

## Breast cancer risk and breast screening for trans people: an integration of 3 systematic reviews

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### Abstract

**Background:** Trans people face uncertain risk for breast cancer and barriers to accessing breast screening. Our objectives were to identify and synthesize primary research evidence on the effect of cross-sex hormones (CSHs) on breast cancer risk, prognosis and mortality among trans people, the benefits and harms of breast screening in this population, and existing clinical practice recommendations on breast screening for trans people.

**Methods:** We conducted 2 systematic reviews of primary research, 1 on the effect of CSHs on breast cancer risk, prognosis and mortality, and the other on the benefits and harms of breast screening, and a third systematic review of guidelines on existing screening recommendations for trans people. We searched PubMed, MEDLINE, Embase, CINAHL, the Cochrane Database of Systematic Reviews and grey literature sources for primary research, guidelines and position statements published in English between 1997 and 2017. Citations were screened by 2 independent reviewers. One reviewer extracted data and assessed methodological quality of included articles; a second reviewer verified these in full. The results were synthesized narratively.

**Results:** Four observational studies, 6 guidelines and 5 position statements were included. Observational evidence of very low certainty did not show 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 screening for distinct trans subpopulations; however, recommendations varied.

**Interpretation:** The limited evidence does not show an effect of CSHs on breast cancer risk. Although there is insufficient evidence to determine the potential benefits and harms of breast screening, existing clinical practice documents generally recommend screening for trans people; further large-scale prospective comparative research is needed.

“Trans” is an umbrella term for people with diverse gender identities and expressions that differ from stereotypical gender norms.<sup>1,2</sup> Recent estimates suggest that there were approximately 200 000 trans people in Canada in 2016.<sup>3</sup> 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.<sup>4</sup> Cross-sex hormone therapy refers to the use of exogenous sex hormones that are opposite to those of a person’s natal sex.<sup>5</sup> Breast cancer risk in trans people is hypothesized to be influenced by CSHs.<sup>6</sup> However, it is unclear whether the potential alteration in risk for breast cancer by CSH therapy should affect eligibility for breast screening. Trans people are medically underserved and face unique challenges in accessing appropriate care.<sup>3,7</sup> With respect to breast health, 25%–30% of

trans people in Ontario with a perceived need for mammography were unable to access it.<sup>8</sup> In addition, trans people are less likely to pursue breast screening than are cis-gender women (i.e., people assigned female sex at birth and who identify as female).<sup>9</sup> Although this shows a disparity in the approach to breast cancer detection when compared to

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the nontrans population, information on the potential benefits and harms of screening in the trans population is limited.<sup>10</sup>

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.<sup>11</sup> In this article, we present the findings of 3 systematic reviews that can be used by organized breast screening programs to initiate a process of breast screening policy development for the trans population. Our objectives were to identify and synthesize 1) primary research on the effect of CSHs on breast cancer risk, prognosis and mortality among trans people (review 1), 2) primary research on the benefits and harms of breast screening among trans people (review 2) and 3) existing clinical practice recommendations on breast screening for trans people (review 3).

## Methods

We developed separate protocols to guide the reviews (Appendix 1, available at [www.cmajopen.ca/content/7/3/E598/suppl/DC1](http://www.cmajopen.ca/content/7/3/E598/suppl/DC1)); they were not publicly registered. We consulted the *Cochrane Handbook for Systematic Reviews of Interventions*<sup>12</sup> when developing these reviews and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline<sup>13</sup> to report this review. The term “trans men” is used for people who were assigned female sex at birth but whose gender identity is male or on the male spectrum.<sup>14</sup> The term “trans women” is used for people who were assigned male sex at birth but whose gender identity is female or on the female spectrum.<sup>14</sup> These terms are used for simplicity and are meant to be inclusive of all those on the female-to-male and male-to-female spectra, respectively.

### Search strategy

For reviews 1 and 2, we searched PubMed, MEDLINE, Embase, CINAHL and the Cochrane Database of Systematic Reviews for primary research published in English between January 1997 and May 2017. For review 3, we searched PubMed, MEDLINE and guidelines databases for guidelines and positions statements published in English between January 1997 and February 2017. We developed all search strategies in consultation with a medical librarian (Appendix 2, available at [www.cmajopen.ca/content/7/3/E598/suppl/DC1](http://www.cmajopen.ca/content/7/3/E598/suppl/DC1)). We also conducted grey literature searches and hand searches of on-topic journals. Reference lists of relevant primary studies, systematic reviews, literature reviews and guidelines were reviewed, and citation recommendations from experts were sought (O.M., L.P., M.F.-K., M.C.-F.).

