people.</b></p> <p>2. The data are likely to be highly limited for each of the three questions however I would use the discussion section to expound upon these things further.</p> <p>• <b>We are unclear as to what revision(s) the reviewer is suggesting, if any. The key findings and limitations of each review are discussed in paragraphs one and three of the Interpretation section, respectively.</b></p> <p>3. The methods and results are conducted in an entirely appropriate fashion using PRISMA guidelines and standard methodologies for conducting these reviews - the authors have done an excellent job conducting these analyses - my inclination though is that these should be three separate manuscripts though.</p> <p>• <b>Thank you for this comment. Please see our comments above regarding the decision to not submit three separate manuscripts for publication.</b></p>
Reviewer 2	Emily Sonnenblick
Institution	Icahn School of Medicine at Mount Sinai Tisch Cancer Institute, Radiology, New York City
General comments (author response in bold)	<p>1. The authors conducted two systematic reviews of primary research on the effect of cross-sex hormones (CSHs) on breast cancer risk, prognosis and mortality, and the benefits and harms of breast screening. They then conducted a third systematic review of guidelines on existing breast cancer screening recommendations for trans people. The meta-analysis approach included primary research papers, guidelines as well as position statements published between 1997 and 2017. After a massive survey of over 2,000 papers that met key words for electronic searches, the authors largely based their conclusions on four primary observational studies, as well as six guidelines and five position statements. They concluded that the data did not demonstrate an effect of CSHs on breast cancer risk, prognosis, or mortality in trans men or trans women, and that there was scant evidence for benefits or other harms of screening, despite recommendations that exist supporting breast screening for distinct trans sub-populations. As a reference work, this synthesis provides a useful and thorough catalogue of the canon of literature on this topic. In addition to the approximately 200 references included in the paper it would be useful to provide an on-line appendix with the entire list of papers reviewed.</p> <p>• <b>We thank reviewer two for their careful and thorough review of our manuscript. For each review, a list of documents excluded at full-text relevance screening is provided in Appendix 3.</b></p> <p>2. While the authors add no meaningful nuance or insight compared to prior reviews, the detailed tabular approach they provide is of value to scholars as well as dedicated practitioners. While the assessment of breast cancer incidence rates and efficacy of screening are vital goals to provide rational care to this community, the review draws attention to the lack of evidence base to draw on. Despite the very large input of publications into the pool for consideration, the authors exclude the vast majority to limit their review to very few articles. Unfortunately, even these "select" papers have methodological limitations that should be made more evident to the casual reader. For example, the conclusion of the first review regarding breast cancer rates in transgender people finds no elevation in transgender people receiving cross sex hormone treatment. However, of the three studies that the meta-analysis group included, only one, the Netherlands study (Gooren et al 2013) provides robust data since this cohort has been followed for over a 30-year period of time and care is centralized in the context of a healthcare system that ensures full access for transgender people. Another of the studies included, based on a retrospective review of data from the U.S. Veterans Administration system (Brown) raises some concerns regarding the authors' criteria for inclusion in a meta-analysis. As the primary authors of the VA study emphasize, their approach was much more limited in its design as it provided no follow up outside the VA system for most of the transgender cohort, and provided no specific data about hormonal or surgical treatment or outcome. The third study chosen for inclusion is based on a study of pathology specimens from mastectomies/chest contouring surgery performed on trans male patients (Kuroda et al). This series compares a small cohort 130 trans men not on CHT compared to 56 trans men on CHT all of whom undergo mastectomy/chest contouring surgery. However a major interpretive limitation of this surgical pathology study highlighted by its authors is that hormones were only taken for an average of 11 months. Only 1 cancer was detected in trans males not taking CHT. Most importantly, patients were a mean of 27.4 years of age at time of surgery and thus very few cancers would be expected. These considerations lead one to wonder why the meta-analysis authors chose to include it.</p> <p>• <b>We thank reviewer 2 for their comments and agree with the majority of the study limitations highlighted</b></p>

