BREAST CANCER RISK AND BREAST SCREENING FOR TRANS PEOPLE: AN INTEGRATION OF THREE SYSTEMATIC REVIEWS

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ABSTRACT (248 words; 250 word limit)

Background: Trans people face uncertain risks for developing breast cancer and barriers to accessing breast screening. We 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, and a third systematic review of guidelines on existing screening recommendations for trans people.

Methods: PubMed, MEDLINE, Embase, CINAHL, the Cochrane Database of Systematic Reviews and grey literature sources were searched for primary research, guidelines and position statements published between 1997 and 2017. Citations were screened by two independent reviewers using pre-defined selection criteria. One reviewer extracted data and assessed methodological quality of included articles; a second reviewer verified these in full. Results were synthesized narratively.

Results: Four observational studies, six guidelines and five position statements were included. Observational evidence of very low certainty did not demonstrate an effect of CSHs on breast cancer risk in trans men or trans women. Among trans women, painfulness of mammography and ultrasonography was low. There was no evidence on the effect of CSHs on breast cancer prognosis and mortality or on benefits and other harms of screening. Existing clinical practice documents recommended breast screening for distinct trans sub-populations; however, recommendations varied.

Interpretation: The limited evidence does not demonstrate an effect of CSHs on breast cancer risk. While there is insufficient evidence to determine the potential benefits and harms of breast screening, existing clinical practice documents generally recommend

breast screening for trans people. Further large-scale, comparative, prospective research is needed.

Protocol Registration: N/A

INTRODUCTION (381 words; 400 word limit)

Trans is an umbrella term for individuals with diverse gender identities and expressions that differ from stereotypical gender norms [1,2]. Recent estimates suggest that there were approximately 200,000 trans individuals living in Canada in 2016 [3]. Many trans people seek gender affirming medical procedures or cross-sex hormone (CSH) therapy, or both, to align their physical appearance with their sense of self [4]. CSH therapy refers to the use of exogenous sex hormones that are opposite to those of an individual's natal sex [5]. Breast cancer risk in trans people is hypothesized to be influenced by CSHs [6]. However, it is unclear whether the potential alteration in risk for developing breast cancer by CSH therapy should affect the individual's eligibility for breast screening.

Trans people are medically underserved and face unique challenges in accessing appropriate care [3,7]. With respect to breast health, 25% to 30% of trans people in Ontario with a perceived need for mammography were unable to obtain a mammogram [8]. In addition, trans people are less likely to pursue breast screening when compared to cisgender women (i.e., individuals born biologically female and identify as female) [9]. While this demonstrates a disparity in the approach to breast cancer detection when compared to the non-trans population, information on the potential benefits and harms of screening in this population is limited [10].

Organized breast screening programs aim to reduce breast cancer mortality through regular screening. At this time, breast screening programs may not have official screening policies for trans people, which may result in inconsistent inclusion of trans people within organized programs. The development of programmatic evidence-based

policies should begin with the systematic identification of evidence and then the use of this information to formulate and implement policy [11]. In this manuscript we present the findings of three systematic reviews that can be used by organized breast screening programs to initiate a process of breast screening policy development for the trans population. The objectives of the reviews were to identify and synthesize:

1) primary research on the effect of CSHs on breast cancer risk, prognosis and mortality among trans people (review one),
2) primary research on the benefits and harms of breast screening among trans people (review two), and
3) existing clinical practice recommendations on breast screening for trans people (review three).

METHODS (1799 words; 1800 word limit for methods and results)

Separate protocols were developed to guide the reviews (Appendix 1); they were not publicly registered. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline was followed [12]. Throughout this report, the terms trans men and trans women are used for simplicity and are meant to be inclusive of all individuals on the female-to-male and male-to-female spectrums, respectively.

Data Sources and Searches

For reviews one and two, PubMed, MEDLINE, Embase, CINAHL and the Cochrane Database of Systematic Reviews were searched for primary research published in English over a 20-year period (January 1997 to May 2017). For the third review, PubMed and MEDLINE were searched for guidelines and positions statements

published in English over a 20-year period (January 1997 to February 2017). All search strategies were developed in consultation with a medical librarian (Appendix 2). Grey literature searches and hand searches of on-topic journals were also conducted. Reference lists of relevant primary studies, systematic reviews, literature reviews and guidelines were reviewed, and citation recommendations from experts were sought.

Study Selection

For all reviews, titles and abstracts of citations were screened independently by two reviewers using pre-defined selection criteria (Table 1). Any citation marked for inclusion by either reviewer went to full-text screening. Dual independent full-text screening was conducted with consensus required for inclusion or exclusion of each citation. Conflicts were resolved through discussion.

Data Management

For reviews one and two, DistillerSR [13] was used to manage screening, data extraction, quality assessment, verification and conflict resolution. For review three, DistillerSR [13] was used for screening and data extraction for citations obtained from electronic databases, whereas these tasks were completed in Excel for citations from the grey literature search. Screening, data extraction and quality assessment forms were developed *a priori* and piloted to ensure validity and inter-rater reliability.

Data Extraction and Quality Assessment

For all reviews, one reviewer extracted data from included citations. A second reviewer verified all extracted data; disagreements were resolved through discussion.

Data extraction items for each review are provided in the respective protocol (Appendix 1). Authors were not contacted for missing data.

For reviews one and two, the quality of cohort studies was assessed using the Newcastle-Ottawa Scale [14]. The quality of cross-sectional studies was assessed by considering key methodological components such as the selection of participants and exposure and outcome assessments. One reviewer conducted quality assessments. A second reviewer verified all ratings; disagreements were resolved through discussion.

For review three, quality assessment of each guideline was conducted independently by two reviewers using the Appraisal of Guidelines for Research and Evaluation 2 (AGREE II) instrument [15]. The quality of position statements was not assessed.

Synthesis

For reviews one and two, similarities and differences in study characteristics, quality, sample and intervention features were examined across the included studies. Results for outcomes of interest for each objective are presented narratively for trans men and trans women separately. Meta-analysis was not possible in either review due to a lack of available count data in the comparison groups (review one) or an insufficient number of included studies (review two). The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the certainty of the available evidence for each outcome [16,17]. One reviewer conducted GRADE assessments. These were verified by a second reviewer.

For review three, a cross-document assessment was conducted to identify similarities and differences in the recommendations on breast screening for trans men and trans women separately.

RESULTS

Search Results

For review one, 1,507 unique citations were identified. After screening, three studies met the inclusion criteria [18-20] (Figure 1A). For review two, 560 unique citations were identified, of which one study met the inclusion criteria [21] (Figure 1B). The search for review three identified 173 unique citations, and after screening, 11 documents were included (Figure 1C) [4,5,22-30]. A list of citations excluded at full-text screening for each review is provided in Appendix 3.

Characteristics of Included Studies and Documents

For review one, three retrospective cohort studies examining the effect of CSHs on breast cancer risk among trans people were identified [18-20] (Table 2). All three included trans men, and two included trans women [18,19]. Across studies, 1,069 trans men and 3,419 trans women were exposed to CSHs (Table 3; Appendix 4, Table S1). The duration of CSH exposure varied within and across studies. In one study, the comparison group was 130 trans men who did not receive CSHs [20], and in the other two studies comparisons were drawn against general population samples [18,19]. Follow-up ranged between nine and 38 years. Funding details were reported for two studies [18,19]; neither received commercial support. Two studies were rated as having fair methodological quality [18,19], and one was rated as poor [20] (Table 2).

For review two, one cross-sectional study reporting on one screening-related harm was identified [21] (Table 2). The sample consisted of 50 trans women, all of whom underwent sex reassignment surgery (Appendix 4, Table S1). Forty-eight (96.0%) participants received augmentative breast surgery, 47 (94.0%) were on estrogen replacement therapy, and two (4.0%) were on an androgen deprivation agent. All participants received a mammogram and sonogram from a single experienced radiologist. There was no comparison group. Funding details were not reported; however, the first author declared commercial supports. This study was considered of poor methodological quality (Table 2).

For review three, eleven documents (six guidelines and five position statements), provided recommendations on breast screening for trans people [4,5,22-30] (Table 4). Documents were developed by groups in Canada [4,5,22,23,26], the United States [24,27,29,30] and the United Kingdom [25,28]. Overall, the quality of the included guidelines was low (Table 4). Across guidelines, the highest scoring AGREE II domains were scope and purpose and clarity of presentation. The lowest scoring domains were applicability and editorial independence.

Trans Men

Effect of CSHs on Breast Cancer Risk, Prognosis and Mortality (Review One)

Three studies examined breast cancer risk among trans men exposed to CSHs [18-20]. The risk among trans men exposed to CSHs was not statistically different compared to trans men not exposed to CSHs [20] or the expected risk based on estimates for the general population of women [18]. In the third study, breast cancer risk among trans men exposed to CSHs was lower than the expected estimates for the

general population of women, but the statistical significance of this finding was not reported [19]. This evidence received a very low GRADE rating due to the observational nature of the study designs and serious concerns regarding risk of bias, indirectness and imprecision (Table 3).

Evidence on the effect of CSHs on breast cancer prognosis or mortality among trans men was not identified.

Benefits and Harms of Breast Screening (Review Two)

Evidence on the benefits and harms of breast screening among trans men was not identified.

Existing Recommendations on Breast Screening (Review Three)

Seven documents provided breast screening recommendations for trans men [4,22,24-26,28,29] (Table 5).

Breast screening was recommended for trans men without chest reconstruction [4,22,24,26,29]. Among this group, screening eligibility also depended on age [22,26,29] and eligibility requirements for cisgender women [4,24,26]. Two documents recommended biennial mammography [22,26], one recommended mammography without specifying the screening interval [4], one recommended annual clinical breast examination (CBE) [26], and one recommended annual breast exams without specifying whether these were CBEs or breast self-examinations (BSEs) [4].

Screening was also recommended for trans men who have had partial chest reconstruction [4,22,24,26]. Recommended modalities varied and included ultrasonography [22,24], MRI [22,24] and mammography [4]. One document

recommended against mammography following chest reconstruction [26]. None of the documents provided a specific recommendation on the screening interval [4,22,24,26].

For trans men in general (i.e., chest reconstruction status not specified), screening recommendations varied [22,25,26,28]. Eligibility depended on having a history of male CSH use [25], developed breast tissue [25,28], family history of breast cancer [22,26], and the presence of other risk factors [22]. One document recommended that those with a strong family history of breast cancer follow guidelines for cisgender women regarding referral to a high risk mammography screening program [26]. The other three documents did not provide specific recommendations on modalities or intervals [22,25,28].

Trans Women

Effect of CSHs on Breast Cancer Risk, Prognosis and Mortality (Review One)

Two studies examined breast cancer risk among trans women exposed to CSHs [18,19]. In one study, the risk among trans women exposed to CSHs was not statistically different from that expected based on estimates for the general population of men [18]. In the second study, breast cancer risk among trans women exposed to CSHs was slightly higher (4.1 cases per 100,000 person-years) than estimates for the general population of men (1.2 cases per 100,000 person-years), but the statistical significance of this finding was not reported [19]. This body of evidence received a very low GRADE rating due to the observational nature of the study designs and serious concerns regarding risk of bias, indirectness and imprecision (Table 3).

Evidence on the effect of CSHs on breast cancer prognosis or mortality among trans women was not identified.

Benefits and Harms of Breast Screening (Review Two)

Evidence on one screening-related harm among trans women was identified [21]. One cross-sectional study reported on pain experienced by 50 trans women undergoing mammography and ultrasonography [21]. Painfulness of both procedures, as assessed by a 10-point visual analogue scale, was rated as low (mammography mean [SD] score range: 1.7 – 2.0 [2.1 – 2.3]; ultrasonography mean [SD] score: 0.5 [1.2]) (Table 6). These two bodies of evidence received very low GRADE ratings due to serious concerns regarding the observational nature of the study design and risk of bias (Table 6).

Evidence on other screening-related harms, and on the benefits of screening among trans women was not identified.

Existing Recommendations on Breast Screening (Review Three)

Ten documents provided breast screening recommendations for trans women [4,5,23-30] (Table 7).

For trans women with a history of CSH use, screening eligibility depended on the duration of CSH use [23,24,26], age [4,23,24,26], breast implants [23] or growth [4], orchiectomy status [4], other risk factors [4,26], and guidelines for biologic women [27]. Recommended modalities and intervals included biennial mammography [23,24,26] and mammography without a specified interval [4]. One document recommended against

periodic BSE and annual CBE [4]. Screening was not recommended for trans women with less than 5 years of CSH use [23] and those without a history of CSH use [4].

For trans women in general (i.e., CSH use not specified), recommendations varied [5,26,28-30]. One document recommended diagnostic mammography for those with breast implants and to consider annual MRI for those 30 to 69 years of age with a family history suggestive of hereditary breast cancer [26]. Two documents recommended screening for those with developed breast tissue [5,28], one recommended screening as per guidelines for biological women [30], and one recommended age-appropriate screening [29]. None of these documents provided specific information on the modality or interval [5,28-30].

INTERPRETATION (793 words; 800 word limit)

The limited evidence of very low certainty did not demonstrate an effect of CSHs on breast cancer risk in trans men or trans women. Evidence on the effect of CSHs on breast cancer prognosis and mortality was not identified. There was a lack of evidence on the benefits of breast screening, and very little evidence on harms. Further evidence of very low certainty found that trans women experienced minimal pain during mammography and ultrasonography. There was minimal agreement on screening recommendations for trans people. The majority of the clinical practice documents located provided recommendations for distinct sub-groups of trans people based on the presence of breast tissue and history of CSH exposure. There was an observed preference for routine screening with mammography for trans men without chest reconstruction. This is not surprising, as trans men without chest reconstruction and without CSH exposure likely have the same risk of developing breast cancer as most

cisgender women [10]. There was also agreement that CSH exposure should be considered, at least in part, when determining breast screening eligibility for trans women.

As demonstrated by these reviews, the topics of breast screening and the effect of CSHs on breast cancer outcomes among trans people have not been rigorously and thoroughly researched. To our knowledge, these are the first systematic reviews to examine these topics, thus limiting comparisons to existing evidence. Previous literature reviews on similar topics have largely summarized published case reports and series on breast cancer in trans people, along with the studies included in our two systematic reviews of primary research [6,10,31,32].

Key strengths of our systematic reviews include comprehensive search strategies, robust citation screening, data extraction and critical appraisal processes, and the application of reputable tools and systems for managing and analyzing the evidence and assessing its certainty.

Key limitations of our systematic reviews are due to methodological decisions and the quantity and quality of the primary studies, guidelines and position statements identified. The three reviews searched only for clinical and scientific evidence available in English, which could have resulted in language bias. Due to the insufficient quantity of primary research, certain domains in the GRADE assessments could not be assessed. While the quality of included guidelines was assessed using AGREE II, we did not verify or critically appraise the evidence that was cited in support of recommendations.

The nature of the included evidence posed a number of limitations. The three studies examining the effect of CSHs on breast cancer risk all used observational designs [18-20], and two studies used indirect comparisons, relying on population-based estimates for expected incidence [18,19]. Across the three studies, few details were provided regarding the nature of CSH exposure. The length of follow-up varied across the three studies, and in many cases, follow-up may have been too short to reasonably examine the effect of CSHs on long-term risk of developing breast cancer. Results from two studies were not statistically significant [18,20], which may be due to a lack of power. The third study did not report the statistical significance of its findings [19]. The single study reporting on painfulness of screening among trans women is limited by its small sample size, insufficient information on validity and reliability of the outcome measure and generalizability [21]. The quality of guidelines in review three was low. Very few documents reported the quality of the evidence upon which their recommendations were based or the strength of their recommendations.

Conclusions cannot be drawn from the sparse evidence of very low certainty in these three reviews. The two systematic reviews of primary research found limited evidence, thus preventing the formation of any definitive conclusions about the impact of breast screening in trans people and the effect of CSHs on breast cancer outcomes. The systematic review of guidelines and position statements found that breast screening is generally recommended for trans people; however, recommendations on eligibility criteria, modalities and intervals varied. In the absence of high-quality scientific evidence, organized breast screening programs will need to supplement scientific evidence with sources of contextual evidence (e.g., professional expertise and lived

experience) when developing breast screening recommendations and policies for trans individuals.

Based on our findings, it is clear that large-scale, comparative, prospective, trans-specific quantitative research with a long duration of follow-up is needed to produce reliable estimates of the effects of CSHs on breast cancer outcomes and the potential benefits and harms of screening [32,33]. Given the large sample size required for such studies, and the challenges with reaching trans people for research [34], future research may benefit from data linkage and algorithms to improve the identification of trans people in existing population-based health databases [33]. Alternatively, future etiologic research of sufficient sample size may include a multi-site cohort study based in community clinics that serve trans people [33].

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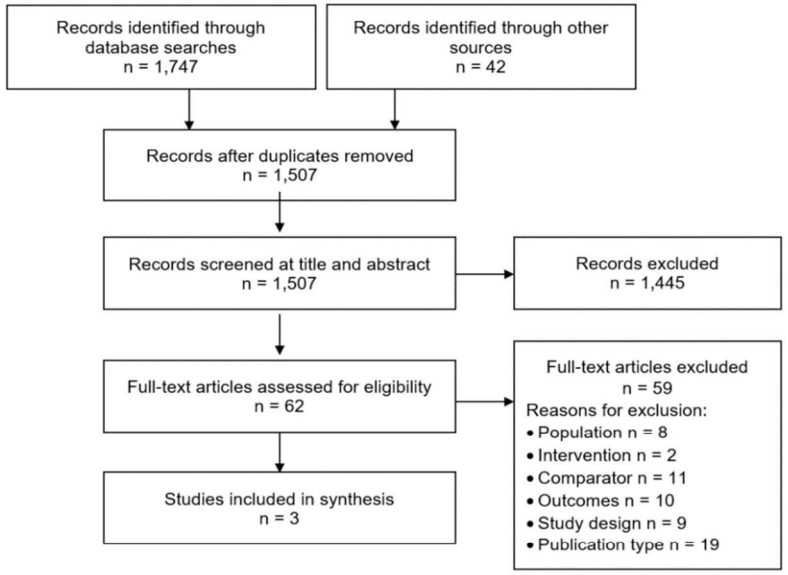
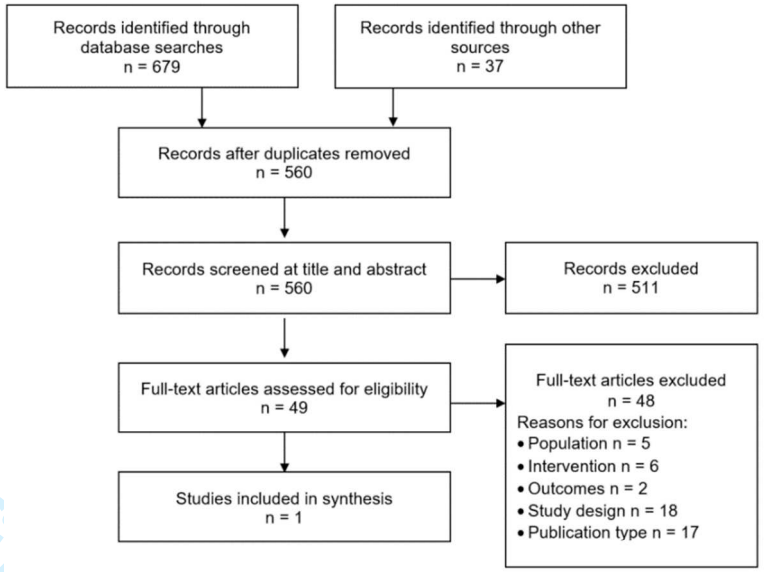
FIGURES

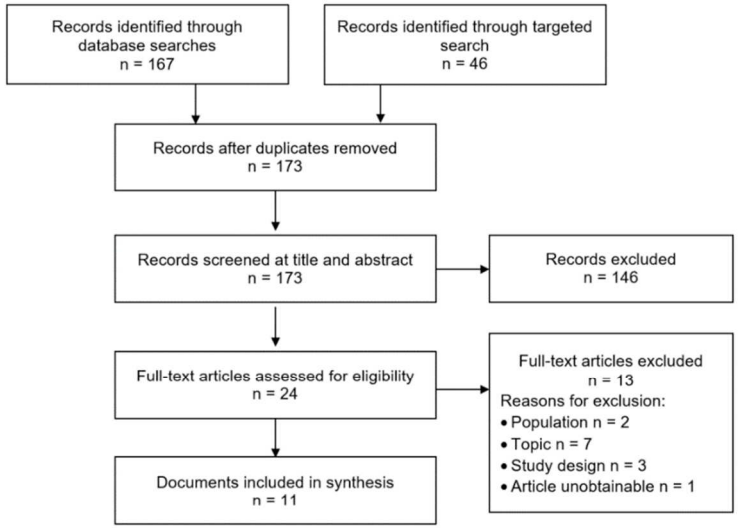
Figure 1: Search and Selection Flow Diagrams for the Three Systematic Reviews



(A) Flow diagram for the systematic review of primary research evidence examining the effect of CSHs on breast cancer risk, prognosis and mortality in trans people (review one).