### Study selection

For all reviews, 2 reviewers independently screened titles and abstracts using predefined selection criteria (review 1: L.P., M.C.-F.; review 2: O.M., M.Y.; review 3: M.F.-K., M.Y.) (Table 1). For assessment of the performance (i.e., sensitivity and specificity) of breast screening technologies, a population, intervention, reference standard and diagnosis (PIRD) framework was applied. Population and intervention components are defined in Table 1. The reference standard for a positive screening result was defined as pathology results available from biopsy, whereas patients with negative screening results must have been followed for at least 1 year. The diagnosis of interest was breast cancer. 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. Disagreements were resolved through discussion.

### Data management

We used DistillerSR<sup>15</sup> (Evidence Partners) to manage all phases of reviews 1 and 2. For review 3, we used DistillerSR for screening and data extraction for citations obtained from electronic databases, whereas these tasks were completed in Microsoft Excel for citations from the grey literature search. We developed screening, data extraction and quality-assessment forms a priori and piloted them to ensure validity and interrater reliability.

### Data extraction and quality assessment

For all reviews, 1 reviewer extracted data from included citations (review 1: L.P.; review 2: O.M.; review 3: M.F.-K.). A second reviewer verified all extracted data (review 1: M.C.-F.; reviews 2 and 3: M.Y.); 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 1 and 2, the quality of cohort studies was assessed with the Newcastle–Ottawa Scale.<sup>16</sup> 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 the quality assessments (review 1: L.P.; review 2: O.M.). A second reviewer verified all ratings (review 1: M.C.-F.; review 2: M.Y.); disagreements were resolved through discussion.

For review 3, quality assessment of each guideline was conducted independently by 2 reviewers (M.Y., M.F.-K.) using the Appraisal of Guidelines for Research & Evaluation II instrument.<sup>17</sup> The quality of position statements was not assessed.

### Synthesis

For reviews 1 and 2, we examined similarities and differences in study characteristics, quality, sample and intervention features 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 owing to a lack of available count data in the comparison groups (review 1) or an insufficient number of included studies

**Table 1: Inclusion criteria for the 3 systematic reviews**

Study component	Review 1	Review 2	Review 3
Populations	<p>Trans men (≥ 18 yr) with:</p> <ul style="list-style-type: none"> <li>All original breast tissue remaining</li> <li>Some breast tissue removed (i.e., breast reduction)</li> <li>Chest-contouring surgery (e.g., liposculpting, pectoral implants)</li> </ul> <p>Trans women (≥ 18 yr) with:</p> <ul style="list-style-type: none"> <li>Breast augmentation/implant</li> <li>No breast augmentation/implant</li> </ul>	<p>Asymptomatic trans men (≥ 18 yr) with:</p> <ul style="list-style-type: none"> <li>All original breast tissue remaining, with a history of CSH use</li> <li>Some breast tissue removed, with or without a history of CSH use</li> <li>Chest-contouring surgery, with or without a history of CSH use</li> </ul> <p>Asymptomatic trans women (≥ 18 yr) with:</p> <ul style="list-style-type: none"> <li>Breast augmentation/implants, with a history of CSH use</li> <li>No breast augmentation/implants, with a history of CSH use</li> </ul>	<p>Trans men (≥ 18 yr) with:</p> <ul style="list-style-type: none"> <li>All original breast tissue remaining, with or without a history of CSH use</li> <li>Some breast tissue removed, with or without a history of CSH use</li> <li>Chest surgery, with or without a history of CSH use</li> </ul> <p>Trans women (≥ 18 yr) with:</p> <ul style="list-style-type: none"> <li>Breast augmentation/implants, with or without a history of CSH use</li> <li>No breast augmentation/implants, with or without a history of CSH use</li> </ul>
Interventions	<ul style="list-style-type: none"> <li>Use of masculinizing CSH (e.g., testosterone) for trans men</li> <li>Use of feminizing CSH (e.g., antiandrogen agents, estrogen or progesterone) for trans women</li> </ul>	<p>Breast screening with:</p> <ul style="list-style-type: none"> <li>Mammography</li> <li>Magnetic resonance imaging</li> <li>Ultrasonography</li> <li>Clinical breast examination</li> <li>Breast self-examination</li> </ul>	<p>Breast screening with:</p> <ul style="list-style-type: none"> <li>Mammography</li> <li>Magnetic resonance imaging</li> <li>Ultrasonography</li> <li>Clinical breast examination</li> <li>Breast self-examination</li> </ul>
Comparators	<ul style="list-style-type: none"> <li>Trans men not taking masculinizing CSHs or cisgender women</li> <li>Trans women not taking feminizing CSHs or cisgender men</li> </ul>	<ul style="list-style-type: none"> <li>Trans people not screened for breast cancer</li> <li>No comparison group required (only for cancer detection rate, interval cancer rate, sensitivity, specificity and all harm outcomes)</li> </ul>	NA
Outcomes	<ul style="list-style-type: none"> <li>Breast cancer risk (incidence)</li> <li>Prognosis: stage at diagnosis, node positivity, tumour size, tumour grade, tumour type, survival</li> <li>Breast cancer mortality</li> </ul>	<ul style="list-style-type: none"> <li>Benefits: breast-cancer-specific mortality, all-cause mortality, cancer detection rate, interval cancer rate, sensitivity, specificity</li> <li>Harms: overdiagnosis, false-positive screen, patient-reported anxiety, patient-reported pain/discomfort</li> </ul>	<p>Breast screening recommendations for trans people with a focus on:</p> <ul style="list-style-type: none"> <li>Eligibility requirements</li> <li>Screening modalities</li> <li>Screening intervals</li> </ul>
Designs/document types	<ul style="list-style-type: none"> <li>Randomized controlled trials</li> <li>Nonrandomized experimental studies</li> <li>Observational studies with comparison groups</li> </ul>	<ul style="list-style-type: none"> <li>Randomized controlled trials</li> <li>Nonrandomized experimental studies</li> <li>Observational studies with or without* comparison groups</li> <li>Diagnostic evaluation studies</li> </ul>	<ul style="list-style-type: none"> <li>Guidelines</li> <li>Position statements</li> </ul>
Other	<ul style="list-style-type: none"> <li>Published between Jan. 1, 1997, and May 19, 2017</li> <li>Peer-reviewed or grey literature</li> <li>Full reports, or conference abstracts and proceedings</li> <li>Published in English</li> </ul>	<ul style="list-style-type: none"> <li>Published between Jan. 1, 1997, and May 9, 2017</li> <li>Peer-reviewed or grey literature</li> <li>Full reports, or conference abstracts and proceedings</li> <li>Published in English</li> </ul>	<ul style="list-style-type: none"> <li>Published between Jan. 1, 1997, and Feb. 13, 2017</li> <li>Peer-reviewed or grey literature</li> <li>Full reports, or conference abstracts and proceedings</li> <li>Published in English</li> </ul>