	<p>above.</p> <ul style="list-style-type: none"> <li>• <b>Within the Interpretation section, we acknowledge many of the limitations of the included studies that reviewer 2 has highlighted. Due to word count limits, we have chosen to not further expand upon some of the limitations within the body of the manuscript, beyond what has already been presented. Instead we refer the reader to Appendix 4, Tables S2 and S5 for a more comprehensive assessment of the methodological limitations of individual studies and the bodies of evidence, respectively.</b></li> <li>• <b>With respect to the reviewer’s comment about the rationale for including Kuroda et al., given its apparent limitations, we agree that very few cancers were to be expected given the participant’s young age and duration of CSH use. While the a priori eligibility criteria for review one (see Appendix 1, Table 3) specified that studies were eligible for inclusion if they examined trans people 18 years of age or older, we did not place inclusion restrictions based on the length of CSH use. Because Kuroda et al. met all a priori inclusion criteria, this study was included in this review.</b></li> </ul> <p>3. For the second meta-analysis of the benefits and harms of screening, the authors rely on a single Belgian study in which 50 trans women post SRS and on hormone treatment received screening mammography and ultrasound. The authors conclude that this study was of poor methodological quality, and thus the meta-analysis is unable to offer perspective on harms and benefit. In fairness, the purpose of the Belgian study was to demonstrate that screening mammography and ultrasound were tolerated by their cohort, and the study design was not constructed or powered to inform analysis of clinical endpoints. The third topic of meta-analysis is variation in breast cancer screening guidelines for transgender individuals. It is well known that these varied screening guidelines are not based on evidence derived from the source population. Organizations in Canada, U.S. and U.K. propose biennial or annual screening for transgender women with two or more risk factors for breast cancer including CHT for 5 years. It is important for the clinician to understand that these guidelines are not meant to endorse screening, but to ensure access to care for those who elect to screen. It should be noted that breast cancer screening guidelines for cisgender women remains controversial to some; evidence based recommendations vary among groups giving expert opinions, although most agree that this option should be available, and covered by government and private insurers, for those cisgender females who elect to screen. While acknowledging the limitations of the data supporting breast cancer screening in the transgender community, the argument can be made that this option should be no less available than for cisgender women.</p> <ul style="list-style-type: none"> <li>• <b>We have added a statement to the last paragraph of the Interpretation section to reflect the comment that breast screening should be available to trans people, as it is for cisgender women.</b></li> </ul> <p>4. Thus, this meta-analysis, while ambitious, does not add a new perspective to the understanding of transgender breast cancer rate and risk. Conclusions are drawn from a paucity of studies most of which have flaws that have been well identified. Until transgender individuals are identified in cancer registries it will not be possible to obtain stable estimates of breast cancer incidence in transgender compared to cisgender people. This reviewer strongly agrees with the authors’ conclusion that large scale prospective follow up of transgender patients is needed to accurately assess breast cancer rates and potential benefit for screening. As one such example, we have established the Transgender Follow up Imaging Registry (TRANSFIR) (transfir.org). The authors should be commended on this exhaustive examination of largely observational studies to begin to address important questions of breast cancer risk for transgender patients.</p> <ul style="list-style-type: none"> <li>• <b>We thank reviewer 2 for their thoughtful review of our manuscript.</b></li> </ul>
Reviewer 3	Lissa Cohen
General comments (author response in bold)	<p>1. Very important subject matter- thank you for taking the time and effort to compose this paper! The scholarly literature is lacking in the area of trans health which is evident from your review of the scholarly literature. There are some areas in the article where I am wondering if you wrote "biological woman" but perhaps meant cis-gender woman vs sex assigned at birth?</p> <ul style="list-style-type: none"> <li>• <b>We thank reviewer 3 for their thoughtful review of our manuscript.</b></li> <li>• <b>For clarity we have revised our definition of cisgender women in the Introduction section to remove reference to “biological sex”.</b></li> <li>• For clarity we have also revised instances of “biological women” to “cisgender women”.</li> </ul> <p>2. The interpretation section was very well written and provided clarity to the somewhat convoluted results section (perhaps a summary chart for the results section rather than paragraph form would simplify this section?). You have presented the abyss that exists within the scholarly literature surrounding this topic thus opening the door for yourself and others to publish in the area.</p> <ul style="list-style-type: none"> <li>• <b>We thank reviewer 3 for their positive feedback and further thank them for their suggestion regarding presenting a summary of the results in a chart form.</b></li> <li>• <b>As currently formatted, we believe Tables 3 and 6 clearly present a summary of the findings obtained for reviews one and two, respectively. Tables 5 and 7 present the results of review three using a tabular approach by trans population. Given the diverse results obtained for review three, we believe they cannot be distilled down any further.</b></li> </ul>