(B) Flow diagram for the systematic review of primary research evidence examining the benefits and harms of breast cancer screening in trans people (review two).



(C) Flow diagram for the systematic review of guidelines and position statements on existing breast screening recommendations for trans people (review three).

TABLES

Table 1: Inclusion Criteria for the Three Systematic Reviews

	Review One[1]	Review Two[2]	Review Three[3]
Populations	Trans men (≥18 years) with: • all original breast tissue remaining • some breast tissue removed (i.e., breast reduction) • chest contouring surgery (e.g., lipo sculpting, pectoral implants) Trans women (≥18 years) with: • breast augmentation/implant • no breast augmentation/implant	Asymptomatic trans men (≥18 years) with: • all original breast tissue remaining, with a history of CSH use • some breast tissue removed, with or without a history of CSH use • chest contouring surgery, with or without a history of CSH use Asymptomatic trans women (≥18 years) with: • breast augmentation/implants, with a history of CSH use • no breast augmentation/implants, with a history of CSH use	Trans men (≥18 years) with: • all original breast tissue remaining, with or without a history of CSH use • some breast tissue removed, with or without a history of CSH use • chest surgery, with our without a history of male CSH use Trans women (≥18 years) with: • breast augmentation/implants, with or without a history of CSH use • no breast augmentation/implants, with or without a history of CSH use
Interventions	• Masculinizing CSH use (e.g., testosterone) for trans men • Feminizing CSH use (e.g., anti-androgen agents, estrogen or progesterone) for trans women	Breast screening with: • Mammography • Magnetic resonance imaging • Ultrasonography • Clinical breast examination • Breast self-examination	Breast screening with: • Mammography • Magnetic resonance imaging • Ultrasonography • Clinical breast examination • Breast self-examination
Comparators	• Trans men not taking masculinizing CSHs or cisgender women • Trans women not taking feminizing CSHs or cisgender men	• Trans individuals not screened for breast cancer • No comparison group required (only for cancer detection rate, interval cancer rate, sensitivity[4], specificity[4] and all harm outcomes)	NA
Outcomes	• Breast cancer risk (incidence) • Prognosis: stage at diagnosis, node positivity, tumor size, tumor grade, tumor type, survival • Breast cancer mortality	• Benefits: breast cancer-specific mortality all-cause mortality, cancer detection rate, interval cancer rate, sensitivity and specificity • Harms: over-diagnosis, false-positives, patient-reported anxiety and patient-reported pain/discomfort	Breast screening recommendations for trans people with a focus on: • eligibility requirements • screening modalities • screening intervals

	Review One[1]	Review Two[2]	Review Three[3]
Study Designs/ Document Types	• RCTs • Non-randomized experimental studies • Observational studies with comparison groups	• RCTs • Non-randomized experimental studies • Observational studies with or without[5] comparison groups • Diagnostic evaluation studies	• Guidelines • Position statements
Other	• Published between January 1, 1997 and May 19, 2017 • Peer-reviewed or grey literature • Full reports, or conference abstracts and proceedings • Published in English	• Published between January 1, 1997 and May 9, 2017 • Peer-reviewed or grey literature • Full reports, or conference abstracts and proceedings • Published in English	• Published between January 1, 1997 and February 13, 2017 • Peer-reviewed or grey literature • Full reports, or conference abstracts and proceedings • Published in English

CSH = cross-sex hormone; NA = not applicable; RCTs = randomized controlled trials

[1] Breast Cancer Risk, Prognosis and Mortality in the Trans Population using Cross-sex Hormones: A Systematic Review of Primary Research

[2] Benefits and Harms of Breast Screening for the Trans Population: A Systematic Review of Primary Research

[3] Breast Screening for Trans Populations: A Systematic Review of Guidelines and Position Statements

[4] For sensitivity and specificity, positive screens must have been compared to the reference standard (i.e., pathology results from biopsy) and negative screens must have been followed for at least one year.

[5] Observational studies without comparison groups were included only if they reported on cancer detection rate, interval cancer rate, sensitivity, specificity and all harm outcomes.

Table 2: Characteristics of Included Primary Studies

Author, Year [ref]	Study Design	Eligibility Criteria	Country	Study Period	Total Sample Size	Source of Funding	Study Quality
Brown, 2014 [18]	Retrospective cohort	• Trans-related diagnosis (i.e., gender identity disorder, gender identity disorder not otherwise specified, transvetic fetishism or transsexualism) • Veteran • Accessed medical and mental health services at a VHA facility	U.S.	17 years (October 1, 1996 to September 30, 2013)	5,135	Authors employed by VHA No grant or commercial funding	Fair[1]
Gooren, 2013 [19]	Retrospective cohort	• Trans person • Minimum of 6 years follow-up	The Netherlands	38 years (1975 to December 31, 2012)	3,102	Two authors received non-commercial support	Fair[1]
Weyers, 2010 [21]	Cross-sectional	• Dutch-speaking trans woman • Received sex reassignment surgery at least 6 months prior to enrollment • Consulted the Ghent University Hospital gender team during past 12 months	Belgium	4 months (March to June 2007)	50	First author received commercial support	Poor[2]
Kuroda, 2008 [20]	Retrospective cohort	• Trans man • Underwent mastectomy at surgical institute	Japan	9 years (1998 to 2006)	186	NR	Poor[1]

NR = not reported; U.S. = United States; VHA = Veterans Health Administration

[1] Methodological quality of individual cohort studies was assessed using the Newcastle Ottawa Scale [14,35]. Detailed results of the quality assessment are provided in Appendix 4, Table S2.

[2] No formal critical appraisal tool was used. Methodological quality of the individual cross-sectional study was assessed by considering key methodological components such as the selection of participants and exposure and outcome assessments. Detailed results of the quality assessment are provided in Appendix 4, Table S3.

Table 3: GRADE Summary of Findings Table for the Effect of CSH Exposure on Breast Cancer Risk, Prognosis and Mortality in Trans Populations

Population: Trans individuals ages 16 to 83 years old **Intervention:** CSH			
Outcome	**Effect**	**Number of Exposed Participants (Number of Studies)**	**Certainty of the Evidence (GRADE)**
Trans men exposed to testosterone			
Breast cancer risk[1]	Differences in incidence rate or cumulative incidence between exposed cohorts and non-exposed cohort or general population samples were either not statistically significant or were not reported[2]	1,069 (3)	⊕OOO VERY LOW[3,4]
Stage at diagnosis	No primary research evidence identified		
Survival			
Breast cancer mortality			
Trans women exposed to estrogen only, androgen deprivation or antiandrogens only, or estrogen with androgen deprivation or antiandrogens			
Breast cancer risk[1]	Differences in incidence rate or cumulative incidence between exposed cohorts and general population samples were either not statistically significant or were not reported[2]	3,419 (2)	⊕OOO VERY LOW[3,4]
Stage at diagnosis	No primary research evidence identified		
Survival			
Breast cancer mortality			

CSH = cross-sex hormone

[1] Assessed using administrative database or medical records with follow-up not reported or at a minimum of six years post CSH therapy initiation.

[2] A single pooled effect estimate was not calculated. Additional information and detailed results for each study are provided in Appendix 4, Table S4.

[3] Very low certainty rating = we have very little confidence in the effect estimate and the true effect is likely to be substantially different from the estimate of effect.

[4] The evidence was downgraded due to the observational nature of the study designs and serious concerns regarding risk of bias, indirectness and imprecision. Detailed GRADE assessments are provided in Appendix 4, Table S5.

Table 4: Characteristics of Included Guidelines and Position Statements

Organization, Year [ref]	Document Type	Country	AGREE II Domain Scores[1]					
			Scope & Purpose	Stakeholder Involvement	Rigor of Development	Clarity of Presentation	Applicability	Editorial Independence
Canadian Cancer Society, 2017 [22,23]	P	Canada	NA	NA	NA	NA	NA	NA
Centre of Excellence for Transgender Health, 2016 [24]	G	U.S.	81%	56%	29%	81%	27%	0%
International Planned Parenthood Federation, 2015 [25]	P	U.K.	NA	NA	NA	NA	NA	NA
Sherbourne Health Centre, 2015 [26]	G	Canada	64%	44%	16%	25%	6%	0%
Transgender Health Information Program, 2015 [5]	G	Canada	67%	67%	6%	14%	13%	0%
Centre for Disease Control and Prevention, 2013 [27]	P	U.S.	NA	NA	NA	NA	NA	NA
National Health Service, 2013 [28]	G	U.K.	64%	25%	0%	28%	17%	0%
American College of Obstetrics and Gynecology, 2011 [29]	P	U.S.	NA	NA	NA	NA	NA	NA
The Endocrine Society, 2009 [30]	G	U.S.	72%	33%	63%	58%	8%	46%
Vancouver Coastal Health, Transcend Transgender Support and Education Society, & Canadian Rainbow Health Coalition, 2006 [4]	G	Canada	86%	61%	17%	89%	0%	0%

AGREE II = Appraisal of Guideline for Research and Evaluation 2; G = guideline; NA = not assessed; P = position statement; U.K. = United Kingdom; U.S. = United States

[1] Quality assessment of position statements was not conducted as they are unlikely to undergo the same development process as guidelines.

Table 5: Existing Breast Screening Recommendations for Trans Men

Organization, Year [ref]	Document Type	Screening Recommendations			
		Additional Eligibility Criteria	Modality	Interval	Additional Recommendation
Without Chest Reconstruction[1]					
CCS, 2017 [22]	P	40–49 years, at average risk	NR	NR	Discuss individual risk of breast cancer and the benefits and risks of mammography.
		50–69 years, at average risk	Mammography	Biennial	NR
		≥70 years, at average risk	NR	NR	Discuss whether and how the client should be screened, according to individual risk factors.
CETH, 2016 [24]	G	NR	NR	NR	Follow guidelines for non-transgender women.
SHC, 2015 [26]	G	NR	CBE	Annual	Follow guidelines for cisgender women.
		50–71 years	Mammography	Biennial	
ACOG, 2011 [29]	P	NR	NR	NR	Age appropriate[2] screening is recommended.
VCH, TTSES & CRHC, 2006 [4]	G	With or without history of CSH use[3,4], with or without oophorectomy	Breast Exam[5]	Annual	NR
			Mammography	NR	Follow guidelines for natal females.
With Partial Chest Reconstruction[1]					
CCS, 2017 [22]	P	NR	US or MRI[6]	NR	Discuss individual risk factors[7] for breast cancer.
CETH, 2016 [24]	G	NR	US or MRI	NR	NR

Organization, Year [ref]	Document Type	Screening Recommendations			
		Additional Eligibility Criteria	Modality	Interval	Additional Recommendation
SHC, 2015 [26]	G	NR	Mammography	NR	Not required following chest reconstruction.
VCH, TTSES & CRHC, 2006 [4]	G	With or without history of CSH use[3,4], with or without oophorectomy	Mammography	NR	Not necessary following chest reconstruction, but should be considered if only a reduction is performed.
Trans Men in General (i.e., Chest Reconstruction Status Not Specified)					
CCS, 2017 [22]	P	High risk[8]	NR	NR	May need to be screened at an earlier age and/or more frequently than trans men at average risk.
IPPF, 2015 [25]	P	With history of CSH use[3,4]	NR	Periodic	Periodic cancer screening for those who retain their breast tissue.
SHC, 2015 [26]	G	Strong family history of breast cancer	Mammography	NR	Follow the same guidelines as for cisgender women regarding indications for referral to a high risk screening program/genetic assessment.
NHS, 2013 [28]	G	With developed breast tissue	NR	NR	Breast screening is recommended.

ACOG = American College of Obstetricians and Gynecologists; CBE = clinical breast examination; CCS = Canadian Cancer Society; CETH = Center of Excellence for Transgender Health; CRHC = Canadian Rainbow Health Coalition; CSH = cross-sex hormone; G = guideline; IPPF = International Planned Parenthood Federation; MRI = magnetic resonance imaging; NHS = National Health Service; NR = not reported; P = position statement; SHC = Sherbourne Health Centre; TTSES= Transcend Transgender Support and Education Society; US = ultrasonography; VCH = Vancouver Coastal Health

[1] Within the included documents “chest reconstruction” was variably termed as mastectomy, gender-affirming chest surgery or chest-surgery.

[2] Age range not specified.

[3] Within the included documents “CSH use” was variably termed as hormone use or testosterone.

[4] Duration of CSH use not specified.

[5] Document did not specify whether they recommended clinical breast examinations, breast self-examinations, or both.

[6] Specific breast screening recommendations for trans men who have had partial chest reconstruction were not provided. However, it was noted that in some cases mammography may not be possible following chest reconstruction surgery and breast ultrasound or MRI may be a preferable method of screening.

[7] Risk factors include: the amount of breast tissue removed, personal risk factors and history, whether the client has had oophorectomy, and whether the client is taking testosterone and other hormones.

[8] High risk is defined as: a genetic mutation in oneself, or having a parent, sibling or child who has a genetic mutation that puts them at a higher risk for breast cancer; a family history that indicates a lifetime risk of breast cancer that is equal to or greater than 25%, confirmed through genetic assessment; or receiving radiation therapy to the chest before 30 years of age as treatment for another cancer or condition.

Table 6: GRADE Summary of Findings Table for Benefits and Harms of Breast Screening for Trans Populations

Population: Asymptomatic, adult trans individuals with mean age [SD] of 43.1 [10.4] years **Intervention**: Breast screening with mammography, MRI, ultrasonography, CBE or BSE			
Outcome	**Effect**	**Number of Participants (Number of Studies)**	**Certainty of the Evidence (GRADE)**
Trans Men			
Benefits[1]	No primary research evidence identified		
Harms[2]			
Trans Women			
Benefits[1]	No primary research evidence identified		
Over-diagnosis, false-positives and patient-reported anxiety			
Painfulness of **mammography**[3]; assessed by the participant after mammography using a VAS ranging from 0 to 10	Mean (SD) scores ranged from 1.7 (2.1) to 2.0 (2.3)[4] points	50 (1)	⊕OOO VERY LOW[5,6]
Painfulness of **ultrasonography**[3]; assessed by the participant after ultrasonography using a VAS ranging from 0 to 10	Mean (SD) score = 0.5 (1.2)[7] points	50 (1)	⊕OOO VERY LOW[5,6]

BSE = breast self-exam; CBE = clinical breast exam; MRI = magnetic resonance imaging; SD = standard deviation; VAS = visual analogue scale

[1] Breast cancer-specific mortality, all-cause mortality, cancer detection rate, interval cancer rate, sensitivity and specificity

[2] Over-diagnosis, false-positives, patient-reported anxiety and patient-reported pain

[3] Performed by a single experienced radiologist.

[4] Two post-mammography assessments of participant-experienced pain were conducted. One assessment was administered by a radiologist and the other by a study nurse. The mean (SD) pain scores when assessed by the radiologist and study nurse were 1.7 (2.1) and 2.0 (2.3) points, respectively.

[5] Very low certainty rating = we have very little confidence in the effect estimate and the true effect is likely to be substantially different from the estimate of effect.

[6] The evidence was downgraded due to serious concerns regarding the observational nature of the study design and risk of bias. Detailed GRADE assessments are provided in Appendix 4, Table S6.

[7] The study personnel responsible for administering the post-ultrasonography assessment of experienced pain was not reported.

Table 7: Existing Breast Screening Recommendations for Trans Women

Organization, Year [ref]	Document Type	Screening Recommendations			
		Additional Eligibility Criteria	Modality	Interval	Additional Recommendation
History of CSH[1] Use					
CCS, 2017 [23]	P	40–49 years, at average risk, with CSH use >5 years	NR	NR	Discuss individual risks of breast cancer and the benefits and risks of mammography.
		50–69 years, at average risk, with CSH use >5 years, without breast implants	Mammography[2]	Biennial	NR
		50–69 years, at average risk, with CSH use >5 years, with breast implants	Diagnostic Mammography[2]	Biennial	NR
		≥70 years, at average risk, with CSH use >5 years	NR	NR	Discuss with client how often she should be screened for breast cancer.
		CSH use <5 years	NA	NA	Breast screening is not recommended.
CETH, 2016 [24]	G	≥50 years[3], with 5–10 years of CSH use	Mammography	Biennial	Clinicians may choose to reduce the age of onset of screening, number of years of female hormone exposure or frequency of screening in clients with significant family risk factors.
		Any age, with CSH use >5 years			
IPPF, 2015 [25]	P	Current CSH use[4]	NR	Periodic	NR
SHC, 2015 [26]	G	50–71 years, with CSH use >5 years	Mammography	Biennial	NR
		<50 years with additional risk factors[5]	Mammography	NR	Due to the lack of consensus on screening for younger trans women, emphasis may be placed on client preference following their counselling on the risks and benefits of screening.

Organization, Year [ref]	Document Type	Screening Recommendations			
		Additional Eligibility Criteria	Modality	Interval	Additional Recommendation
CDC, 2013 [27]	P	Past or current CSH use[4], meet all NBCCEDP eligibility requirements[6]	NR	NR	Providers should discuss benefits and harms of screening and discuss individual risk factors to determine if screening is medically indicated.
VCH, TTSES, & CRHC, 2006 [4]	G	>50 years[3], with additional risk[5], past (but not current) CSH use, breast growth, no orchiectomy	Mammography	NR	NR
		>50 years[3], with additional risk[5], current CSH use[7], no orchiectomy	Mammography	NR	NR
		>50 years[3], with additional risk[5], past or current CSH use, post-orchiectomy	Mammography	NR	NR
		NR	CBE	Annual	Not recommended.
		NR	BSE	Periodic	Not recommended.
No History of CSH[1] Use					
VCH, TTSES, & CRHC, 2006 [4]	G	No orchiectomy	NA	NA	Routine screening is not recommended.
Trans Women in General (i.e., Female CSH Use Not Specified)					
SHC, 2015 [26]	G	30–69 years, family history suggestive of hereditary breast cancer	MRI	Annual	Consider obtaining expert opinion regarding need for annual MRI in this group.
		With breast implants	Diagnostic Mammography	NR	NR
THIP, 2015 [5]	G	With developed breast tissue	NR	NR	Screening is recommended.