Note: CSH = cross-sex hormone, NA = not applicable.  
 \*Observational studies without comparison groups were included only if they reported on cancer detection rate, interval cancer rate, sensitivity, specificity or any harm outcomes.

(review 2). The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the certainty of the available evidence for each outcome.<sup>18,19</sup> One reviewer conducted GRADE assessments (review 1: L.P.; review 2: O.M.), which were verified by a second reviewer (review 1: M.C.-F.; review 2: M.Y.).

For review 3, similarities and differences across breast screening recommendations were examined for trans men and trans women separately.

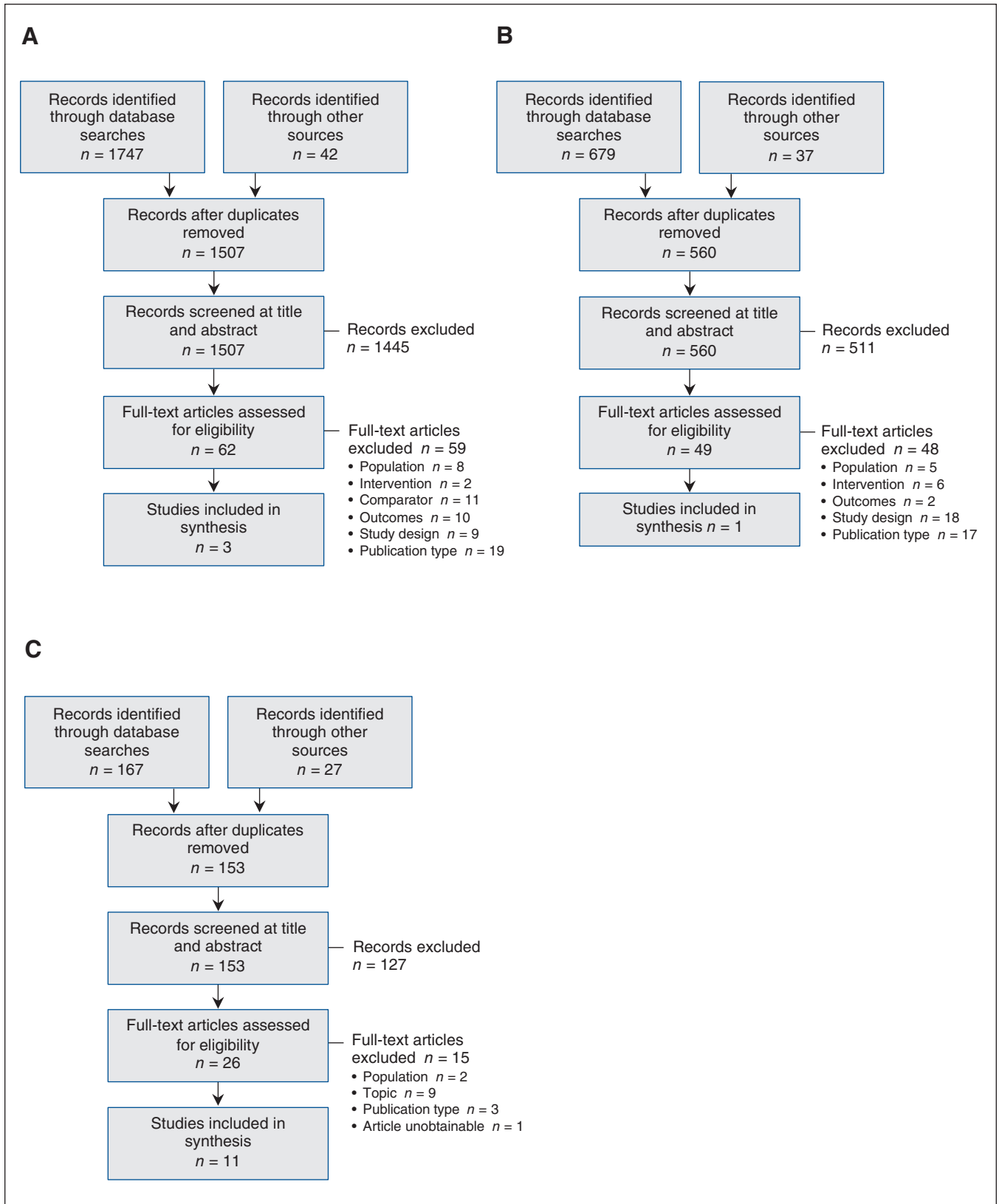
**Ethics approval**

Because human subjects were not involved in this study as it was a systematic review, ethics approval was not sought.

**Results**

**Search results**

For review 1, 1507 unique citations were identified. After screening, 3 studies met the inclusion criteria<sup>20-22</sup> (Figure 1, A).



**Figure 1:** Flow diagrams showing study selection for the systematic review of primary research evidence examining the effect of cross-sex hormones on breast cancer risk, prognosis and mortality in trans people (review 1) (A), the systematic review of primary research evidence examining the benefits and harms of breast cancer screening in trans people (review 2) (B) and the systematic review of guidelines and position statements on existing breast cancer screening recommendations for trans people (review 3) (C).

**Table 2: Characteristics of included primary studies (reviews 1 and 2)**

Investigator (review)	Study design	Eligibility criteria	Country	Study period	Total sample size	Source of funding	Study quality
Brown et al., 2015 <sup>20</sup> (review 1)	Retrospective cohort	<ul style="list-style-type: none"> <li>• Trans-related diagnosis (i.e., gender identity disorder, gender identity disorder not otherwise specified, transvestic fetishism, transsexualism)</li> <li>• Veteran</li> <li>• Accessed medical and mental health services at VHA facility</li> </ul>	United States	17 yr (Oct. 1, 1996, to Sept. 30, 2013)	5135	Authors employed by VHA No grant or commercial funding	Fair*
Gooren et al., 2013 <sup>21</sup> (review 1)	Retrospective cohort	<ul style="list-style-type: none"> <li>• Trans person</li> <li>• Minimum 6-yr follow-up</li> </ul>	The Netherlands	38 yr (1975 to Dec. 31, 2012)	3102	Two authors received noncommercial support	Fair*
Weyers et al., 2010 <sup>23</sup> (review 2)	Cross-sectional	<ul style="list-style-type: none"> <li>• Dutch-speaking trans women</li> <li>• Received sex reassignment surgery at least 6 mo before enrolment</li> <li>• Consulted Ghent University Hospital gender team during previous 12 mo</li> </ul>	Belgium	4 mo (Mar–June 2007)	50	First author received commercial support	Poor†
Kuroda et al., 2008 <sup>22</sup> (review 1)	Retrospective cohort	<ul style="list-style-type: none"> <li>• Trans men</li> <li>• Underwent mastectomy at surgical institute</li> </ul>	Japan	9 yr (1998–2006)	186	NR	Poor*

Note: NR = not reported, VHA = Veterans Health Administration.

\*Assessed with the Newcastle–Ottawa Scale.<sup>16,33</sup> Detailed results of the quality assessment are provided in Supplementary Table S2, Appendix 4 (available at [www.cmajopen.ca/content/7/3/E598/suppl/DC1](http://www.cmajopen.ca/content/7/3/E598/suppl/DC1)).

†No formal critical appraisal tool was used; methodological quality 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 Supplementary Table S3, Appendix 4.

For review 2, 560 unique citations were identified, among which 1 study met the inclusion criteria<sup>23</sup> (Figure 1, B). The search for review 3 identified 153 unique citations, and, after screening, 11 documents were included (Figure 1, C).<sup>4,5,24–32</sup> Citations excluded at full-text screening are listed in Appendix 3 (available at [www.cmajopen.ca/content/7/3/E598/suppl/DC1](http://www.cmajopen.ca/content/7/3/E598/suppl/DC1)).