Organization, Year [ref]	Document Type	Screening Recommendations			
		Additional Eligibility Criteria	Modality	Interval	Additional Recommendation
NHS, 2013 [28]	G	With developed breast tissue	NR	NR	Screening is recommended.
ACOG, 2011 [29]	P	NR	NR	NR	Age appropriate screening is recommended.
TES, 2009 [30]	G	Who have no known increased risk of breast cancer	NR	NR	Follow screening guidelines for biological women.

ACOG = American College of Obstetricians and Gynecologists; BSE = breast self-examination; CBE = clinical breast examination; CCS = Canadian Cancer Society; CDC = Centers for Disease Control and Prevention; CETH = Center of Excellence for Transgender Health; CRHC = Canadian Rainbow Health Coalition; CSH = cross-sex hormone; G = guideline; IPPF = International Planned Parenthood Federation; MRI = magnetic resonance imaging; NA = not applicable; NBCCEDP = National Breast and Cervical Cancer Early Detection Program; NHS = National Health Service; NR = not reported; P = position statement; SHC = Sherbourne Health Centre; TTSES = Transcend Transgender Support and Education Society; THIP = Transgender Health Information Program; US = ultrasonography; VCH = Vancouver Coastal Health

[1] "CSH use" was variably termed as hormone use, feminizing hormone use, gender affirming hormone, estrogen or progestin within the included documents.

[2] Or other screening test (not specified) as appropriate.

[3] Upper age limit not reported.

[4] Duration of CSH use not reported.

[5] Additional risk factors include: estrogen + progestin use for > 5 years, family history of breast cancer, body mass index >35.

[6] Specific eligibility requirements not reported.

[7] CSH regimen that includes estrogen.

Appendix 1: Protocols for the Three Systematic Reviews

- Review One – Breast Cancer Risk, Prognosis and Mortality in the Trans Population using Cross-sex Hormones: Protocol for a Systematic Review (page 2–10)
- Review Two – Benefits and Harms of Breast Screening for the Trans Population: Protocol for a Systematic Review (page 11–20)
- Review Three – Breast Screening for Trans Populations: Protocol for a Systematic Review of Guidelines and Position Statements (page 21–29)

Review One: Breast Cancer Risk, Prognosis and Mortality in the Trans Population using Cross-sex Hormones: Protocol for a Systematic Review

INTRODUCTION

Rationale and Context

Trans is an umbrella term for individuals with diverse gender identities and expressions that differ from stereotypical gender norms [1]. It includes but is not limited to people who identify as transgender, trans woman (male-to-female), trans man (female-to-male), transsexual, cross-dresser, gender non-conforming, gender variant or gender queer (non-binary) [1]. A population-based study conducted in Massachusetts reported that 0.5% of the adult population identifies as trans [2]. Based on this value, it is estimated that in 2008, there were 53,500 trans individuals over age 15 living in Ontario [3].

Many trans individuals seek gender affirming medical interventions such as surgery and/or cross-sex hormone therapy to align their physical appearance with their sense of self, and as such, face unique healthcare needs [4]. The goal of cross-sex hormone therapy in trans individuals is to reduce gender dysphoria by facilitating a physical presentation of gender that is consistent with one's felt gender [5]. Endocrinologic feminization among those who were born male but identify as female, or are on the male-to-female spectrum, is achieved through the use of agents that directly or indirectly suppress the effects of androgens (e.g., gonadotrophic releasing hormone antagonists) and agents that induce female secondary sex characteristics (e.g., estrogen) [5]. Among individuals who were born female but identify as male or are on the female-to-male spectrum, endocrinologic masculinization is primarily achieved through the use of testosterone to induce male secondary sex characteristics [5].

The risk of breast cancer among trans individuals is unclear. Among cisgender females, reproductive factors that influence one's lifetime endogenous exposure to female sex hormones such as early age at menarche, nulliparity and late age at menopause, as well as exogenous use of these hormones (i.e., hormone replacement therapy) have been identified as risk factors for the development of breast cancer [6]. In addition to the presence of varying amounts of breast tissue, the risk of breast cancer in trans individuals is hypothesized to be influenced by the use of exogenous cross-sex hormones that alter one's exposure to female sex hormones [7,8]. Furthermore, the effect of cross-sex hormone therapy on prognostic features at breast cancer diagnosis and mortality from breast cancer is unclear [9,10].

A review of the literature is needed to better understand breast cancer risk, prognosis and mortality in trans individuals who use cross-sex hormones. This knowledge can help inform guidelines and policies related to breast cancer prevention, detection and care for this population.

Objective

The purpose of this systematic review is to identify and synthesize evidence on the impact of cross-sex hormone therapy on breast cancer risk, prognosis and mortality in the trans population. This systematic review, in conjunction with its companion evidence review (on the benefits and harms of breast screening for the trans population) and guideline review (on existing breast screening recommendations for the trans population), will be used to inform policy development for the appropriate inclusion of trans persons in the OBSP.

Key Questions

The key questions (KQ) for this review are:

KQ1: Among trans men, what is the impact of cross-sex hormone therapy[1] on breast cancer risk, prognosis and mortality?

KQ2: Among trans women, what is the impact of cross-sex hormone therapy[1] on breast cancer risk, prognosis and mortality?

Components of the Key Questions

The populations (P), interventions (I), comparisons (C) and outcomes (O), or the PICOs of interest for the KQs are outlined in the table below.

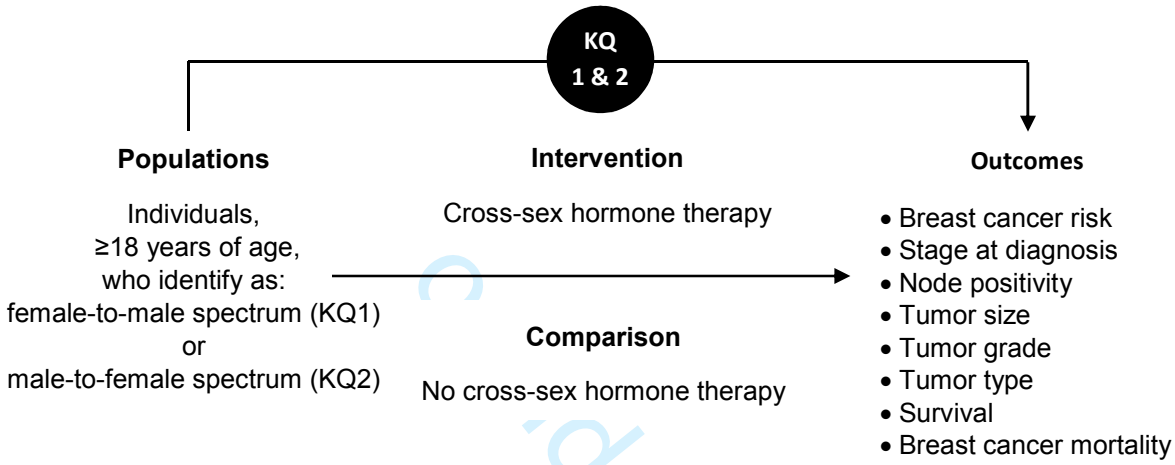
KQ	KQ1	KQ2
P	Individuals (≥18 years) born female who identify as non-binary, transmasculine or on the female-to-male spectrum with: • All original breast tissue remaining • Some breast tissue removed (i.e., breast reduction) • Chest contouring surgery (e.g., lipo sculpting, pectoral implants)	Individuals (≥18 years) born male who identify as non-binary, transfeminine or on the male-to-female spectrum with: • Breast augmentation/implant • No breast augmentation/implant
I	Male cross-sex hormone therapy (e.g., testosterone)	Female cross-sex hormone therapy (e.g., anti-androgen agents, estrogen or progesterone)
C	No cross-sex hormone therapy	No cross-sex hormone therapy
O	• Breast cancer risk (i.e., incidence of invasive breast cancer or ductal carcinoma in situ) • Prognostic features of breast cancer (i.e., stage at diagnosis; node positivity; tumor size, grade and type)	• Breast cancer risk (i.e., incidence of invasive breast cancer or ductal carcinoma in situ) • Prognostic features of breast cancer (i.e., stage at diagnosis; node positivity; tumor size, grade and type)

[1] For the purposes of this review, cross-sex hormone therapy is defined as the use of exogenous sex hormones that are opposite to those of an individual's natal sex for the purpose of aligning one's physical appearance to one's self-identified gender. Female cross-sex hormone therapy can include the use of estrogen, anti-androgen agents and progesterone. Male cross-sex hormone therapy generally consists of the use of testosterone [5].

KQ	KQ1	KQ2
	• Survival • Breast cancer mortality	• Survival • Breast cancer mortality

Analytic Framework

The analytic framework presented below provides a visual illustration of the key questions for this review, showing the links between the populations, the interventions and comparisons, and the clinically relevant outcomes.



METHODS

Data Sources and Search Strategies

To address the KQs of this systematic review, PubMed, MEDLINE, EMBASE, CINAHL, the Cochrane Database of Systematic Reviews, and websites of relevant professional associations, government bodies and community organizations will be searched for primary research articles and systematic reviews. The search strategy for PubMed, developed in consultation with the medical librarian, is provided in Table 1. This strategy will be adapted to search the other electronic databases. The medical librarian and members of the working group were consulted to generate a list of relevant websites and keywords for the targeted search (Table 2). Searches will be limited to articles published in English within the last 20 years (i.e., January 1, 1997). Reference lists of included studies and on topic systematic reviews will also be checked to identify potentially relevant citations missed by the database searches. Clinical experts within and outside of the requesting group may be contacted to recommend relevant citations.

Table 1: PubMed Search Strategy

Search	Query
1	transgender persons[mh] OR health services for transgender persons[mh] OR transsexualism[mh] OR transvestism[mh]
2	transgend*[tw] OR transsex*[tw] OR transman[tw] OR transmen[tw] OR transwom*[tw] OR transfem*[tw] OR transmasc*[tw] OR transmale*[tw] OR transidentified[tw] OR transperson[tw] OR transpeople[tw] OR transpeoples[tw] OR transpersons[tw]
3	((trans*[tw]) AND (sex*[tw] OR gender*[tw] OR woman[tw] OR women[tw] OR female*[tw] OR feminine[tw] OR male[tw] OR males[tw] OR man[tw] OR men[tw] OR masc*[tw] OR identified[tw] OR people[tw] OR peoples[tw] OR person[tw] OR persons[tw]))
4	((gender*[tw] OR sex*[tw]) AND (trans*[tw] OR variant[tw] OR identity[tw] OR non-binary[tw] OR nonbinary[tw] OR queer[tw] OR fluid[tw] OR nonconform*[tw] OR non-conform*[tw] OR reassign*[tw] OR re assign*[tw] OR dysphori*[tw]))
5	female-to-male[tw] OR male-to-female[tw] OR FTM[tw] OR MTF[tw] OR sexual minorit*[tw] OR cross gender*[tw] OR crossgender*[tw] OR transvesti*[tw] OR cross dress*[tw] OR crossdress*[tw] OR cross sex*[tw] OR crosssex*[tw] OR agender[tw] OR bigender[tw] OR bi-gender[tw] OR genderqueer[tw] OR cisgender[tw] OR cis-gender[tw] OR two-spirit*[tw] OR twospirit*[tw] OR 2 spirit*[tw] OR 2spirit*[tw]
6	1 OR 2 OR 3 OR 4 OR 5
7	"Hormone Replacement Therapy"[Mesh] OR "Gonadotropin-Releasing Hormone"[Mesh] OR (hormon*[tw] OR cross-sex hormon*[tw] OR crosssex hormon*[tw] OR sex hormon*[tw]) OR (endocrinologic*[tw] AND (Feminization[tw] OR Feminisation[tw] OR masculinization[tw] OR Masculinisation[tw])) OR ((hormone[tw] OR hormones[tw] OR hormonal[tw]) AND (antagonist[tw] OR supplement*[tw] OR agonist*[tw] OR exogenous[tw] OR management[tw] OR gonadotropin[tw] OR "gonadal releasing"[tw] OR sequel*[tw] OR replacement[tw] OR HRT[tw])) OR (therap*[tw] AND (estrogen[tw] OR testosterone[tw] OR progesterone[tw]))
8	breast neoplasm[mh] OR "Carcinoma, Intraductal, Noninfiltrating"[Mesh] OR ((breast*[tw] OR mammar*[tw]) AND (neoplasm*[tw] OR cancer*[tw] OR carcinoma*[tw] OR tumor[tw] OR tumour[tw] OR tumors[tw] OR tumours[tw] OR malignan*[tw])) OR ((hyperplasia[tw] OR Carcinoma*[tw]) AND (Intraductal[tw] OR DCIS[tw] OR Ductal[tw] OR In Situ[tw] OR Noninfiltrating[tw]))
9	6 AND 7 AND 8 Filters: Publication date from 1997/01/01 to 2017/12/31; English

Table 2: Sources and Keywords for Targeted Search

Relevant Websites for Grey Literature Search	Keywords
Professional Association Websites: • Canadian Medical Association • Canadian Professional Association for Transgender Health • College of Physicians and Surgeons of Ontario • Canadian Association of Radiology • Ontario Medical Association • Ontario College of Family Physicians • Ontario Association of Radiologists • American College of Radiology • Canadian Association of Radiologists • The European Society of Breast Cancer Specialists • Society of Breast Imaging • World Professional Association for Transgender Health **Government Bodies and Agencies:** • Public Health Agency of Canada • Canadian provincial and territorial cancer agencies • Health Canada • National Health Service (United Kingdom): Breast Screening Program (BSP) • Australian Cancer Screening Programs and Guidelines: BreastScreen Australia **Other:** • International Agency for Research on Cancer • World Health Organization • Canadian Cancer Society • American Cancer Society • Fenway Health • Rainbow Health Ontario • Sherbourne Health Centre • Trans PULSE project • Transgender Health Information Program • Trans Care BC • TransGender Care • The GLBT Health Access Project • Center of Excellence for Transgender Health	**Step 1:** • Transgend*/trans gend* • Transsex*/trans sex* • Transwom*/trans wom* • Transman/transmen/trans man/trans men • Nonbinary/non-binary • Nonbinary gender/non-binary gender • Gender variant • Gender identity • Gender reassign* • Genderqueer/gender queer • Gender nonconform*/gender non conform* • Twospirit*/two spirit*/2 spirit* • Crossdress*/cross dress* • Cross sex*/crosssex* • Cross gender*/crossgender* • Sexual minorit* • Male-to-Female/MTF • Female-to-Male/FTM • Gender fluid • Agender • Bigender/bi-gender • Cisgender/cis-gender • Dysphori* **Step 2:** • Cross-sex hormon*/cross sex hormon*/crosssex hormon* • Hormone replacement therapy • HRT • Sex hormon* • Gonadotropin releasing hormone • Progesterone • Estrogen • Testosterone **Step 3:** • Breast cancer* • Breast neoplasm* • Ductal Carcinoma In Situ • DCIS • Noninfiltrating intraductal carcinoma* • Intraductal carcinoma*

Eligibility Criteria

Studies will be selected for this review based on the inclusion and exclusion criteria outlined in Table 3.

Table 3: Eligibility Criteria

	In Scope → Include	Out of Scope → Exclude
Populations	**KQ1**: Individuals (≥18 years) born female who identify as non-binary, transmasculine or on the female-to-male spectrum with: • All original breast tissue remaining • Some breast tissue removed (i.e., breast reduction) • Chest contouring surgery (e.g., lipo sculpting, pectoral implants) **KQ2**: Individuals (≥18 years) born male who identify as non-binary, transfeminine or on the male-to-female spectrum with: • Breast augmentation/implant • No breast augmentation/implant	• Individuals <18 years of age • Individuals who have had a complete bilateral mastectomy
Interventions	**KQ1**: Male cross-sex hormone therapy (e.g., testosterone) **KQ2**: Female cross-sex hormone therapy (e.g., anti-androgen agents, estrogen or progesterone)	
Comparisons	**KQ1:** • Trans individuals not taking masculinizing cross-sex hormone therapy • Cisgender females **KQ2:** • Trans individuals not taking feminizing cross-sex hormone therapy • Cisgender males	• Studies without comparison groups
Outcomes	• Breast cancer risk (incidence) • Stage at diagnosis • Node positivity • Tumor size • Tumor grade • Tumor type • Survival • Breast cancer mortality	
Setting	No restrictions	
Study Designs	• Randomized controlled trials • Non-randomized experimental studies • Observational studies with comparison groups (i.e., cohort, case-control or cross-sectional)	• Systematic reviews • Qualitative studies • Modelling studies • Case series or reports
Location	No restrictions	

	In Scope → Include	Out of Scope → Exclude
Document Characteristics	• Published in past 20 years • Peer-reviewed • Full reports • Published in English • Grey literature • Conference proceedings and abstracts	• Commentaries and editorials • Non-systematic literature reviews

Data Management

Search results will be merged and de-duplicated in EndNote [11]. The remaining citations will be uploaded to DistillerSR [12], a web-based systematic review software program, to manage all phases of citation screening, data extraction, quality assessment, verification tasks and conflict resolution. Forms will be developed *a priori* for the screening levels based on the eligibility criteria and piloted to ensure that the questions are valid and that all reviewers are consistently applying the rules. Forms will also be developed *a priori* for data extraction and quality assessment; forms will be piloted and revised if necessary. All team members involved in screening, data extraction, quality assessment and verification will be familiar with the review protocol, trained to use Distiller and instructed in how to complete the forms.

Selection Process

All titles and abstracts identified by the search will be reviewed by two independent reviewers who will not be blinded to journal titles or author details; any citation marked for inclusion by either team member will move forward to full text relevance testing. Full text relevance testing will be conducted by two independent reviewers with consensus required for inclusion or exclusion. If consensus cannot be achieved, a third member of the review team will be consulted. Reasons for full text exclusion will be recorded and reported in a list of studies excluded at full text. Articles that reach full text relevance testing but cannot be retrieved in a complete version through an open access source, our membership in the Health Science Information Consortium of Toronto, or through our previously and legally obtained holdings may be excluded. Depending on costs and resource availability, for-purchase articles may be acquired for this review. We will not contact authors to obtain articles.

Data Extraction Process and Items

One reviewer will extract data from each of the included studies using forms that will be tailored for this review and housed on Distiller. A second reviewer will verify the accuracy and completeness of all extracted data; disagreements will be resolved through discussion and/or through third party consultation when consensus cannot be reached.

The list below identifies the data to be extracted, if provided from each included study. Information on these items must be contained within the paper(s); study authors will not be contacted for missing data.