### Characteristics of included studies and documents

For review 1, 3 retrospective cohort studies examining the effect of CSHs on breast cancer risk among trans people were identified<sup>20–22</sup> (Table 2). All 3 included trans men, and 2 included trans women.<sup>20,21</sup> Across studies, 1069 trans men and 3419 trans women were exposed to CSHs (Table 3, Supplementary Table S1, Appendix 4, available at [www.cmajopen.ca/content/7/3/E598/suppl/DC1](http://www.cmajopen.ca/content/7/3/E598/suppl/DC1)). The duration of CSH exposure varied within and across studies. In 1 study, the comparison group was 130 trans men who did not receive CSHs,<sup>22</sup> and in 2 studies, comparisons were drawn against general population samples.<sup>20,21</sup> The length of follow-up ranged from 9 to 38 years. Funding details were reported for 2 studies;<sup>20,21</sup> neither received commercial support. Two studies were rated as having fair methodological quality,<sup>20,21</sup> and 1 was rated as poor<sup>22</sup> (Table 2).

For review 2, 1 cross-sectional study reporting on 1 screening-related harm was identified<sup>23</sup> (Table 2). The sample consisted of 50 trans women, all of whom underwent sex-reassignment surgery (Supplementary Table S1, Appendix 4). Forty-eight participants (96%) received augmentative breast surgery, 47 (94%) were receiving estrogen replacement therapy, and 2 (4%) were receiving an androgen-deprivation agent. All participants received mammography and sonography performed by 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.

For review 3, 11 documents (6 guidelines and 5 position statements), provided recommendations on breast screening for trans people<sup>4,5,24–32</sup> (Table 4). Documents were developed by groups in Canada,<sup>4,5,24,25,28</sup> the United States<sup>26,29,31,32</sup> and the United Kingdom.<sup>27,30</sup> The quality of the included guidelines was low. Across guidelines, the highest-scoring Appraisal of Guidelines for Research & Evaluation II domains were scope and purpose, and clarity of presentation. The lowest-scoring domains were applicability and editorial independence.

**Table 3: Grading of Recommendations Assessment, Development and Evaluation (GRADE) summary of findings table for the effect of exposure to cross-sex hormones on breast cancer risk, prognosis and mortality in trans people (review 1)**

Population: trans people aged 16–83 yr Intervention: cross-sex hormone therapy		No. of exposed participants (no. of studies)	Certainty of evidence (GRADE)
Outcome; population	Effect		
<b>Trans men exposed to testosterone</b>			
Breast cancer risk*	Differences in incidence rate or cumulative incidence between exposed cohorts and nonexposed cohorts or general population samples were not statistically significant or were not reported†	1069 (3) <sup>20–22</sup>	⊕○○○ Very low‡§
Stage at diagnosis	No primary research evidence identified		
Survival			
Breast cancer mortality			
<b>Trans women exposed to estrogen only, androgen deprivation or antiandrogens only, or estrogen with androgen deprivation or antiandrogens</b>			
Breast cancer risk*	Differences in incidence rate or cumulative incidence between exposed cohorts and general population samples were not statistically significant or were not reported†	3419 (2) <sup>20,21</sup>	⊕○○○ Very low‡§
Stage at diagnosis	No primary research evidence identified		
Survival			
Breast cancer mortality			

\*Assessed with the use of administrative database or medical records, with follow-up not reported or at a minimum of 6 years after cross-sex hormone therapy started.  
 †We did not calculate a single pooled effect estimate. Additional information and detailed results for each study are provided in Supplementary Table S4, Appendix 4.  
 ‡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 effect estimate.  
 §The evidence was downgraded owing to the observational nature of the study designs and serious concerns regarding risk of bias, indirectness and imprecision. Detailed Grading of Recommendations Assessment, Development and Evaluation assessments are provided in Supplementary Table S5, Appendix 4.

**Trans men**

**Effect of cross-sex hormones on breast cancer risk, prognosis and mortality (review 1)**

Three studies examined breast cancer risk among trans men exposed to CSHs.<sup>20–22</sup> The risk was not statistically different than that for trans men not exposed to CSHs (0.0% v. 0.8%,  $p < 0.05$ )<sup>22</sup> or the expected risk based on estimates for the general population of women (standardized incidence ratio 0.3, 95% confidence interval 0.0–3.7).<sup>20</sup> In the third study,<sup>21</sup> the risk (5.9 cases per 100 000 person-years) was lower than that expected for the general population of women (154.7 cases per 100 000 person-years), but the statistical significance of this finding was not reported. This evidence received a very low GRADE rating owing to the observational 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 2)**

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

**Recommendations on breast screening (review 3)**

Seven documents provided breast screening recommendations for trans men<sup>4,24,26–28,30,31</sup> (Table 5). Breast screening was recommended for trans men without chest reconstruction.<sup>4,24,26,28,31</sup> Screening eligibility in this group also depended on age<sup>24,28,31</sup> and eligibility requirements for cisgender women.<sup>4,26,28</sup> Two documents recommended mammography every 2 years,<sup>24,28</sup> 1 recommended mammography without specifying the screening interval,<sup>4</sup> 1 recommended annual clinical breast examination,<sup>28</sup> and 1 recommended annual breast examinations without specifying whether these were clinical examinations or self-examinations.<sup>4</sup>

Screening was also recommended for trans men who have had partial chest reconstruction.<sup>4,24,26,28</sup> Recommended modalities varied and included ultrasonography,<sup>24,26</sup> magnetic

**Table 4: Characteristics and quality of included guidelines and position statements (review 3)**

Organization, year	Document type	Country	Appraisal of Guidelines for Research & Evaluation II domain scores, %*					
			Scope and purpose	Stakeholder involvement	Rigor of development	Clarity of presentation	Applicability	Editorial independence
Canadian Cancer Society, 2017 <sup>24</sup>	Position statement	Canada	NA	NA	NA	NA	NA	NA
Canadian Cancer Society, 2017 <sup>25</sup>	Position statement	Canada	NA	NA	NA	NA	NA	NA
Centre of Excellence for Transgender Health, 2016 <sup>26</sup>	Guideline	United States	81	56	29	81	27	0
International Planned Parenthood Federation, 2015 <sup>27</sup>	Position statement	United Kingdom	NA	NA	NA	NA	NA	NA
Sherbourne Health Centre, 2015 <sup>28</sup>	Guideline	Canada	64	44	16	25	6	0
Transgender Health Information Program, 2015 <sup>5</sup>	Guideline	Canada	67	67	6	14	13	0
Centers for Disease Control and Prevention, 2013 <sup>29</sup>	Position statement	United States	NA	NA	NA	NA	NA	NA
National Health Service, 2013 <sup>30</sup>	Guideline	United Kingdom	64	25	0	28	17	0
American College of Obstetricians and Gynecologists, 2011 <sup>31</sup>	Position statement	United States	NA	NA	NA	NA	NA	NA
Endocrine Society, 2009 <sup>32</sup>	Guideline	United States	72	33	63	58	8	46
Vancouver Coastal Health, Transcend Transgender Support & Education Society and Canadian Rainbow Health Coalition, 2006 <sup>4</sup>	Guideline	Canada	86	61	17	89	0	0

Note: NA = not assessed.  
\*We did not assess the quality of position statements as they are unlikely to undergo the same development process as guidelines.

resonance imaging<sup>24,26</sup> and mammography.<sup>4</sup> One document stated that mammography was not required following chest reconstruction.<sup>28</sup> None of the documents provided a specific recommendation on the screening interval.

For trans men in general (i.e., chest reconstruction status not specified), screening recommendations varied.<sup>24,27,28,30</sup> Eligibility depended on having a history of male CSH use,<sup>27</sup> having developed breast tissue,<sup>30</sup> having a family history of breast cancer<sup>24,28</sup> and the presence of other risk factors.<sup>24</sup> 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.<sup>28</sup> The other 3 documents did not provide specific recommendations on modalities or intervals.<sup>24,27,30</sup>

### Trans women

#### Effect of cross-sex hormones on breast cancer risk, prognosis and mortality (review 1)

Two studies examined breast cancer risk among trans women exposed to CSHs.<sup>20,21</sup> In 1 study, the risk among trans women exposed to CSHs was not statistically different from that

expected for the general population of men (standardized incidence ratio 0.0, 95% confidence interval 0.0–3.7).<sup>20</sup> 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.<sup>21</sup> This body of evidence received a very low GRADE rating owing to the observational 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 2)

Evidence on 1 screening-related harm among trans women was identified.<sup>23</sup> One cross-sectional study reported on pain experienced by 50 trans women during mammography and ultrasonography.<sup>23</sup> The painfulness of both procedures, as assessed with an 11-point visual analogue scale, was rated as low (mean score range for mammography 1.7 [standard deviation 2.1] to 2.0 [standard deviation 2.3], mean score for ultrasonography 0.5 [standard deviation 1.2]) (Table 6). These