- **Study characteristics**: design, objective, eligibility criteria, participant recruitment and selection methods, dates, sample size, geographic location, funding source

- **Participant characteristics**: age at study enrollment (mean, median, range or categorical), self-identified gender/sex (e.g., trans woman, trans man, non-binary), type of surgical procedure(s) undergone (e.g., breast augmentation, implants, breast reduction, total bilateral mastectomy, chest contouring surgery, total hysterectomy, oophorectomy or none), age when surgical procedure was completed
- **Intervention details**: type of hormone(s) used (e.g., testosterone, estrogen, progesterone) and dosage, route of hormone delivery (e.g., oral, intravenous, transdermal), age at hormone therapy initiation, age at cessation of hormone therapy, duration of hormone use
- **Outcome details:** definitions, how outcomes were assessed, units of measurement, when outcome data were collected and follow-up duration
- **Key results for each outcome:** number (%) with outcome in each group, crude and/or adjusted effect estimates, 95% confidence intervals and/or *p* values

Quality Assessment of Individual Studies

The quality of individual studies will be assessed by a single reviewer. A second reviewer will verify all risk of bias assessment ratings; disagreements will be resolved through discussion and through third party consultation when consensus cannot be reached. The following quality assessment tools will be used: Cochrane's Risk of Bias tool [13] for randomized and non-randomized controlled trials and the Newcastle Ottawa Scale [14] for cohort and case-control studies. We are unaware of a formal tool that is widely used to assess the methodological quality of cross-sectional studies. In light of this, quality assessment of cross-sectional studies using a formal tool will not be conducted. The methodological quality of cross-sectional studies will be examined qualitatively through consideration of key methodological components such as the selection of participants, exposure and outcome assessment and evaluation of confounding.

Analysis, Synthesis and Reporting

The lead reviewer will conduct the synthesis and a second member of the review team, who is familiar with the included studies, will verify its accuracy and completeness. The results of the literature search will be described using a PRISMA flow diagram and a narrative summary. Similarities and differences in study details, quality, samples and intervention features will be examined across the included studies. Details about the body of included evidence will be presented narratively and in tables. To address each KQ, data relating to each outcome of interest from the included body of evidence will be presented narratively and in tables. Key messages for each outcome will be presented in the light of the quality of evidence. There will be no statistical pooling of data across studies.

GRADE Assessments

We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [15,16] to assess the quality of the evidence available for four outcomes: breast cancer risk, stage at diagnosis, survival and mortality. These outcomes have been identified by the requesting group as critical and important for

decision-making. GRADE assessments produce overall ratings (high, moderate, low or very low) that reflect the level of confidence in the estimates of effect. The evidence for each outcome will be grouped by study design. As per the GRADE system, RCT evidence will begin with a high quality rating and non-randomized trials and observational studies with comparison groups will begin with a low quality rating. Each body of evidence will be evaluated against the relevant GRADE criteria, rating down if there are serious or very serious concerns related to risk of bias, inconsistency, indirectness, imprecision or publication bias. GRADEpro software [17] will be used to perform these assessments and to generate the Evidence Profile and Summary of Findings tables.

Review Two: Benefits and Harms of Breast Screening for the Trans Population: Protocol for a Systematic Review

INTRODUCTION

Rationale and Context

Trans is an umbrella term for individuals with diverse gender identities and expressions that differ from stereotypical gender norms [1]. It includes but is not limited to people who identify as transgender, trans woman (male-to-female), trans man (female-to-male), transsexual, cross-dresser, gender non-conforming, gender variant or gender queer (non-binary) [1]. A population-based study conducted in Massachusetts reported that 0.5% of the adult population identifies as trans [2]. Based on this value, it is estimated that in 2008, there were 53,500 trans individuals over the age of 15 living in Ontario [3].

It is recognized that the trans population is medically underserved [18]. A retrospective study demonstrated that trans individuals were less likely to pursue breast screening with mammography as compared to women who do not identify as trans (i.e., cisgender females) [19]. A survey of 431 trans individuals living in Ontario found that, among those who reported a perceived need for a mammogram, 30% of female-to-male individuals and 25% of male-to-female individuals were unable to access one [20]. While these studies demonstrate that trans individuals face barriers in accessing and participating in breast screening, the evidence pertaining to the effectiveness, performance and harms of breast screening in the trans population has been lacking [8].

Currently, the OBSP screens average risk women between the ages of 50 and 74 years old biennially with mammography, and high risk women between the ages of 30 and 69 years old with annual mammography and magnetic resonance imaging [21]. Cancer Care Ontario is currently developing a policy pertaining to the appropriate inclusion of trans persons in its organized breast screening program. Screening recommendations for trans individuals should be based on the best available evidence, thus a thorough review of the potential benefits and harms of breast screening with various modalities is needed.

Objective

The purpose of this systematic review is to identify and synthesize evidence on the potential benefits and harms of breast screening in the trans population. This systematic review, in conjunction with its companion evidence and guideline reviews for both breast and cervical screening, will be used to inform policy development for the appropriate inclusion of trans persons in the OBSP and the Ontario Cervical Screening Program.

Key Questions

KQ1. Is breast screening with mammography, magnetic resonance imaging (MRI), ultrasound, clinical breast exam (CBE) or breast self-exam (BSE) effective in reducing breast cancer-specific mortality or all-cause mortality in the trans population?

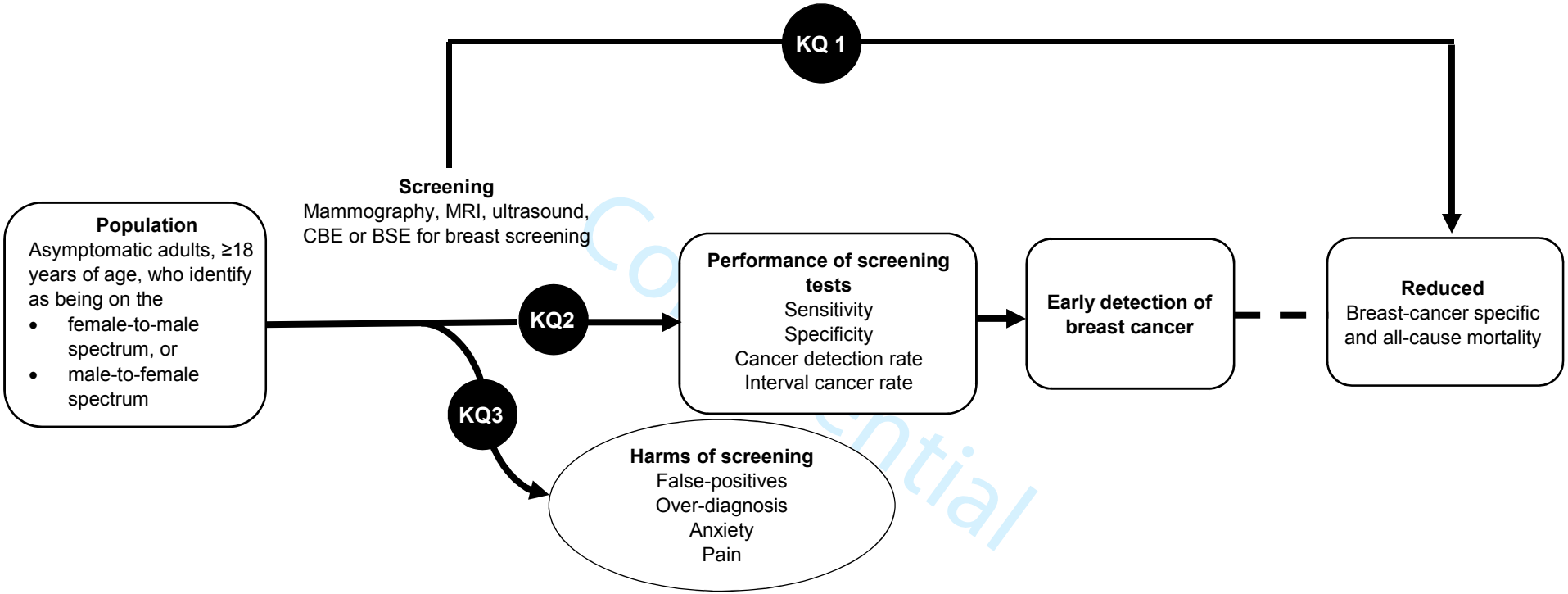
SQ1a. Does the effectiveness of breast screening in the trans population vary by screening modality?

KQ2. What is the performance of mammography, MRI, ultrasound, CBE or BSE for breast screening in the trans population?

KQ3. What are the potential harms of breast screening with mammography, MRI, ultrasound, CBE or BSE in the trans population?

Analytic Framework

The analytic framework provides a visual illustration of the key questions, showing the links between the population, the intervention and the clinically relevant outcomes.



Components of the Key Questions

The population (P), intervention (I), comparison (C) and outcomes (O), or the PICO of interest for the KQs are outlined in the table below.

KQ	1	1a	2	3
P	Asymptomatic individuals (≥18 years) born female who identify as non-binary, transmasculine or on the female-to-male spectrum with: • All original breast tissue remaining with a history of male hormone use • Some original breast tissue remaining with or without a history of male hormone use • Chest contouring surgery with or without a history of male hormone use Asymptomatic individuals (≥18 years) born male who identify as non-binary, transfeminine or on the male-to-female spectrum with: • Breast augmentation/implants with a history of female hormone use • No breast augmentation/implants with a history of feminizing hormone use	Same as KQ1	Same as KQ1	Same as KQ1
I	Breast screening with mammography, MRI, ultrasound, CBE or BSE	Same as KQ1	Same as KQ1	Same as KQ1
C	No breast screening	Comparisons between screening modalities	No comparison group required[1]	No comparison group required
O	• Breast-cancer-specific mortality • All-cause mortality • Number needed to screen to prevent one breast-cancer-related death	Same as KQ1	• Sensitivity • Specificity • Cancer detection rate • Interval cancer rate	• Over-diagnosis • False-positives • Anxiety • Pain/discomfort

[1] Positive screens must be compared to the reference standard (i.e., pathology results from biopsy) and negative results must be followed for one year

METHODS

Data Sources and Search Strategies

To address the KQs of this review, PubMed, MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews, and websites of relevant professional associations, government bodies and community organizations will be searched for primary research articles and systematic reviews. The search strategy for PubMed, developed in consultation with the medical librarian, is provided below. This strategy will be adapted to search the other electronic databases. The medical librarian and members of the working group were consulted to generate a list of relevant websites and keywords for the targeted search (Table 1). Searches will be limited to articles published in English within the last 20 years (i.e., January 1, 1997). Reference lists of included studies, on topic systematic reviews and literature reviews will also be checked to identify citations missed by the database searches. Clinical experts within and outside of the requesting group may be contacted to recommend relevant citations.

Draft PubMed Search Strategy

1. transgender persons[mh] OR health services for transgender persons[mh] OR transsexualism[mh] OR transvestism[mh]
2. transgend*[tiab] OR transsex*[tiab] OR transman[tiab] OR transmen[tiab] OR transwom*[tiab] OR transfem*[tiab] OR transmasc*[tiab]
3. (trans[tiab]) AND (sex*[tiab] OR gender*[tiab] OR woman[tiab] OR women[tiab] OR female*[tiab] OR male[tiab] OR males[tiab] OR man[tiab] OR men[tiab] OR identified[tiab])
4. (gender*[tiab]) AND (trans[tiab] OR variant[tiab] OR identity[tiab] OR non-binary[tiab] OR nonbinary[tiab] OR queer[tiab] OR fluid[tiab] OR nonconforming[tiab] OR non-conforming[tiab] OR reassign*[tiab] OR re assign*[tiab])
5. Female-to-Male[tiab] OR male-to-female[tiab] OR FTM[tiab] OR MTF[tiab] OR sexual minority[tiab] OR sexual minorities[tiab] OR cross gender*[tiab] OR crossgender*[tiab] OR transvesti*[tiab] OR cross dress*[tiab] OR crossdress*[tiab] OR agender[tiab] OR bigender[tiab] OR bi-gender[tiab] OR genderqueer[tiab] OR cisgender[tiab] OR cis-gender[tiab] OR two-spirit[tiab] OR twospirit[tiab]
6. 1 or 2 or 3 or 4 or 5
7. mass screening[mh] OR early detection of cancer[mh] OR mammography[mh] OR magnetic resonance imaging[mh:noexp] OR ultrasonography, mammary[mh]
8. clinical breast exam[tiab] OR breast self-exam[tiab] OR CBE[tiab] OR BSE[tiab] OR mammogr*[tiab] OR xeromammogra*[tiab] OR tomosynthesis[tiab] OR Scintimammogra*[tiab] OR MRI[tiab] OR magnetic resonance imaging[tiab] OR ultrasound*[tiab] OR ultrasonograph*[tiab] OR imaging[tiab]
9. 7 or 8

10. breast neoplasm[mh] OR ((breast*[tiab] OR mammar*[tiab]) AND (neoplasm*[tiab] OR cancer[tiab] OR carcinoma[tiab] OR tumor[tiab] OR tumour[tiab] OR tumors[tiab] OR tumours[tiab] OR malignan*[tiab]))
11. 6 and 9 and 10 Filters: Publication date from 1997/01/01 to 2017/12/31; English

Table 1: Sources and Keywords for Grey Literature Search

Relevant Websites for Grey Literature Searches	Keywords
Professional Association Websites: • Canadian Medical Association • Canadian Professional Association for Transgender Health • College of Physicians and Surgeons of Ontario • Canadian Association of Radiology • Ontario Medical Association • Ontario College of Family Physicians • Ontario Association of Radiologists • American College of Radiology • Canadian Association of Radiologists • The European Society of Breast Cancer Specialists • Society of Breast Imaging • World Professional Association for Transgender Health **Government Bodies and Agencies:** • Public Health Agency of Canada • Canadian provincial and territorial cancer agencies • Health Canada • National Health Service (United Kingdom): Breast Screening Program (BSP) • Australian Cancer Screening Programs and Guidelines: BreastScreen Australia **Other:** • International Agency for Research on Cancer • World Health Organization • Canadian Cancer Society • American Cancer Society • Fenway Health • Rainbow Health Ontario • Sherbourne Health Centre • Trans PULSE project • Transgender Health Information Program • Trans Care BC • TransGender Care • The GLBT Health Access Project • Center of Excellence for Transgender Health	**Step 1:** • Transgend* • Transsex* • Transwom* • Transman/ transmen • Non-binary • Gender variant • Gender queer/ genderqueer • Gender nonconforming • Non-binary gender • Two spirit*/ two-spirit*/ 2 spirit*/ 2-spirit* • Cross dresser/ crossdresser • Male-to-Female/ MTF • Female-to-Male/ FTM • Gender fluid • Agender • Bigender/ bi-gender • Cisgender/ Cis-gender **Step 2:** • Breast cancer screening • Mammography or Mammogram • Magnetic resonance imaging / “MRI” • Ultrasonography or Ultrasound • Clinical Breast Exam or “CBE” • Breast Self Exam or “BSE”

Eligibility Criteria

Studies will be selected for this review based on the inclusion and exclusion criteria outlined in Table 2 below.

Table 2: Eligibility Criteria

	In Scope → Include	Out of Scope → Exclude
Populations	Asymptomatic individuals (≥18 years) born female who identify as non-binary, transmasculine or on the female-to-male spectrum with: • All original breast tissue remaining with a history of male hormone use • Some original breast tissue remaining (i.e., breast reduction) with or without a history of male hormone use • Chest contouring surgery (e.g. lipo sculpting, pectoral implants) with or without a history of male hormone use Asymptomatic individuals (≥18 years) born male who identify as non-binary, transfeminine or on the male-to-female spectrum with: • Breast augmentation/implants with a history of female hormone use • No breast augmentation/implants with a history of female hormone use	• Individuals born female with all breast tissue remaining and do not have a history of male hormone use • Individuals born female who have had a complete bilateral mastectomy • Individuals born male who do not have a history of female hormone use (with or without breast augmentation/implants)
Interventions	Breast screening using one of the following: • mammography • MRI • ultrasound • CBE • BSE	• Thermography • Tissue sampling • Diagnostic testing
Comparisons	**KQ1:** Trans individuals not screened for breast cancer **SQ1a:** Comparisons of two or more screening modalities among trans individuals **KQ2:** No comparison group required; however, positive screens must be compared to the reference standard (i.e., pathology results from biopsy) and negative screens must be followed for one year **KQ3**: Trans individuals not screened for breast cancer, or no comparison group	• Studies without a comparison group (KQs 1)
Outcomes	• Breast cancer-specific mortality • All-cause mortality • Number needed to screen to prevent one breast cancer-related death • Cancer detection rate • Interval cancer rate • Sensitivity • Specificity • Over-diagnosis • False-positives • Patient-reported anxiety • Patient-reported pain/discomfort	
Settings	No restrictions	

	In Scope → Include	Out of Scope → Exclude
Study Designs	• Randomized controlled trials • Non-randomized experimental studies • Observational studies with or without (KQ2 and KQ3 only) comparison groups • Diagnostic evaluation studies	• Systematic reviews • Modelling studies • Qualitative studies • Case series or reports
Location	No restrictions	
Document Characteristics	• Published in past 20 years • Peer-reviewed • Full reports • Published in English • Grey literature • Conference proceedings and abstracts	• Commentaries and editorials • Guidelines • Position statements • Non-systematic literature reviews

Data Management

Search results will be merged and de-duplicated in EndNote [11]. The remaining citations will be uploaded to DistillerSR [12], a web-based systematic review software program, to manage all phases of citation screening and data extraction. Forms will be developed for the screening levels based on the eligibility criteria and piloted to ensure that the questions are valid and that all reviewers are consistently applying the rules. Forms will also be developed *a priori* for data extraction and will be piloted and revised if necessary. All team members involved in screening, data extraction and verification will be familiar with the review protocol, trained to use Distiller and instructed in how to complete the forms.

Selection Process

All titles and abstracts identified by the search will be reviewed by two independent reviewers who will not be blinded to journal titles or author details; any citation marked for inclusion by either team member will move forward to full text relevance screening. Reasons for exclusion at the title and abstract phases will be recorded. Full text relevance screening will be conducted by two independent reviewers with consensus required for inclusion or exclusion. If consensus cannot be achieved, a third member of the review team will be consulted. Reasons for full text exclusion will be recorded and reported in a list of studies excluded at the full text phase. Articles that reach full text relevance screening but cannot be retrieved in a complete version through an open access source, our membership in the Health Science Information Consortium of Toronto, or through our previously and legally obtained holdings may be excluded. Depending on costs and resource availability, for-purchase articles may be acquired for a review. We will not contact authors to obtain articles.

Data Extraction Process and Items

One reviewer will extract data from each of the included studies using forms that will be tailored for this review and housed on Distiller. A second reviewer will verify all extracted data; disagreements will be resolved through discussion and/or through third party consultation when consensus cannot be reached.