**Table 5: Existing breast screening recommendations for trans men (review 3)**

Organization, year; population	Document type	Screening recommendations			
		Additional eligibility criteria	Modality	Interval	Additional recommendations
<b>Without chest reconstruction*</b>					
CCS, 2017 <sup>24</sup>	Position statement	40–49 yr, at average risk	NR	NR	Discuss individual risk of breast cancer and benefits and risks of mammography
		50–69 yr, at average risk	Mammography	Every 2 yr	NR
		≥ 70 yr, at average risk	NR	NR	Discuss whether and how client should be screened according to individual risk factors
CETH, 2016 <sup>26</sup>	Guideline	NR	NR	NR	Follow guidelines for cisgender women
SHC, 2015 <sup>28</sup>	Guideline	NR	Clinical breast examination	Annual	Follow guidelines for cisgender women
		50–71 yr	Mammography	Every 2 yr	
ACOG, 2011 <sup>31</sup>	Position statement	NR	NR	NR	Age-appropriate† screening
VCH, TTSES & CRHC, 2006 <sup>4</sup>	Guideline	With or without history of CSH use,‡§ with or without oophorectomy	Breast examination¶	Annual	NR
			Mammography	NR	Follow guidelines for natal females
<b>With partial chest reconstruction*</b>					
CCS, 2017 <sup>24</sup>	Position statement	NR	Ultrasonography or MRI**	NR	Discuss individual risk factors†† for breast cancer
CETH, 2016 <sup>26</sup>	Guideline	NR	Ultrasonography or MRI	NR	NR
SHC, 2015 <sup>28</sup>	Guideline	NR	Mammography	NR	Not required following chest reconstruction
VCH, TTSES & CRHC, 2006 <sup>4</sup>	Guideline	With or without history of CSH use,‡§ with or without oophorectomy	Mammography	NR	Not necessary following chest reconstruction, but should be considered if only a reduction is performed
<b>Trans men in general (i.e., chest reconstruction status not specified)</b>					
CCS, 2017 <sup>24</sup>	Position statement	High risk‡‡	NR	NR	May need to be screened at earlier age or more frequently than trans men at average risk, or both
IPPF, 2015 <sup>27</sup>	Position statement	With history of CSH use‡§	NR	Periodic	Periodic cancer screening for those who retain their breast tissue
SHC, 2015 <sup>28</sup>	Guideline	Strong family history of breast cancer	Mammography	NR	Follow the same guidelines as for cisgender women regarding indications for referral to high-risk screening program/genetic assessment
NHS, 2013 <sup>30</sup>	Guideline	With developed breast tissue	NR	NR	Breast screening

Note: 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, IPPF = International Planned Parenthood Federation, MRI = magnetic resonance imaging, NHS = National Health Service, NR = not reported, SHC = Sherbourne Health Centre, TTSES = Transcend Transgender Support & Education Society, VCH = Vancouver Coastal Health.

\*Chest reconstruction was variably termed as mastectomy, gender-affirming chest surgery or chest surgery.

†Age range not specified.

‡Cross-sex hormone use was variably termed as hormone use or testosterone.

§Duration not specified.

¶Document did not specify whether clinical breast examinations, breast self-examinations or both were recommended.

\*\*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 ultrasonography or magnetic resonance imaging may be a preferable screening method.

††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.

‡‡Defined as a genetic mutation in oneself, or having a parent, sibling or child who has a genetic mutation that puts them at higher risk for breast cancer; a family history that indicates a lifetime risk of breast cancer of 25% or greater, confirmed through genetic assessment; or having received radiation therapy to the chest before 30 years of age as treatment for another cancer or condition.



**Table 6: Grading of Recommendations Assessment, Development and Evaluation (GRADE) summary of findings table for benefits and harms of breast screening for trans people (review 2)**

<b>Population:</b> asymptomatic adult trans people with mean age of 43.1 (SD 10.4) yr			
<b>Intervention:</b> breast screening with mammography, MRI, ultrasonography, clinical breast examination or breast self-examination			
Outcome; population	Effect	No. of participants (no. of studies)	Certainty of evidence (GRADE)
<b>Trans men</b>			
Benefits*	No primary research evidence identified		
Harms†			
<b>Trans women</b>			
Benefits*	No primary research evidence identified		
Overdiagnosis, false-positive screen and patient-reported anxiety			
Painfulness of mammography‡§	Mean scores ranged from 1.7 (SD 2.1) to 2.0 (SD 2.3)¶	50 (1) <sup>23</sup>	⊕000 Very low**††
Painfulness of ultrasonography‡§	Mean score 0.5 (SD 1.2)‡‡	50 (1) <sup>23</sup>	⊕000 Very low**††
<p>Note: MRI = magnetic resonance imaging, SD = standard deviation.          *Breast-cancer-specific mortality, all-cause mortality, cancer detection rate, interval cancer rate, sensitivity and specificity.          †Overdiagnosis, false-positive screen, patient-reported anxiety and patient-reported pain.          ‡Assessed by participant using a visual analogue scale ranging from 0 to 10.          §Performed by a single experienced radiologist.          ¶Two postmammography assessments of participant-experienced pain were conducted, 1 by a radiologist and the other by a study nurse. The corresponding mean scores were 1.7 and 2.0.          **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 effect estimate.          ††The evidence was downgraded owing to serious concerns regarding the observational nature of the study design and risk of bias. Detailed Grading of Recommendations Assessment, Development and Evaluation assessments are provided in Supplementary Table S6, Appendix 4.          ‡‡The study personnel responsible for administering the assessment of experienced pain were not reported.</p>			

2 bodies of evidence received very low GRADE ratings owing to serious concerns regarding the observational 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.