Data items to be extracted include:

- **Study characteristics:** study design, objective, eligibility criteria, participant recruitment and selection methods, study dates, sample size, geographic location, setting (community- vs. hospital-based screening), study funding source
- **Population characteristics:**
  - Age at study enrollment (mean, median, range or categorical)
  - Self-identified gender/sex (e.g., trans woman, trans man, non-binary)
  - Type of surgical procedure(s) undergone (i.e., breast augmentation, breast implants, breast reduction, total bilateral mastectomy, chest contouring surgery, none), and age when surgical procedure was completed
  - Past or current use of cross-sex hormone therapy (yes/no), type of hormone(s) used (e.g., testosterone, estrogen, progesterone) and dosage, route of hormone delivery (e.g., oral, intravenous, transdermal), age at initiation of hormone therapy, age at cessation of hormone therapy, duration of hormone use
- **Intervention characteristics:** type of screening test(s) evaluated (i.e., mammography, MRI, ultrasound, CBE, BSE), screening interval
- **Outcome characteristics:** definitions, how outcomes were assessed, unit of measurement, when outcome data was collected and follow-up duration
- **Key results for effectiveness and harms outcomes:** number (%) with the outcome of interest in each group, crude and/or adjusted effect estimates, 95% confidence intervals and/or p-values. If the study does not provide an estimate of the number needed to screen, the event rate in the screening (intervention) and no screening (control) groups will be used to calculate it using the formula:

$$Number\ needed\ to\ screen = \frac{1}{Event\ rate_{control} - Event\ rate_{intervention}}$$

- **Key results for performance metric outcomes:** study reported cancer detection rate, interval cancer rate, sensitivity and specificity will be used. If the study does not report the outcomes of interest, the number of true positives, false positives, true negatives and false negatives will be used to calculate the outcomes of interest using the following formulas:

$$Cancer\ detection\ rate = \frac{number\ of\ breast\ cancers}{total\ number\ of\ screens}$$

$$Interval\ cancer\ rate = \frac{\begin{array}{c}Number\ of\ screen-eligible\ individuals\ who\\ developed\ invasive\ breast\ cancer\ in\ the\ XX\ year(s)\\ following\ a\ normal\ breast\ screening\ result\end{array}}{Number\ of\ screens}\ \text{x}\ 1{,}000$$

where XX is the period of time between scheduled screenings.

$$Sensitivity = \frac{true\ positives}{true\ positives + false\ negatives}$$

$$Specificity = \frac{true\ negatives}{true\ negatives + false\ positives}$$

Information on these items must be contained within the paper(s); study authors will not be contacted for missing data.

Quality Assessment of Individual Studies

The quality of individual studies will be assessed by a single reviewer. A second reviewer will verify all risk of bias assessment ratings; disagreements will be resolved through discussion and through third party consultation when consensus cannot be reached. The following quality assessment tools will be used: Cochrane's Risk of Bias tool [13] for randomized and non-randomized controlled trials, the Newcastle-Ottawa Scale [14] for cohort and case-control studies and the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) II tool [22] for diagnostic evaluation studies. We are unaware of a formal tool that is widely used to assess the methodological quality of cross-sectional studies. In light of this, quality assessment of cross-sectional studies using a formal tool will not be conducted. The methodological quality of cross-sectional studies will be examined qualitatively through consideration of key methodological components such as the selection of participants, exposure and outcome assessment and evaluation of confounding.

Analysis, Synthesis and Reporting

The lead reviewer will conduct the synthesis and a second member of the review team, who is familiar with the included studies, will verify its accuracy and completeness. The results of the literature search will be described using a PRISMA flow diagram and a narrative summary. Similarities and differences in study details, quality, samples and intervention features will be examined across the included studies. Details about the body of included evidence will be presented narratively and in tables.

For each KQ, results will be organized by screening modality. Key messages for each outcome will be presented in the light of the quality of evidence. Given the novelty of this topic, we do not anticipate the ability to perform a meta-analysis. However, where possible and when appropriate, a meta-analysis will be considered.

GRADE Assessments

We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [15,16] to assess the quality of the evidence available for a limited selection of outcomes. These outcomes will be chosen by the requesting group upon completion of article screening. GRADE assessments produce overall ratings (high, moderate, low or very low) that reflect the level of confidence in the estimates of effect. The evidence for each outcome will be grouped by study design. As per the GRADE system, RCT evidence will begin with a high quality rating and non-randomized trials and observational studies with comparison groups will begin with a low quality rating. Each body of evidence will be evaluated against the relevant GRADE criteria, rating down if there are serious or very serious concerns related to risk of bias, inconsistency, indirectness, imprecision or publication bias. GRADEpro software [17] will be used to perform these assessments and to generate the Evidence Profile and Summary of Findings tables.

Review Three: Breast Screening for Trans Populations: Protocol for a Systematic Review of Guidelines and Position Statements

INTRODUCTION

Rationale and Context

Trans is an umbrella term for individuals with diverse gender identities and expressions that differ from stereotypical gender norms [1]. It includes but is not limited to people who identify as transgender, trans woman (male-to-female), trans man (female-to-male), transsexual, cross-dresser, gender non-conforming, gender variant or gender queer (non-binary) [1]. A recent population-based survey conducted in the United States reported that approximately 0.5% of the adult population identifies as trans [2]. Based on this value, it is estimated that in 2008, there were 53,500 trans individuals over age 15 living in Ontario [3].

It is recognized that the trans population is medically underserved [18]. A retrospective study reported that trans individuals were less likely to pursue breast screening with mammography as compared to women who do not identify as trans (i.e., cisgender females) [19]. Additionally, both the trans and medical communities have identified gaps in the knowledge and training of healthcare providers on trans healthcare needs, as well as appropriate clinical guidance for providing and managing their care [18,23-25]. A recent survey of obstetrics and gynecology care providers across the United States reported that 59% were unaware of the recommendations for breast screening in male-to-female patients, and only 29% were comfortable caring for trans individuals [26].

Currently, the Ontario Breast Screening Program (OBSP) screens average risk women between the ages of 50 and 74 biennially with mammography, and high risk women between the ages of 30 and 69 with annual mammography and magnetic resonance imaging [21]. The risk of breast cancer and effectiveness of breast screening in trans populations has not been well studied [8]. Screening recommendations for trans individuals should be based on the best available evidence, thus a thorough review of existing breast screening guidelines for the trans population is needed.

Objective

The purpose of this guideline review is to identify and synthesize published recommendations for breast screening in trans populations. A separate review will be conducted assessing the published recommendations pertinent to cervical cancer screening. This guideline review, in conjunction with the cervical companion evidence reviews, will be used to inform policy development for the appropriate inclusion of trans persons in the OBSP and the Ontario Cervical Screening Program.

Key Question

The key question (KQs) for this review is:

KQ1. What are the recommended eligibility requirements, screening modalities and screening intervals for breast screening in trans populations?

METHODS

Information Sources and Search Strategies

To address the KQ of this review, PubMed, Medline, guideline databases, the websites of relevant guideline development groups, professional associations, government bodies and community organizations will be searched for guidelines and position statements on breast screening in trans populations. The medical librarian (JC), members of the requesting group and the CADTH's Grey Matters tool for searching health-related grey literature [27] were consulted to help generate the list of websites, databases and keywords for the targeted search (Table 1). The PubMed search strategy was developed in consultation with the medical librarian (JC) and is outlined in the Tables 2 and 3. Searches will be limited to guideline documents published in English within the last 20 years (i.e., January 1, 1997). Reference lists of included documents will be checked to identify citations missed by the database searches. Clinical experts within and outside of the requesting group may be contacted to recommend relevant citations.

Table 1: Sources and Keywords for Targeted Search

Guideline Databases and Websites	Keywords
Guideline Databases • Agency for Health Research and Quality (AHRQ) National Guideline Clearinghouse • Canadian Medical Association Infobase • Canadian Partnership Against Cancer Standards and Guidelines Evidence Database • International Guideline Library • National Health and Medical Research Council • TRIP Database • Standards and Guidelines Evidence (SAGE) Repository **Guideline Development Groups** • Canadian Task Force on Preventive Health Care • United States Preventive Services Task Force • National Comprehensive Cancer Network • National Institute for Health and Care Excellence • Program in Evidence-Based Care • Scottish Intercollegiate Guideline Network **Professional Association Websites** • Canadian Medical Association • Canadian Professional Association for Transgender Health • World Professional Association for Transgender Health • College of Physicians and Surgeons of Ontario • Canadian Association of Radiology • Ontario Medical Association • Ontario College of Family Physicians • Ontario Association of Radiologists • American College of Radiology • Canadian Association of Radiologists • The European Society of Breast Cancer Specialists	**Step 1:** • Transgend* • Transsex* • Transwom* • Transman/ transmen • Non-binary • Gender variant • Gender queer/ genderqueer • Gender nonconforming • Non-binary gender • Two spirit*/ two-spirit*/ 2 spirit*/ 2-spirit* • Cross dresser/ crossdresser • Male-to-Female/ MTF • Female-to-Male/ FTM • Gender fluid • Agender • Bigender/ bi-gender • Cisgender/ Cis-gender **Step 2:** • Breast cancer screening • Mammography or Mammogram • Magnetic resonance imaging / "MRI" • Ultrasonography or Ultrasound • Clinical Breast Exam or "CBE" • Breast Self Exam or "BSE"

Guideline Databases and Websites	Keywords
• Society of Breast Imaging **Government Bodies and Agencies** • Public Health Agency of Canada • Canadian provincial and territorial cancer agencies • Health Canada • National Health Service (United Kingdom): Breast Screening Program (BSP) • Australian Cancer Screening Programs and Guidelines: BreastScreen Australia **Other** • International Agency for Research on Cancer • World Health Organization • Canadian Cancer Society • American Cancer Society • Fenway Health • Rainbow Health Ontario • Sherbourne Health Centre • Trans PULSE project • Transgender Health Information Program • Trans Care BC • TransGender Care • The GLBT Health Access Project • Center of Excellence for Transgender Health	

Table 2: Search Strategy for PubMed

Search	Query
1	"transgender persons"[mh] OR "health services for transgender persons"[mh] OR transsexualism[mh] OR "Transvestism"[mh]
2	transgender*[tiab] OR transsex*[tiab] OR transman[tiab] OR transwoman[tiab] OR transmen[tiab] OR transwomen[tiab] transfem*[tiab]
3	((Trans[tiab]) AND (sexual[tiab] OR sexuals[tiab] OR gender[tiab] OR gendered[tiab] OR woman[tiab] OR women[tiab] OR man[tiab] OR men[tiab] OR identified[tiab]))
4	((gender*[tiab]) AND (trans[tiab] OR variant[tiab] OR identity[tiab] OR variant[tiab] OR "two spirit"[tiab] OR "twospirit"[tiab] OR "non-binary"[tiab] OR “nonbinary”[tiab] OR “non-binary”[tiab] OR queer[tiab] OR "genderqueer"[tiab] OR fluid[tiab] OR “nonconforming"[tiab] OR “non conforming"[tiab] OR reassign*[tiab] OR re assign*[tiab]))
5	"Female-to-Male"[tiab] OR "male-to-female"[tiab] OR "FTM"[tiab] OR "MTF"[tiab] OR "sexual minority"[tiab] OR "sexual minorities”[tiab] OR "cross gender"[tiab] OR "cross gendered"[tiab] OR transvesti*[tiab] OR "cross dress"[tiab] OR "cross dresser"[tiab] OR "cross dressing"[tiab] OR “agender”[tiab] OR “a gender” [tiab] OR “bigender”[tiab] OR “bi-gender”[tiab] or “bi gender”[tiab] or
6	1 OR 2 OR 3 OR 4 OR 5
7	"mass screening"[mh] OR "early detection of cancer"[mh] OR mammography[mh] OR "magnetic resonance imaging"[mh:noexp] OR "ultrasonography, mammary"[mh]
8	"clinical breast exam"[tiab] OR "breast self-exam"[tiab] OR "CBE”[tiab] OR “BSE"[tiab] OR xeromammogra*[tiab] OR "MRI"[tiab] OR magnetic resonance imaging[tiab] OR mammogr*[tiab] OR ultrasound*[tiab] OR ultrasonograph*[tiab] OR Scintimammogra*[tiab] OR imaging[tiab] OR tomosynthesis[tiab]
9	7 OR 8
10	breast neoplasm[mh] OR ((breast*[tiab] OR mammar*[tiab]) AND (neoplasm*[tiab] OR cancer[tiab] OR carcinoma[tiab] OR tumor[tiab] OR tumour[tiab] OR tumors[tiab] OR tumours[tiab] OR malignan*[tiab]))
11	#6 AND #9 AND #10 Filters: Publication date from 1997/01/01 to 2017/12/31; English

Table 3: Search Strategy for Medline

Search	Query
1	exp "transgender persons"/ or exp "health services for transgender persons"/ or exp transsexualism/ or exp transvestism/
2	(transgender* or transsex* or transman or transwoman or transmen or transwomen or transfem*).ti,ab,kw.
3	(Trans adj2 (sexual or sexuals or gender* or gendered or woman or women or man or men or identified)).ti,ab,kw.
4	(gender* adj1 (trans or variant or identity or "two spirit" or "twospirit" or "non-binary" or “nonbinary” or “non binary” or queer or "genderqueer" or fluid or "nonconforming" or "non conforming" or reassign* or re assign*)).ti,ab,kw.
5	("Female-to-Male" or "male-to-female" or "FTM" or "MTF" or "sexual minority" or "sexual minorities" or "cross gender" or "cross gendered" or "cross dressing" or "cross dress" or "cross dresser" or “agender” or “ a gender” “bigender” or “bi-gender” or “bi gender” or “cisgender” or “cis gender” or transvesti*).ti,ab,kw.
6	or/1-5
7	exp breast neoplasm/
8	((breast* or mammar*) adj2 (neoplasm* or cancer or carcinoma or tumor or tumour or tumors or tumours or malignan*)).ti,ab,kw.
9	or/7-8
10	exp "mass screening"/ or exp "early detection of cancer"/ or "magnetic resonance imaging"/ or exp "ultrasonography, mammary"/ or exp "mammography"/
11	(ultrasonograph* or ultrasound* or "clinical breast exam" or "breast self-exam" or "CBE" or "BSE" or mammogra* or "magnetic resonance imaging" or "MRI" or xeromammogra* or Scintimammogra* or tomosynthesis or imaging).ti,ab,kw.
12	or/10-11
13	6 and 9 and 12
14	limit 13 to (english language and yr="1997 -Current")

Eligibility Criteria

Documents will be selected for this review based on the inclusion and exclusion criteria outlined in the Table 4.

Table 4: Eligibility Criteria

	In Scope → Include	Out of Scope → Exclude
Population	Individuals (≥18 years) born female but do not identify as female (i.e., identify as non-binary, transmasculine or as someone on the female-to-male spectrum) with: • All original breast tissue remaining and history of male hormone use • All original breast tissue remaining and no history of male hormone use • Some original breast tissue remaining (i.e., breast reduction) and history of male hormone use • Some original breast tissue remaining and no history of male hormone use • With or without chest contouring surgery (e.g. lipo sculpting, pectoral implants) Individuals (≥18 years) born male but do not identify as male (i.e., identify as non-binary, transfeminine, or as someone on the male-to-female spectrum) with: • History of female hormone use and breast augmentation/ implant • History of female hormone use without breast augmentation/ implant • No history of female hormone use, with or without breast augmentation/ implant	• Individuals < 18 years of age • Individuals born male with no history of feminizing hormone usage • Individuals who have had complete bilateral mastectomy
Interventions	Breast screening using one of the following: • mammography • magnetic resonance imaging (MRI) • ultrasound • Clinical Breast Exam (CBE) • Breast Self-Exam (BSE)	• Thermography • Tissue sampling • Diagnostic testing
Domains	Recommendations/ guidelines for breast screening in trans populations with focus on: • eligibility requirements • screening modalities • screening intervals	
Type of documents	• Guidelines • Position statements	• Commentaries and editorials • Systematic reviews without an accompanying guideline • Primary literature on breast screening in trans populations
Settings	No restrictions	
Location	No restriction	

	In Scope → Include	Out of Scope → Exclude
Time frame	1997 to present	
Document Characteristics	• Peer-reviewed • Grey literature • Conference proceedings and abstracts • English	

Data Management

Results of the PubMed and targeted website searches will be merged and de-duplicated in EndNote [11]. The remaining citations will be uploaded to DistillerSR [12], a web-based systematic review software program, to manage all phases of citation screening and data extraction. Forms will be developed for the title and abstract screening and full text screening levels based on the eligibility criteria and piloted to ensure that the questions are valid and that both reviewers are consistently applying the rules. Data extraction form will be developed in Excel, piloted and revised if necessary. All team members involved in screening, data extraction and verification will be familiar with the review protocol, trained to use Distiller and instructed in how to complete the forms.

Selection Process

Titles and abstracts of the citations located through the PubMed search will be reviewed by a single reviewer; any citation marked for inclusion will move forward to full-text review. A second reviewer will validate the selection for relevance at the title and abstract screening stage with a partial verification (30%) of the total set of documents. A single reviewer will examine the content of the identified websites and guideline databases using keywords to identify potentially relevant documents for full text review. Where a search box is available on the website, the reviewer will follow the stepwise search approach in Table 1, which uses keywords to identify relevant publications. When a search box is not available, website menus will be navigated to locate relevant documents.

Full text review will be conducted by two independent reviewers with consensus required for inclusion or exclusion. If consensus cannot be achieved, a third member of the review team will be consulted. Reasons for full text exclusion will be recorded and reported in a list of documents excluded at full text.

Documents that reach full text review stage but cannot be retrieved in a complete version through an open access source, through our membership in the Health Science Information Consortium of Toronto, or through our previously and legally obtained holdings may be excluded. Depending on costs and resource availability, a limited number of for-purchase documents may be acquired for a review. We will not contact authors to obtain documents.

Protocol Amendment (February 17, 2017): As the number of search results was less than anticipated, a second reviewer verified 100% of the citations screened at title and abstract.

Data Extraction Process and Items

One reviewer will extract data from each of the included documents using Excel forms. A second reviewer will verify all extracted data; disagreements will be resolved through discussion and/or through third party consultation when consensus cannot be reached. Data items to be extracted include:

- Descriptive information about the document (i.e., guideline developer, title, year of publication, jurisdiction/location)
- Recommendation(s) pertaining to breast screening in each identified subgroup of the trans population. Specifically, the recommended screening modality, eligibility criteria, interval for screening, and logistic considerations such as appropriate language and staff sensitivity
- For each included recommendation, the source (i.e., peer-reviewed published, grey literature) and level of evidence (i.e., systematic review, RCT, observational study, expert opinion) will be recorded
- Consensus level, if available, will also be recorded

Quality Assessment of Individual Documents

Quality assessment of each included guideline will be conducted independently by two reviewers using the Appraisal of Guideline for Research and Evaluation 2 (AGREE II) instrument, a validated tool to assess the quality and reporting of practice guidelines [28]. Quality assessment of position statements will not be conducted as they are unlikely to undergo the same development process as guidelines. In addition, we are unaware of any critical appraisal tools to assess the quality of position statements.

Analysis, Synthesis and Reporting

The results of the search will be described using a flow diagram and a narrative summary. For each trans population subgroup of interest, a cross-document assessment using a high-level matrix will be conducted to identify similarities, differences and gaps in the recommendations for breast screening and their respective evidentiary base.

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Appendix 2: Search Strategies

Electronic Database Searches for Review One (Breast Cancer Risk, Prognosis and Mortality in the Trans Population using Cross-sex Hormones: A Systematic Review)

Database: PubMed
Date Run: May 19, 2017
Filters Applied: language English; publication date January 1, 1997 to December 31, 2017
Result Number: 975
Search Strategy:

Search	Query
1	"transgender persons"[mh] OR "health services for transgender persons"[mh] OR transsexualism[mh] OR transvestism[mh]
2	transgend*[tw] OR transsex*[tw] OR transman[tw] OR transmen[tw] OR transwom*[tw] OR transfem*[tw] OR transmasc*[tw] OR transmale*[tw] OR transidentified[tw] OR transperson[tw] OR transpeople[tw] OR transpeoples[tw] OR transpersons[tw]
3	((trans*[tw]) AND (sex*[tw] OR gender*[tw] OR woman[tw] OR women[tw] OR female*[tw] OR feminine[tw] OR male[tw] OR males[tw] OR man[tw] OR men[tw] OR masc*[tw] OR identified[tw] OR person[tw] OR persons[tw] OR people[tw] OR peoples[tw]))
4	((gender*[tw] OR sex*[tw]) AND (trans*[tw] OR variant[tw] OR identity[tw] OR "non binary"[tw] OR nonbinary[tw] OR queer[tw] OR fluid[tw] OR nonconform*[tw] OR non conform*[tw] OR reassign*[tw] OR re assign*[tw] OR dysphori*[tw]))
5	("female-to-male"[tw] OR "male-to-female"[tw] OR FTM[tw] OR MTF[tw] OR sexual minorit*[tw] OR cross gender*[tw] OR crossgender*[tw] OR transvesti*[tw] OR cross dress*[tw] OR crossdress*[tw] OR cross sex*[tw] OR crosssex*[tw] OR agender[tw] OR bigender[tw] OR "bi gender"[tw] OR genderqueer[tw] OR cisgender[tw] OR "cis gender"[tw] OR two spirit*[tw] OR twospirit*[tw] OR 2 spirit*[tw] OR 2spirit*[tw])
6	1 OR 2 OR 3 OR 4 OR 5
7	"hormone replacement therapy"[mh] OR "gonadotropin-releasing hormone"[mh] OR "Gonadal Steroid Hormones"[mh] OR Testosterone[mh] OR "Ethinyl Estradiol"[mh] OR Estrogens[mh] OR Progesterone[mh] OR Cyproterone[mh] OR ((hormon*[tw] OR estrogen[tw] OR oestrogen[tw] OR testosterone[tw] OR androgen[tw] OR estradiol[tw] OR progesterone[tw] OR Cyproterone[tw] OR GnRH[tw] OR endocrinologic*[tw] OR gonad*[tw] OR HRT[tw]) AND (crosssex[tw] OR “cross sex”[tw] OR sex*[tw] OR CSH[tw] OR antagonist*[tw] OR supplement*[tw] OR agonist*[tw] OR exogenous[tw] OR manag*[tw] OR sequel*[tw] OR replacement[tw] OR therap*[tw] OR feminization[tw] OR feminisation[tw] OR masculinization[tw] OR masculinisation[tw]))
8	"Neoplasms/epidemiology"[mh] OR "breast neoplasms"[mh] OR "carcinoma, intraductal, noninfiltrating"[mh] OR ((breast*[tw] OR mammar*[tw] OR “hormone sensitive”[tw] OR "hormone related"[tw]) AND (neoplas*[tw] OR cancer*[tw] OR carcinoma*[tw] OR tumor[tw] OR tumour[tw] OR tumors[tw] OR tumours[tw] OR malignan*[tw])) OR ((hyperplasia[tw] OR carcinoma*[tw]) AND (intraductal[tw] OR DCIS[tw] OR ductal[tw] OR "in situ"[tw] OR noninfiltrating[tw]))
9	6 AND 7 AND 8

Database: Medline
Date Run: May 19, 2017
Filters Applied: language English; publication date 1997 to current
Result Number: 290
Search Strategy:

Search	Query
1	exp "transgender persons"/ or exp "health services for transgender persons"/ or exp transsexualism/ or exp transvestism/
2	(transgend* or transsex* or transman or transmen or transwom* or transfem* or transmasc* or transmale* or transidentified or transperson or transpersons or transpeople or transpeoples).ti,ab,kw.
3	(trans* adj2 (sex* or gender* or woman or women or female* or feminine or male or males or man or men or masc* or identified or person or persons or people or peoples)).ti,ab,kw.
4	((gender* or sex*) adj2 (trans* or variant or identity or "non binary" or nonbinary or queer or fluid or nonconform* or "non conform*" or reassign* or "re assign*" or dysphori*)).ti,ab,kw.
5	("female-to-male" or "male-to-female" or FTM or MTF or "sexual minorit*" or "cross gender*" or crossgender* or transvesti* or "cross dress*" or crossdress* or "cross sex*" or crosssex* or agender or bigender or "bi gender" or genderqueer or cisgender or "cis gender" or "two spirit*" or twospirit* or "2 spirit*" or 2spirit*).ti,ab,kw.
6	or/1-5
7	exp "hormone replacement therapy"/ or exp "gonadotropin-releasing hormone"/ or exp "Gonadal Steroid Hormones"/ or exp Testosterone/ or exp "Ethinyl Estradiol"/ or exp Estrogens/ or exp Progesterone/ or exp Cyproterone/
8	((hormon* or estrogen or oestrogen or testosterone or androgen or estradiol or cyproterone or progesterone or GnRH or endocrinologic* or gonad* or HRT) and ("crosssex" or crosssex or sex or CSH or antagonist* or supplement* or agonist* or exogenous or manag* or sequel* or replacement or therap* or feminization or feminisation or masculinization or masculinisation)).ti,ab,kw.
9	or/7-8
10	exp neoplasms/ep or exp "breast neoplasms"/ or exp "carcinoma, intraductal, noninfiltrating"/
11	((breast* or mammar* or "hormone sensitive" or "hormone related") adj2 (neoplas* or cancer* or carcinoma* or tumor or tumour or tumors or tumours or malignan*)).ti,ab,kw.
12	((hyperplasia or carcinoma*) adj2 (intraductal or DCIS or ductal or "in situ" or noninfiltrating)).ti,ab,kw.
13	or/10-12
14	6 and 9 and 13

Database: Embase
Date Run: May 19, 2017
Filters Applied: language English; publication date 1997 to current
Result Number: 326
Search Strategy:

Search	Query
1	exp transgender/ or *"health service"/ or exp transsexualism/ or exp "cross dressing"/
2	(transgend* or transsex* or transman or transmen or transwom* or transfem* or transmasc* or transmale* or transidentified or transperson or transpersons or transpeople or transpeoples).ti,ab,kw.
3	(trans* adj2 (sex* or gender* or woman or women or female* or feminine or male or males or man or men or masc* or identified or person or persons or people or peoples)).ti,ab,kw.
4	((gender* or sex*) adj1 (trans* or variant or identity or "non binary" or nonbinary or queer or fluid or nonconform* or "non conform*" or reassign* or "re assign*" or dysphori*)).ti,ab,kw.
5	("female-to-male" or "male-to-female" or FTM or MTF or "sexual minorit*" or "cross gender*" or crossgender* or transvesti* or "cross dress*" or crossdress* or "cross sex*" or crosssex* or agender or bigender or "bi gender" or genderqueer or cisgender or "cis gender" or "two spirit*" or twospirit* or "2 spirit*" or 2spirit*).ti,ab,kw.
6	or/1-5
7	*"hormone substitution"/ or *gonadorelin/ or "sex hormone"/ or *Testosterone/ or *"ethinylestradiol"/ or *Estrogens/ or *Progesterone/ or *Cyproterone/
8	((hormon* or estrogen or oestrogen or testosterone or androgen or estradiol or cyproterone or progesterone or GnRH or endocrinologic* or gonad* or HRT) and ("crosssex" or crosssex or sex or CSH or antagonist* or supplement* or agonist* or exogenous or manag* or sequel* or replacement or therap* or feminization or feminisation or masculinization or masculinisation)).ti,ab,kw.
9	or/7-8
10	neoplasm/ep or *"breast tumor"/ or *"intraductal carcinoma"/
11	((breast* or mammar* or "hormone sensitive" or "hormone related") adj2 (neoplas* or cancer* or carcinoma* or tumor or tumour or tumors or tumours or malignan*)).ti,ab,kw.
12	((hyperplasia or carcinoma*) adj2 (intraductal or DCIS or ductal or "in situ" or noninfiltrating)).ti,ab,kw.
13	or/10-12
14	6 and 9 and 13

Database: CINAHL
Date Run: May 19, 2017
Filters Applied: language English; publication date January 1, 1997 to December 31, 2017; exclude Medline records
Result Number: 12
Search Strategy:

Search	Query
1	(TI transgend* or TI transsex* or TI transman or TI transmen or TI transwom* or TI transfem* or TI transmasc* or TI transmale* or TI transidentified or TI transperson or TI transpersons or TI transpeople or TI transpeoples)
2	MH "transgender persons+" or MH "health services needs and demand+" or MH "transsexualism" or MH "transvestism"
3	(AB transgend* or AB transsex* or AB transman or AB transmen or AB transwom* or AB transfem* or AB transmasc* or AB transmale* or AB transidentified or AB transperson or AB transpersons or AB transpeople or AB transpeoples)
4	(TX transgend* or TX transsex* or TX transman or TX transmen or TX transwom* or TX transfem* or TX transmasc* or TX transmale* or TX transidentified or TX transperson or TX transpersons or TX transpeople or TX transpeoples)
5	((TI trans*) w2 (TI sex* or TI gender* or TI woman or TI women or TI female* or TI feminine or TI male or TI males or TI man or TI men or TI masc* or TI identified or TI person or TI persons or TI people or TI peoples))
6	((AB trans*) w2 (AB sex* or AB gender* or AB woman or AB women or AB female* or AB feminine or AB male or AB males or AB man or AB men or AB masc* or AB identified or AB person or AB persons or AB people or AB peoples))
7	((TX trans*) w2 (TX sex* or TX gender* or TX woman or TX women or TX female* or TX feminine or TX male or TX males or TX man or TX men or TX masc* or TX identified or TX person or TX persons or TX people or TX peoples))
8	((TI gender* or TI sex*) w1 (TI trans* or TI variant or TI identity or TI "non binary" or TI nonbinary or TI queer or TI fluid or TI nonconform* or TI "non conform*" or TI reassign* or TI "re assign*" or TI dysphori*))
9	((AB gender* or AB sex*) w1 (AB trans* or AB variant or AB identity or AB "non binary" or AB nonbinary or AB queer or AB fluid or AB nonconform* or AB "non conform*" or AB reassign* or AB "re assign*" or AB dysphori*))
10	((TX gender* or TX sex*) w1 (TX trans* or TX variant or TX identity or TX "non binary" or TX nonbinary or TX queer or TX fluid or TX nonconform* or TX "non conform*" or TX reassign* or TX "re assign*" or TX dysphori*))
11	(TI “female-to-male” or TI “male-to-female” or TI FTM or TI MTF or TI "sexual minorit*" or TI "cross gender*" or TI crossgender* or TI transvesti* or TI "cross dress*" or TI crossdress* or TI "cross sex*" or TI crosssex* or TI agender or TI bigender or TI "bi gender" or TI genderqueer or TI cisgender or TI "cis gender" or TI "two spirit*" or TI twospirit* or TI "2 spirit*" or TI 2spirit*)
12	(AB “female-to-male” or AB “male-to-female” or AB FTM or AB MTF or AB "sexual minorit*" or AB "cross gender*" or AB crossgender* or AB transvesti* or AB "cross dress*" or AB crossdress* or AB "cross sex*" or AB crosssex* or AB agender or AB bigender or AB "bi gender" or AB genderqueer or AB cisgender or AB "cis gender" or AB "two spirit*" or AB twospirit* or AB "2 spirit*" or AB 2spirit*)
13	(TX "female-to-male" or TX "male-to-female" or TX FTM or TX MTF or TX "sexual minorit*" or TX "cross gender*" or TX crossgender* or TX transvesti* or TX "cross dress*" or TX crossdress* or TX "cross sex*" or TX crosssex* or TX agender or TX bigender or TX "bi gender" or TX genderqueer or TX cisgender or TX "cis gender" or TX "Two spirit*" or TX

Search	Query
	Twospirit* or TX "2 spirit*" or TX 2spirit*)
14	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13
15	MH "Hormone Replacement Therapy+" or MH "Gonadorelin+" or MH "Sex Hormones+" or MH "Testosterone+" or MH "Estradiol" or MH "Estrogens+" or MH "Progesterone+"
16	((TI hormon* or TI estrogen or TI oestrogen or TI testosterone or TI progesterone OR TI androgen OR TI estradiol or TI cyproterone or TI "Gonadal Steroid Hormones" TI GnRH or TI endocrinologic* or TI gonad* or TI HRT) and (TI "crosssex" or TI crosssex or TI sex or TI "CSH" or TI antagonist* or TI supplement* or TI agonist* or TI exogenous or TI manag* or TI sequel* or TI replacement or TI therap* or TI feminization or TI feminisation or TI masculinization or TI masculinisation))
17	((AB hormon* or AB estrogen or AB oestrogen or AB testosterone or AB progesterone OR AB androgen OR AB estradiol or AB cyproterone or AB "Gonadal Steroid Hormones" AB GnRH or AB endocrinologic* or AB gonad* or AB HRT) and (AB "crosssex" or AB crosssex or AB sex or AB "CSH" or AB antagonist* or AB supplement* or AB agonist* or AB exogenous or AB manag* or AB sequel* or AB replacement or AB therap* or AB feminization or AB feminisation or AB masculinization or AB masculinisation))
18	((TX hormon* or TX estrogen or TX oestrogen or TX testosterone or TX progesterone OR TX androgen OR TX estradiol or TX cyproterone or TX "Gonadal Steroid Hormones" TX GnRH or TX endocrinologic* or TX gonad* or TX HRT) and (TX "crosssex" or TX crosssex or TX sex or TX "CSH" or TX antagonist* or TX supplement* or TX agonist* or TX exogenous or TX manag* or TX sequel* or TX replacement or TX therap* or TX feminization or TX feminisation or TX masculinization or TX masculinisation))
19	15 OR 16 OR 17 OR 18
20	MH "Neoplasms+/EP or MH "breast neoplasms+" or MH "carcinoma, ductal, breast+"
21	((TI breast* or TI mammar* or TI "hormone sensitive" OR TI "hormone related") w2 (TI neoplas* or TI cancer* or TI carcinoma* or TI tumor or TI tumour or TI tumors or TI tumours or TI malignan*))
22	((AB breast* or AB mammar* or AB "hormone sensitive" OR AB "hormone related") w2 (AB neoplas* or AB cancer* or AB carcinoma* or AB tumor or AB tumour or AB tumors or AB tumours or AB malignan*))
23	((TX breast* or TX mammar* OR TX "hormone sensitive" OR TX "hormone related") w2 (TX neoplas* or TX cancer* or TX carcinoma* or TX tumor or TX tumour or TX tumors or TX tumours or TX malignan*))
24	((TI hyperplasia or TI carcinoma*) w2 (TI intraductal or TI DCIS or TI ductal or TI "in situ" or TI noninfiltrating))
25	((AB hyperplasia or AB carcinoma*) w2 (AB intraductal or AB DCIS or AB ductal or AB "in situ" or AB noninfiltrating))
26	((TX hyperplasia or TX carcinoma*) w2 (TX intraductal or TX DCIS or TX ductal or TX "in situ" or TX noninfiltrating))
27	20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26
28	14 AND 19 AND 27

Database: Cochrane Database of Systematic Reviews
Date Run: May 19, 2017
Filters Applied: language English; publication date January 1, 1997 to current
Result Number: 123
Search Strategy:

Search	Query
1	(transgend* or transsex* or transman or transmen or transwom* or transfem* or transmasc* or transmale* or transidentified or transperson or transpersons or transpeople or transpeoples).ti,ab,kw.
2	(trans* adj2 (sex* or gender* or woman or women or female* or feminine or male or males or man or men or masc* or identified or person or persons or people or peoples)).ti,ab,kw.
3	((gender* or sex*) adj1 (trans* or variant or identity or "non binary" or nonbinary or queer or fluid or nonconform* or non conform* or reassign* or re assign* or dysphori*)).ti,ab,kw.
4	("female-to-male" or "male-to-female" or FTM or MTF or "sexual minorit*" or "cross gender*" or crossgender* or transvesti* or "cross dress*" or crossdress* or "cross sex*" or crosssex* or agender or bigender or "bi gender" or genderqueer or cisgender or "cis gender" or "two spirit*" or twospirit* or "2 spirit*" or 2spirit*).ti,ab,kw.
5	or/1-4

Electronic Database Searches for Review Two (Benefits and Harms of Breast Screening for the Trans Population: A Systematic Review)

Database: PubMed
Date Run: May 9, 2017
Filters Applied: language English; publication date January 1, 1997 to December 31, 2017
Result Number: 283
Search Strategy:

Search	Query
1	(“transgender persons”[mh] OR “health services for transgender persons”[mh] OR transsexualism[mh] OR transvestism[mh])
2	(transgend*[tw] OR transsex*[tw] OR transman[tw] OR transmen[tw] OR transwom*[tw] OR transfem*[tw] OR transmasc*[tw] OR transmale*[tw] OR transidentified[tw] OR transperson[tw] OR transpersons[tw] OR transpeople[tw] OR transpeoples[tw])
3	((trans*[tw]) AND (sex*[tw] OR gender*[tw] OR woman[tw] OR women[tw] OR female*[tw] OR feminine[tw] OR male[tw] OR males[tw] OR man[tw] OR men[tw] OR masc*[tw] OR identified[tw] OR person[tw] OR persons[tw] OR people[tw] OR peoples[tw]))
4	((gender*[tw] OR sex*[tw]) AND (trans*[tw] OR variant[tw] OR identity[tw] OR “non binary”[tw] OR nonbinary[tw] OR queer[tw] OR fluid[tw] OR nonconform*[tw] OR non conform*[tw] OR reassign*[tw] OR re assign*[tw] OR dysphori*[tw]))
5	(“female-to-male”[tw] OR “male-to-female”[tw] OR “FTM”[tw] OR “MTF”[tw] OR sexual minorit*[tw] OR cross gender*[tw] OR crossgender*[tw] OR transvesti*[tw] OR cross dress*[tw] OR crossdress*[tw] OR cross sex*[tw] OR crosssex*[tw] OR agender[tw] OR bigender[tw] OR “bi gender”[tw] OR genderqueer[tw] OR cisgender[tw] OR “cis gender”[tw] OR two spirit*[tw] OR twospirit*[tw] OR 2 spirit*[tw] OR 2spirit*[tw])
6	#1 OR #2 OR #3 OR #4 OR #5
7	mass screening”[mh] OR “early detection of cancer”[mh] OR “mammography”[mh] OR “magnetic resonance imaging”[majr] OR “ultrasonography, mammary”[mh]
8	"clinical breast exam"[tw] OR "breast self-exam"[tw] OR “CBE”[tw] OR “BSE”[tw] OR mammogra*[tw] OR xeromammogra*[tw] OR tomosynthesis[tw] OR scintimammogra*[tw] OR MRI[tw] OR "magnetic resonance imaging"[tw] OR ultrasound*[tw] OR ultrasonograph*[tw] OR imaging[tw]
9	#7 OR #8
10	("breast neoplasms"[mh] OR "carcinoma, intraductal, noninfiltrating"[mh])
11	((breast*[tw] OR mammar*[tw]) AND (neoplasm*[tw] OR cancer*[tw] OR carcinoma*[tw] OR tumor[tw] OR tumour[tw] OR tumors[tw] OR tumours[tw] OR malignan*[tw]))
12	((hyperplasia[tw] or carcinoma*[tw]) AND (intraductal[tw] OR “DCIS”[tw] OR ductal[tw] OR “in situ”[tw] OR noninfiltrating[tw]))
13	#10 OR #11 OR #12
14	#6 AND #9 AND #13

Database: Medline
Date Run: May 9, 2017
Filters Applied: language English; publication date 1997 to current
Result Number: 135
Search Strategy:

Search	Query
1	exp "transgender persons"/ or exp "health services for transgender persons"/ or exp transsexualism/ or exp transvestism/
2	(transgend* or transsex* or transman or transmen or transwom* or transfem* or transmasc* or transmale* or transidentified or transperson or transpersons or transpeople or transpeoples).ti,ab,kw
3	((trans*) adj2 (sex* or gender* or woman or women or female* or feminine or male or males or man or men or masc* or identified or person or persons or people or peoples)).ti,ab,kw
4	((gender* or sex*) adj1 (trans* or variant or identity or "non binary" or nonbinary or queer or fluid or nonconform* or "non conform*" or reassign* or "re assign*" or dysphori*)).ti,ab,kw
5	("female-to-male" or "male-to-female" or “FTM” or “MTF” or "sexual minorit*" or "cross gender*" or crossgender* or transvesti* or "cross dress*" or crossdress* or "cross sex*" or crosssex* or agender or bigender or "bi gender" or genderqueer or cisgender or "cis gender" or "two spirit*" or twospirit* or "2 spirit*" or 2spirit*).ti,ab,kw
6	or/1-5
7	exp "mass screening"/ OR exp "early detection of cancer"/ OR "magnetic resonance imaging"/ or exp "ultrasonography, mammary"/ OR exp "mammography"/
8	(ultrasonograph* or ultrasound* or "clinical breast exam" or "breast self-exam" or "CBE" or "BSE" or mammogra* or "magnetic resonance imaging" or "MRI" or xeromammogra* or scintimammogra* or tomosynthesis or imaging).ti,ab,kw
9	or/7-8
10	exp "breast neoplasms"/ OR exp "carcinoma, intraductal, noninfiltrating"/
11	((breast* or mammar*) adj2 (neoplasm* or cancer* or carcinoma* or tumor or tumour or tumors or tumours or malignan*)).ti,ab,kw.
12	((hyperplasia or carcinoma*) adj2 (intraductal or “DCIS” or ductal or "in situ" or noninfiltrating)).ti,ab,kw
13	or/10-12
14	6 and 9 and 13
15	limit 14 to (english language and yr="1997 -Current")

Database: EMBASE
Date Run: May 9, 2017
Filters Applied: language English; publication date 1997 to current
Result Number: 222
Search Strategy:

Search	Query
1	exp transgender/ or *"health service"/ or exp transsexualism/ or exp "cross dressing"/
2	(transgend* or transsex* or transman or transmen or transwom* or transfem* or transmasc* or transmale* or transidentified or transperson or transpersons or transpeople or transpeoples).ti,ab,kw
3	((trans*) adj2 (sex* or gender* or woman or women or female* or feminine or male or males or man or men or masc* or identified or person or persons or people or peoples)).ti,ab,kw
4	((gender* or sex*) adj1 (trans* or variant or identity or "non binary" or nonbinary or queer or fluid or nonconform* or "non conform*" or reassign* or "re assign*" or dysphori*)).ti,ab,kw
5	("female-to-male" or "male-to-female" or “FTM” or “MTF” or "sexual minorit*" or "cross gender*" or crossgender* or transvesti* or "cross dress*" or crossdress* or "cross sex*" or crosssex* or agender or bigender or "bi gender" or genderqueer or cisgender or "cis gender" or "two spirit*" or twospirit* or "2 spirit*" or 2spirit*).ti,ab,kw
6	or/1-5
7	*"mass screening"/ or *"early detection of cancer"/ or *"nuclear magnetic resonance imaging"/ or *echomammography/ or *mammography/ or *"digital mammography"/
8	(ultrasonograph* or ultrasound* or "clinical breast exam" or "breast self-exam" or "CBE" or "BSE" or mammogra* or "magnetic resonance imaging" or "MRI" or xeromammogra* or scintimammogra* or tomosynthesis or imaging).ti,ab,kw
9	or/7-8
10	*"breast tumor"/ or "intraductal carcinoma"/
11	((breast* or mammar*) adj2 (neoplasm* or cancer* or carcinoma* or tumor or tumour or tumors or tumours or malignan*)).ti,ab,kw
12	((hyperplasia or carcinoma*) adj2 (intraductal or “DCIS” or ductal or "in situ" or noninfiltrating)).ti,ab,kw
13	or/10-12
14	6 and 9 and 13

Database: CINAHL
Date Run: May 9, 2017
Filters Applied: language English; publication date January 1, 1997 to December 31, 2017; exclude Medline records
Result Number: 36
Search Strategy:

Search	Query
1	(MH "transgender persons+") or (MH "health services needs and demand+") or (MH "transsexualism") or (MH "transvestism")
2	(TI transgend* or TI transsex* or TI transman or TI transmen or TI transwom* or TI transfem* or TI transmasc* or TI transmale* or TI transidentified or TI transperson or TI transpersons or TI transpeople or TI transpeoples)
3	(AB transgend* or AB transsex* or AB transman or AB transmen or AB transwom* or AB transfem* or AB transmasc* or AB transmale* or AB transidentified or AB transperson or AB transpersons or AB transpeople or AB transpeoples)
4	(TX transgend* or TX transsex* or TX transman or TX transmen or TX transwom* or TX transfem* or TX transmasc* or TX transmale* or TX transidentified or TX transperson or TX transpersons or TX transpeople or TX transpeoples)
5	((TI trans*) w2 (TI sex* or TI gender* or TI woman or TI women or TI female* or TI feminine or TI male or TI males or TI man or TI men or TI masc* or TI identified or TI person or TI persons or TI people or TI peoples))
6	((AB trans*) w2 (AB sex* or AB gender* or AB woman or AB women or AB female* or AB feminine or AB male or AB males or AB man or AB men or AB masc* or AB identified or AB person or AB persons or AB people or AB peoples))
7	((TX trans*) w2 (TX sex* or TX gender* or TX woman or TX women or TX female* or TX feminine or TX male or TX males or TX man or TX men or TX masc* or TX identified or TX person or TX persons or TX people or TX peoples))
8	((TI gender* or TI sex*) w1 (TI trans* or TI variant or TI identity or TI "non binary" or TI nonbinary or TI queer or TI fluid or TI nonconform* or TI "non conform*" or TI reassign* or TI "re assign*" or TI dysphori*))
9	((AB gender* or AB sex*) w1 (AB trans* or AB variant or AB identity or AB "non binary" or AB nonbinary or AB queer or AB fluid or AB nonconform* or AB "non conform*" or AB reassign* or AB "re assign*" or AB dysphori*))
10	((TX gender* or TX sex*) w1 (TX trans* or TX variant or TX identity or TX "non binary" or TX nonbinary or TX queer or TX fluid or TX nonconform* or TX "non conform*" or TX reassign* or TX "re assign*" or TX dysphori*))
11	(TI “female-to-male” or TI “male-to-female” or TI “FTM” or TI “MTF” or TI "sexual minorit*" or TI "cross gender*" or TI crossgender* or TI transvesti* or TI "cross dress*" or TI crossdress* or TI "cross sex*" or TI crosssex* or TI agender or TI bigender or TI "bi gender" or TI genderqueer or TI cisgender or TI "cis gender" or TI "two spirit*" or TI twospirit* or TI "2 spirit*" or TI 2spirit*)
12	(AB “female-to-male” or AB “male-to-female” or AB “FTM” or AB “MTF” or AB "sexual minorit*" or AB "cross gender*" or AB crossgender* or AB transvesti* or AB "cross dress*" or AB crossdress* or AB "cross sex*" or AB crosssex* or AB agender or AB bigender or AB "bi gender" or AB genderqueer or AB cisgender or AB "cis gender" or AB "two spirit*" or AB twospirit* or AB "2 spirit*" or AB 2spirit*)
13	(TX "female-to-male" or TX "male-to-female" or TX “FTM” or TX “MTF” or TX "sexual minorit*" or TX "cross gender*" or TX crossgender* or TX transvesti* or TX "cross dress*" or TX crossdress* or TX "cross sex*" or TX crosssex* or TX agender or TX bigender or TX "bi gender" or TX genderqueer or TX cisgender or TX "cis gender" or TX "two spirit*" or TX

Search	Query
	twospirit* or TX "2 spirit*" or TX 2spirit*)
14	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13
15	MH "early detection of cancer+" or MH "magnetic resonance imaging+" or MH "mammography+"
16	(TI ultrasonograph* or TI ultrasound* or TI "clinical breast exam" or TI "breast self-exam" or TI "CBE" or TI "BSE" or TI mammogra* or TI "magnetic resonance imaging" or TI "MRI" or TI xeromammogra* or TI scintimammogra* or TI tomosynthesis or TI imaging)
17	(AB ultrasonograph* or AB ultrasound* or AB "clinical breast exam" or AB "breast self-exam" or AB "CBE" or AB "BSE" or AB mammogra* or AB "magnetic resonance imaging" or AB "MRI" or AB xeromammogra* or AB scintimammogra* or AB tomosynthesis or AB imaging)
18	(TX ultrasonograph* or TX ultrasound* or TX "clinical breast exam" or TX "breast self-exam" or TX "CBE" or TX "BSE" or TX mammogra* or TX "magnetic resonance imaging" or TX "MRI" or TX xeromammogra* or TX scintimammogra* or TX tomosynthesis or TX imaging)
19	S15 OR S16 OR S17 OR S18
20	MH "breast neoplasms+" or MH “carcinoma, ductal, breast+”
21	((TI breast* or TI mammar*) w2 (TI neoplasm* or TI cancer* or TI carcinoma* or TI tumor or TI tumour or TI tumors or TI tumours or TI malignan*))
22	((AB breast* or AB mammar*) w2 (AB neoplasm* or AB cancer* or AB carcinoma* or AB tumor or AB tumour or AB tumors or AB tumours or AB malignan*))
23	((TX breast* or TX mammar*) w2 (TX neoplasm* or TX cancer* or TX carcinoma* or TX tumor or TX tumour or TX tumors or TX tumours or TX malignan*))
24	((TI hyperplasia or TI carcinoma*) w2 (TI intraductal or TI “DCIS” or TI ductal or TI "in situ" or TI noninfiltrating))
25	((AB hyperplasia or AB carcinoma*) w2 (AB intraductal or AB “DCIS” or AB ductal or AB "in situ" OR AB noninfiltrating))
26	((TX hyperplasia or TX carcinoma*) w2 (TX intraductal or TX “DCIS” or TX ductal or TX "in situ" OR TX noninfiltrating))
27	S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26
28	S14 AND S19 AND S27

Database: Cochrane Database of Systematic Reviews
Date Run: May 9, 2017
Filters Applied: language English; publication date January 1, 1997 to current
Result Number: 3
Search Strategy:

Search	Query
1	(transgend* or transsex* or transman or transmen or transwom* or transfem* or transmasc* or transmale* or transidentified or transperson or transpersons or transpeople or transpeoples).ti,ab,kw.
2	(trans* adj2 (sex* or gender* or woman or women or female* or feminine or male or males or man or men or masc* or identified or person or persons or people or peoples)).ti,ab,kw.
3	((gender* or sex*) adj1 (trans* or variant or identity or "non binary" or nonbinary or queer or fluid or nonconform* or non conform* or reassign* or re assign* or dysphori*)).ti,ab,kw.
4	("female-to-male" or "male-to-female" or FTM or MTF or "sexual minorit*" or "cross gender*" or crossgender* or transvesti* or "cross dress*" or crossdress* or "cross sex*" or crosssex* or agender or bigender or "bi gender" or genderqueer or cisgender or "cis gender" or "two spirit*" or twospirit* or "2 spirit*" or 2spirit*).ti,ab,kw.
5	or/1-4
6	(ultrasonograph* or ultrasound* or "clinical breast exam" or "breast self-exam" or "CBE" or "BSE" or mammogra* or "magnetic resonance imaging" or "MRI" or xeromammogra* or scintimammogra* or tomosynthesis or imaging).ti,ab,kw.
7	((breast* or mammar*) adj2 (neoplasm* or cancer* or carcinoma* or tumor or tumour or tumors or tumours or malignan*)).ti,ab,kw.
8	((hyperplasia or carcinoma*) adj2 (intraductal or DCIS or ductal or "in situ" or noninfiltrating)).ti,ab.kw.
9	or/6-8
10	5 and 9

Electronic Database Searches for Review Three (Breast Screening for Trans Populations: A Systematic Review of Guidelines and Position Statements)

Database: Medline
Date Run: February 13, 2017
Filters Applied: language English; publication date 1997 to current
Result Number: 76
Search Strategy:

Search	Query
1	exp "transgender persons"/ or exp "health services for transgender persons"/ or exp transsexualism/ or exp transvestism/
2	(transgender* or transsex* or transman or transwoman or transmen or transwomen or transfem*).ti,ab,kw.
3	(Trans adj2 (sexual or sexuals or gender* or gendered or woman or women or man or men or identified)).ti,ab,kw.
4	(gender* adj1 (trans or variant or identity or "two spirit" or "twospirit" or "non-binary" or queer or "genderqueer" or fluid or "nonconforming" or "non conforming" or reassign* or re assign*)).ti,ab,kw.
5	("Female-to-Male" or "male-to-female" or "FTM" or "MTF" or "sexual minority" or "sexual minorities" or "cross gender" or "cross gendered" or "cross dressing" or "cross dress" or "cross dresser" or transvesti* or agender or bigender or cisgender or "a gender" or "bi gender" or "cis gender").ti,ab,kw.
6	or/1-5
7	exp breast neoplasm/
8	((breast* or mammar*) adj2 (neoplasm* or cancer or carcinoma or tumor or tumour or tumors or tumours or malignan*)).ti,ab,kw.
9	or/7-8
10	exp "mass screening"/ or exp "early detection of cancer"/ or "magnetic resonance imaging"/ or exp "ultrasonography, mammary"/ or exp "mammography"/
11	(ultrasonograph* or ultrasound* or "clinical breast exam" or "breast self-exam" or "CBE" or "BSE" or mammogra* or "magnetic resonance imaging" or "MRI" or xeromammogra* or Scintimammogra* or tomosynthesis or imaging).ti,ab,kw.
12	or/10-11
13	6 and 9 and 12

Database: PubMed
Date Run: February 13, 2017
Filters Applied: language English; publication date January 1, 1997 to December 31, 2017
Result Number: 91
Search Strategy:

Search	Query
1	"transgender persons"[mh] OR "health services for transgender persons"[mh] OR transsexualism[mh] OR "Transvestism"[Mesh]
2	transgender*[tiab] OR transsex*[tiab] OR transman[tiab] OR transwoman[tiab] OR transmen[tiab] OR transwomen[tiab] OR transfem*[tiab]
3	((Trans[tiab]) AND (sexual[tiab] OR sexuals[tiab] OR gender[tiab] OR gendered[tiab] OR woman[tiab] OR women[tiab] OR man[tiab] OR men[tiab] OR identified[tiab]))
4	((gender*[tiab]) AND (trans[tiab] OR variant[tiab] OR identity[tiab] OR variant[tiab] OR "two spirit"[tiab] OR "twospirit"[tiab] OR "non-binary"[tiab] OR queer[tiab] OR "genderqueer"[tiab] OR fluid[tiab] OR “nonconforming"[tiab] OR “non conforming"[tiab] OR reassign*[tiab] OR re assign*[tiab]))
5	"Female-to-Male"[tiab] OR "male-to-female"[tiab] OR "FTM"[tiab] OR "MTF"[tiab] OR "sexual minority"[tiab] OR "sexual minorities”[tiab] OR "cross gender"[tiab] OR "cross gendered"[tiab] OR transvesti*[tiab] OR "cross dress"[tiab] OR "cross dresser"[tiab] OR "cross dressing"[tiab] OR agender[tiab] OR bigender[tiab] OR "a gender"[tiab] OR "bi gender"[tiab] OR "cis gender"[tiab]
6	#1 OR #2 OR #3 OR #4 OR #5
7	breast neoplasm[mh] OR ((breast*[tiab] OR mammar*[tiab]) AND (neoplasm*[tiab] OR cancer[tiab] OR carcinoma[tiab] OR tumor[tiab] OR tumour[tiab] OR tumors[tiab] OR tumours[tiab] OR malignan*[tiab]))
8	"mass screening"[mh] OR "early detection of cancer"[mh] OR mammography[mh] OR "magnetic resonance imaging"[mh] OR "ultrasonography, mammary"[mh] OR "clinical breast exam"[tiab] OR "breast self-exam"[tiab] OR "CBE”[tiab] OR “BSE"[tiab] OR xeromammogra*[tiab] OR "MRI"[tiab] OR magnetic resonance imaging[tiab] OR mammogr*[tiab] OR ultrasound*[tiab] OR ultrasonograph*[tiab] OR Scintimammogra*[tiab] OR imaging[tiab] OR tomosynthesis[tiab]
9	#6 AND #7 AND #8

Appendix 3 – Excluded Documents List

Review One: Breast Cancer Risk, Prognosis and Mortality in the Trans Population using Cross-sex Hormones: A Systematic Review

Documents excluded at full-text screening (n = 59)

Reason for exclusion: Population out of scope (n = 8)

1. Beral V, Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet. 2003;362(9390):1160.
2. Dimitrov, NV, Colucci P, Nagpal, S. Some aspects of the endocrine profile and management of hormone-dependent male breast cancer. Oncologist. 2007;12:798-807.
3. El-Beshbeshi W, Abo-Elnaga EM. Male breast cancer: 10-year experience at Mansoura University Hospital in Egypt. Cancer Biol Med. 2012;9:23-8.
4. Glaser RL, Dimitrakakis C. Reduced breast cancer incidence in women treated with subcutaneous testosterone, or testosterone with anastrozole: a prospective, observational study. Maturitas. 2013;76(4):342-9.
5. O'Brien B, Koru-Sengul T, Saclarides C, Franceschi D, Lee DJ, Miao F, Tannenbaum S, Bryne MM, Avisar E. Disparities in male breast cancer - the Florida experience. Ann Surg Oncol. 2014;21:88-9.
6. Talpur KAH, Laghari AA, Malik AM, Memon A. Clinico-pathological profile of patients with breast diseases at university hospital, Jamshoro. J Liaquat Uni Med Health Sci. 2006;5(2):71-75.
7. Yu E, Stitt L, Vujovic O, Joseph K, Assouline A, Au J, Younus J, Perera F, Tai P. Prognostic factors for male breast cancer: similarity to female counterparts. Anticancer Res. 2013;33(5):2227-31.
8. Yu E, Stitt L, Vujovic O, Joseph K, Assouline A, Au J, Younus J, Perera F, Tai P. Male breast cancer prognostic factors: similarity to female counterparts with propensity scores and matched-pair analysis. Int J Radiat Oncol Biol Phys. 2014;90(1):S221.

Reason for exclusion: Intervention out of scope (n = 2)

9. Scheim A, Bauer G, for the TransPULSE Team. Breast and cervical cancer screening among trans Ontarians: a report prepared for the Screening Saves Lives Program of the Canadian Cancer Society [Internet]. Ontario, Canada: TransPULSE Project; 2013 [cited 2017 May 9]. Available at: http://transpulseproject.ca/wp-content/uploads/2013/11/Trans-PULSE-Cancer-Screening-Report-for-Screening-Saves-Lives-V_Final.pdf.

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Reason for exclusion: Outcomes of interest not reported (n = 10)

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Reason for exclusion: Study design out of scope (n = 9)

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Review Two: Benefits and Harms of Breast Screening for the Trans Population: A Systematic Review

Documents excluded at full-text screening (n = 48)

Reason for exclusion: Population out of scope (n = 5)

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Reason for exclusion: Intervention out of scope (n = 6)

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Reason for exclusion: Outcomes of interest not reported (n = 2)

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Reason for exclusion: Study design out of scope (n = 18)

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Reason for exclusion: Publication type out of scope (n = 17)

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Review Three: Breast Screening for Trans Populations: A Systematic Review of Guidelines and Position Statements

Documents excluded at full-text screening (n = 13)

Reason for exclusion: Population out of scope (n = 2)

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Reason for exclusion: Does not address key question (n = 7)

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Reason for exclusion: Publication type out of scope (n = 3)

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Reason for exclusion: Article could not be obtained (n = 1)

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Appendix 4 – Supplementary Tables

- Table S1: Characteristics of Study Populations from Included Primary Studies
- Table S2: Quality Assessment of Included Cohort Studies
- Table S3: Quality Assessment of the Included Cross-sectional Study
- Table S4: Effect of CSH Exposure on Breast Cancer Risk in Trans Populations
- Table S5: GRADE Evidence Profile for the Effect of CSH Exposure on Breast Cancer Risk in Trans Populations
- Table S6: GRADE Evidence Profile for Pain Experienced by Trans Women During Breast Screening

Table S1: Characteristics of Study Populations from Included Primary Studies

Author, Year [ref]	Gender Identity	Sample Size	Age (Years) at Study Entry, Mean (SD)	Surgical Procedures, n (%)	CSH Use Details			
					Type of Hormone	Exposed, n (%)	Dose and Delivery	Duration of Use
Brown, 2014 [18]	Trans men	1,579	55.7 (12.9)	NR	Testosterone[1]	218 (17.3%)	NR	950.8 person-years[2]
	Trans women	3,556	55.8 (13.7)	NR	Estrogen[1]	1,112 (80.2%)	NR	NR
Gooren, 2013 [19]	Trans men	795	23.2 (6.5)	NR	Testosterone	795 (100%)	NR	15,974 person-years[2] 8.2% exposed <10 years 53.5% exposed 10–20 years 38.4% exposed ≥20 years
	Trans women	2,307	29.3 (12.7)	NR	Androgen deprivation,[3] antiandrogen[3] and/or estrogen	2,307 (100%)	NR	52,370 person-years[2] 21.7% exposed <10 years 51.3% exposed 10–20 years 27.0% exposed ≥20 years
Weyers, 2010 [21]	Trans women	50	43.1 (10.4)	Breast augmentation, 48 (96.0%) Vaginoplasty, 50 (100%)	Estrogen	47 (94.0%)	NR	NR
					Androgen deprivation[4]	2 (4.0%)	10 mg[5]	NR
Kuroda, 2008 [20]	Trans men	186	27.4 (NR)	Mastectomy[6], 186 (100%)	Testosterone	56 (30.1%)	≤125 mg, biweekly, intramuscular injections	11 months[7]

CSH = cross-sex hormone; mg = milligram; NR = not reported; SD = standard deviation

[1] During the 17-year period examined in the study of United States veterans, 1,259 trans men and 1,386 trans women were found to have received at least one prescription for sex hormones (testosterone, estrogen or both hormones) from Veterans Health Administration clinicians during the time they were enrolled for care. Of these individuals, 218 trans men (17.3%) and 1,112 trans women (80.2%) were prescribed CSHs. This review was interested specifically in these two sub-groups of trans people.

[2] Cumulative exposure to CSHs among all participants during study period, as recorded in study sources.

[3] Agent(s) not specified.

[4] Cyproterone acetate.

[5] Method of hormone delivery not reported.

[6] Type of mastectomy (e.g., total or partial) not specified.

[7] Mean duration of CSH use.

Table S2: Quality Assessment of Included Cohort Studies[1]

Author, Year [ref]	Representativeness of Exposed Cohort	Selection of the Non-Exposed Cohort	Ascertainment of Exposure	Demonstration that Outcome of Interest was Not Present at Start of Study	Selection (Maximum 4 ★)	Comparability of Cohorts: Controls for Age	Comparability of Cohorts: Controls for Additional Factor	Comparability (Maximum 2 ★)	Assessment of Outcome	Appropriate Duration of Follow-up	Adequacy of Follow-up of Cohorts	Outcome/Exposure (Maximum 3 ★)	Total Score (Maximum 9 ★)	Methodological Quality Rating[2]
Brown, 2014 [18]			★		1	★	★	2	★		★	2	5	Fair
Gooren, 2013 [19]	★		★		2	★	★	2	★	★	★	3	7	Fair
Kuroda, 2008 [20]		★	★		2			0	★		★	2	4	Poor

[1] Assessed using the Newcastle-Ottawa Scale for cohort studies [14].

[2] Scoring algorithm [35] (all domain thresholds must be met for a rating to apply): good = selection ≥3★, comparability ≥2★, outcome ≥2★; fair = selection 2★, comparability ≥1★, outcome ≥2★; poor = selection 0 – 1★, comparability 0★, outcome 0 – 1★.

Table S3: Quality Assessment of the Included Cross-sectional Study

Author, Year [ref]	Risk of Selection Bias	Risk of Information Bias	Methodological Quality Rating
Weyers, 2010 [21]	Unclear[1]	High[2]	Poor[3]

[1] The sample size of this study was small (n = 50); however, 71.4% (50 out of 70 eligible individuals) of the target population agreed to participate in the study. Reasons for study refusal were not reported. The authors reported no statistically significant differences observed in the age, or surgical or psychiatric morbidity between the 50 consenting and 20 non-consenting participants, but as these data were not presented, independent assessment of this interpretation was not possible. Methods of recruitment were not sufficiently described, as such the possibility of these methods impacting study participation could not be assessed.

[2] Pain experienced during breast imagining was assessed using a visual analogue scale (VAS). The validity and reliability of this instrument to assess pain during breast imaging was not described. Of note, participants reported lower pain scores for mammography when the VAS was administered by the radiologist as compared to when it was administered by the study nurse. It is unclear whether this difference is statistically significant, or whether it is a result of measurement error due to validity and reliability issues with the instrument or potential self-reporting or interviewer bias. Although participants were asked to rate their experienced pain during breast imaging, they did not self-administer these surveys. It is possible that participants over- or under-reported their experienced pain to study personnel. Information on the procedures for outcome assessment were also not sufficiently described. For mammography, both the radiologist and a study nurse administered the VAS survey to participants; however, for ultrasonography the study personnel responsible for administering the survey was not reported. Additionally, while the authors state that pain experienced during mammography was assessed post-mammography, it is unclear when the assessment of pain experienced during ultrasonography took place in relation to that of mammography. If pain experienced during each procedure was not assessed immediately after the completion of that procedure, there is a greater risk for recall bias.

[3] This rating was provided due to insufficient information on the characteristics of participants and non-participants, recruitment methods, validity and reliability of the instrument used to assess the outcome and procedures for outcome assessment.

Table S4: Effect of CSH Exposure on Breast Cancer Risk in Trans Populations

		Exposed Group			Comparison Group				
Author, Year [ref]	Case Definition and Data Source(s)	Follow-up Duration (Person-Years)	Number of Cases / Sample Size (%)	Incidence Rate per 100,000 Person-Years (95% CI)	Description	Follow-up Duration (Person-Years)	Number of Cases / Sample Size (%)	Incidence Rate per 100,000 Person-Years (95% CI)	Statistical Significance of Differences
Trans Men									
Brown, 2014 [18]	ICD-9-CM codes from existing VHA records[1] and U.S. population database[2] (i.e., SEER)	NR	1 / 218 (0.5%)	105.2 (3.2, 585.8)[3]	General population of women	NR	3.6[4]	NR	0.3 (0.0, 3.7)[5], NS at $p < 0.05$
Gooren, 2013 [19]	Case definition not provided; data obtained from medical centre database[1] and Dutch population database[2]	17,025[6]	1 / 795 (0.1%)	5.9 (0.5, 27.4)[7]	General population of women	NR	NR	154.7[8] (NR)	NR
Kuroda, 2008 [20]	Pathological diagnosis of epithelial proliferation from surgical institute records	NR	0 / 56 (0%)	NR	Trans men not exposed to male CSHs	NR	1 / 130 (0.8%)	NR	NS, $p = 0.5$
Trans Women									
Brown, 2014 [18]	ICD-9-CM codes from existing VHA records[1] and U.S. population database[2] (i.e., SEER)	NR	0 / 1,112 (0%)	NR	General population of men	NR	0.03[4]	NR	0.0 (0.0, 3.7)[5], NS at $p < 0.05$
Gooren, 2013 [19]	Case definition not provided; data obtained from medical centre database[1] and Dutch population database[2]	49,370[9]	2 / 2,307 (0.1%)	4.1 (0.8, 13.0)	General population of men	NR	NR	1.2[8] (NR)	NR

CI = confidence interval; ICD-9-CM = International Statistical Classification of Diseases, Ninth Revision, Clinical Modification; NR = not reported; NS = not statistically significant; SD = standard deviation; SEER = Surveillance, Epidemiology and End Results; SIR = standardized incidence ratio; U.S. = United States; VHA = Veterans Health Administration

[1] For exposed group (i.e., observed cases).

[2] For comparison group (i.e., expected cases).

[3] Incidence rate per 100,000 person-years of cross-sex hormone use.

[4] Number of expected cases calculated based on SEER data from 2007 to 2011.

[5] Standardized incidence ratio (95% CI).

[6] Minimum follow-up duration = 6 years; mean (SD) = 20.1 (7.3) years; median (range) = 16.8 (6.0 to 36.0) years.

[7] Observed incidence rate per 100,000 person-years of follow-up.

[8] Expected incidence rate per 100,000, based on Dutch incidence numbers for 2009.

[9] Minimum follow-up duration = 6 years; mean (SD) = 21.4 (8.7) years; median (range) = 17.6 (6.0 to 43.5) years. It should be noted that the upper value of the age range reported in the paper is likely an error, as based on the study dates (i.e., 1975 to 2012) the maximum range should be 38 years.

Table S5: GRADE Evidence Profile for the Effect of CSH Exposure on Breast Cancer Risk in Trans Populations

Quality Assessment							Results	GRADE Certainty Rating
Number of Studies	Design	Risk of Bias	Indirectness	Inconsistency	Imprecision	Other Considerations		
Trans Men – **Breast Cancer Risk** (follow-up: varied from unreported to minimum 6 years post CSH therapy initiation; assessed using: medical records)								
3[1]	observational[2]	serious[3]	serious[4]	not serious[5]	serious[6]	none[7]	fewer observed cases than expected; no statistically significant difference between observed and expected or between CSHs and no CSHs groups[8]	⊕OOO VERY LOW
Trans Women – Breast Cancer Risk (follow-up: varied from unreported to minimum 6 years post CSH therapy initiation; assessed using: medical records)								
2[9]	observational[2]	serious[10]	serious[11]	not serious[12]	serious[13]	none[7]	one study found no cases and no statistically significant difference between observed and expected rates; a second study found two cases (0.09%) and did not report statistical significance of difference between observed and expected[8]	⊕OOO VERY LOW

CSH = cross-sex hormone; very low certainty rating = we have very little confidence in the effect estimate—the true effect is likely to be substantially different from the estimate of effect

[1] Brown, 2104 [18], Gooren, 2013 [19], Kuroda, 2008 [20].

[2] Assessment began with a low certainty rating due to limitations of observational designs [17]. All studies used retrospective cohort designs.

[3] Using the Newcastle-Ottawa Scale [14] and a scoring algorithm [35], the studies received poor to fair methodological quality ratings. Across studies a main area of concern was related to the selection of participants in terms of the questionable representativeness of the sample for the target population, the reliance on population estimates for risk comparisons in the two larger studies, and the lack of certainty that breast cancer was not present prior to initiating CSH therapy. Given these methodological concerns, this body of evidence was downgraded for risk of bias.

[4] Despite some variability in demographics (e.g., veterans, age at CSH therapy initiation, nationality, surgical procedures), the study participants were all adult trans men which matched the key question. In terms of the interventions, the variability in dose, delivery and duration of CSH therapy was noted but acceptable. The smallest study (n = 186), which was conducted in Japan, was designed to provide evidence from a direct comparison between trans men who were exposed to CSHs and trans men who were not exposed to CSHs. This study, however, did not demonstrate that the intervention and control groups were indeed comparable. However, the two larger studies relied on indirect sources for their comparisons; both used expected breast cancer cases/rates drawn from general

population samples of women. Although there was some variability in descriptions, all three studies were interested in the detection of breast cancer. Given concerns regarding the comparison groups used in the two larger studies, this body of evidence was downgraded for indirectness.

[5] The studies reported similar results for the effect of exposure to CSHs on risk of developing breast cancer in trans men. Any variations could be explained by differences in populations and CSH therapies. This body of evidence was not downgraded for inconsistency.

[6] For assessing the risk of breast cancer, there was uncertainty regarding sufficient sample size to detect a difference between trans men exposed to CSHs and trans men who were not exposed to CSHs or the general population of women. Across studies the total number of cases of breast cancer (n = 3) was low. The confidence intervals across study effect estimates were wide. This body of evidence was downgraded for imprecision.

[7] There was an insufficient number of studies (n < 10) for statistical evaluation of publication bias [17]; the search for studies was comprehensive. No factors (i.e., large effect, dose-response gradient, plausible confounders) were noted that would provide reasons to raise certainty in the evidence.

[8] As per protocol we did not pool the available data; meta-analysis would not have been possible due to study heterogeneity and the lack of counts data for the comparison groups.

[9] Brown, 2104 [18], Gooren, 2013 [19].

[10] Using the Newcastle-Ottawa Scale [14] and a scoring algorithm [35], the studies received fair methodological quality ratings. Across studies a main area of concern was related to the selection of participants who may not be representative of the target population, the reliance on population estimates for risk comparisons and the lack of certainty that breast cancer was not present prior to initiating CSH therapy. Given these methodological concerns, this body of evidence was downgraded for risk of bias.

[11] Despite some variability in demographics (e.g., veterans, age at CSH therapy initiation, nationality), the study participants were all adult trans women which matched the key question. In terms of exposure to CSHs, the variability in dose, delivery and duration of CSH therapy was noted but acceptable. Both studies relied on indirect sources for their comparisons, drawing expected breast cancer cases/rates from general population samples of men. Although there was some variability in descriptions, both studies were interested in the detection of breast cancer. Given concerns regarding the uncertainty around the comparison groups used in both studies, this body of evidence was downgraded for indirectness.

[12] The studies reported similar results for the effect of exposure to CSHs on risk of developing breast cancer in trans women. Any variations could be explained by differences in populations and CSH therapies. This body of evidence was not downgraded for inconsistency.

[13] For assessing the risk of breast cancer, there was uncertainty regarding sufficient sample size to detect a difference between trans women exposed to CSHs and the general population of men. Across studies the total number of cases of breast cancer (n = 2) was low. This body of evidence was downgraded for imprecision.

Table S6: GRADE Evidence Profile for Pain Experienced by Trans Women during Breast Screening

Quality Assessment							Results Mean (SD) Score	GRADE Certainty Rating
Number of Studies	Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations		
Painfulness of Mammography (assessment point: post-mammography; assessed using: VAS administered by radiologist and study nurse)								
1[1]	cross-sectional[2]	serious[3]	cannot assess[4]	not serious[5]	cannot assess[6]	none[7]	Scores ranged from 1.7 (2.1) to 2.0 (2.3)[8, 9]	⊕OOO VERY LOW
Painfulness of Ultrasonography (assessment point: post-ultrasonography; assessed using: VAS administered by unknown study personnel)								
1[1]	cross-sectional[2]	serious[3]	cannot assess[4]	not serious[5]	cannot assess[6]	none[7]	0.5 (1.2)[9,10]	⊕OOO VERY LOW

SD = standard deviation; VAS = visual analogue scale; very low GRADE certainty rating = we have very little confidence in the effect estimate—the true effect is likely to be substantially different from the estimate of effect

[1] Weyers, 2010 [21].

[2] Assessment begins with a low certainty rating due to limitations of observational designs [17].

[3] In the absence of a widely accepted tool to assess the methodological quality of cross-sectional studies, a qualitative approach considering the selection of participants and measurement of study variables was used to assess the risk of bias for this cross-sectional study. Given that insufficient information was provided on the characteristics of study participants and non-participants, the validity and reliability of the outcome measure and outcome assessment procedures, this study was considered to be of low methodological quality and downgraded for risk of bias.

[4] Because this was a single study, inconsistency could not be assessed.

[5] Results from this study are based on data for 50 adult (mean age: 43.1 years, SD: 10.4 years) trans women who received two of the screening modalities of interest (mammography and ultrasonography) in a hospital-based setting in Belgium. All 50 participants received sex reassignment surgery (i.e., vaginoplasty) and 48 (96.0%) received breast augmentation. Forty-seven (94.0%) participants were currently taking estrogen replacement therapy and 2 (4.0%) were also taking anti-androgen therapy (i.e., cyproterone acetate). The population characteristics of this study are similar to the criteria specified by the key questions for this review, thus no serious concerns regarding the indirectness of this evidence were noted.

[6] The sample size for this study was small (n = 50). Because no confidence intervals were provided, the precision of the study results could not be assessed.

[7] There was an insufficient number of studies (n < 10) for statistical evaluation of publication bias [17]; the search for studies was comprehensive. No factors (i.e., large effect, dose-response gradient, plausible confounders) were noted that would provide reasons to raise certainty in the evidence.

[8] Two post-mammography assessments of participant-experienced pain were conducted. One assessment was administered by a radiologist and the other by a study nurse. The mean (SD) pain scores from the assessments administered by the radiologist and study nurse were 1.7 (2.0) and 2.0 (2.3) points, respectively.

[9] Data for this body of evidence were not statistically combined due to an insufficient number of studies.

[10] The study personnel responsible for administering the post-ultrasonography assessment of experienced pain was not reported.

PRISMA 2009 Checklist: Breast cancer risk and breast screening for trans people: an integration of three systematic reviews (Meggetto et al.)

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6, 22
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Appendix 1 (p. 8-9, 19, 28)
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Not applicable

PRISMA 2009 Checklist: Breast cancer risk and breast screening for trans people: an integration of three systematic reviews (Meggetto et al.)

Section/topic	#	Checklist item	Reported on page #
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7-8
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7-8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Not applicable
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8, 21
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8-9, 24-25, 28-29, Appendix 4 (p.2-3)
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8-9, 24-25, 28-29, Appendix 4 (p.4-5)
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-13, Appendix 4(p.6-7)
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Not applicable
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9-13, 26-27, 33-24, Appendix 4(p.8-11)
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Not applicable
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14-15

PRISMA 2009 Checklist: Breast cancer risk and breast screening for trans people: an integration of three systematic reviews (Meggetto et al.)

Section/topic	#	Checklist item	Reported on page #
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15-16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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