### Recommendations on breast screening (review 3)

Ten documents provided breast screening recommendations for trans women<sup>4,5,25-32</sup> (Table 7). For those with a history of CSH use, screening eligibility depended on the duration of CSH use,<sup>25,26,28</sup> age,<sup>4,25,26,28</sup> presence of breast implants,<sup>25</sup> breast growth,<sup>4</sup> orchiectomy status,<sup>4</sup> other risk factors<sup>4,28</sup> and guidelines for cisgender women.<sup>29</sup> Recommended modalities and intervals included mammography every 2 years<sup>25,26,28</sup> and mammography without a specified interval.<sup>4</sup> One document recommended against periodic breast self-examination and annual clinical breast examination.<sup>4</sup> Screening was not recommended for trans women with less than 5 years of CSH use<sup>25</sup> and those without a history of CSH use.<sup>4</sup>

For trans women in general (i.e., CSH use not specified), recommendations varied.<sup>5,28,30-32</sup> One document recommended diagnostic mammography for those with breast implants and consideration of annual magnetic resonance

imaging for those 30–69 years of age with a family history suggestive of hereditary breast cancer.<sup>28</sup> Two documents recommended screening for those with developed breast tissue,<sup>5,30</sup> 1 recommended screening as per guidelines for cisgender women,<sup>32</sup> and 1 recommended age-appropriate screening.<sup>29</sup> None of these documents provided specific information on the modality or interval.

### Interpretation

We found limited evidence of very low certainty that did not show an effect of CSHs on breast cancer risk in trans women or trans men. 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 showed 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 identified provided recommendations for distinct subgroups of trans people based on the presence of breast tissue and history of CSH exposure. There was an observed preference for routine

**Table 7: Existing breast screening recommendations for trans women (review 3)**

Organization, year; population	Document type	Screening recommendations			
		Additional eligibility criteria	Modality	Interval	Additional recommendations
<b>History of CSH use*</b>					
CCS, 2017 <sup>25</sup>	Position statement	40–49 yr, at average risk, CSH use > 5 yr	NR	NR	Discuss individual risks of breast cancer and benefits and risks of mammography
		50–69 yr, at average risk, CSH use > 5 yr, without breast implants	Mammography†	Every 2 yr	NR
		50–69 yr, at average risk, CSH use > 5 yr, with breast implants	Diagnostic mammography†	Every 2 yr	NR
		≥ 70 yr, at average risk, CSH use > 5 yr	NR	NR	Discuss how often client should be screened for breast cancer
		CSH use < 5 yr	NA	NA	Breast screening not recommended
CETH, 2016 <sup>26</sup>	Guideline	≥ 50 yr,‡ CSH use 5–10 yr	Mammography	Every 2 yr	Clinicians may choose to reduce age at onset of screening, number of years of female hormone exposure or frequency of screening in clients with significant family risk factors
		Any age, CSH use > 5 yr			
IPPF, 2015 <sup>27</sup>	Position statement	Current CSH use§	NR	Periodic	NR
SHC, 2015 <sup>28</sup>	Guideline	50–71 yr, CSH use > 5 yr	Mammography	Every 2 yr	NR
		< 50 yr, additional risk factors¶	Mammography	NR	Owing to lack of consensus on screening for younger trans women, emphasis may be placed on client preference following counselling on risks and benefits of screening
CDC, 2013 <sup>29</sup>	Position statement	Past or current CSH use,§ meet all NBCCEDP eligibility requirements**	NR	NR	Providers should discuss benefits and harms of screening and individual risk factors to determine whether screening is medically indicated
VCH, TTSES, & CRHC, 2006 <sup>4</sup>	Guideline	> 50 yr,‡ additional risk factors,¶ past (but not current) CSH use, breast growth, no orchiectomy	Mammography	NR	NR
		> 50 yr,‡ additional risk factors,¶ current CSH use,†† no orchiectomy	Mammography	NR	NR
		> 50 yr,‡ additional risk factors,¶ past or current CSH use, postorchiectomy	Mammography	NR	NR
		NR	Clinical breast examination	Annual	Not recommended
		NR	Breast self-examination	Periodic	Not recommended
<b>No history of CSH use*</b>					
VCH, TTSES, & CRHC, 2006 <sup>4</sup>	Guideline	No orchiectomy	NA	NA	Routine screening not recommended
<b>Trans women in general (i.e., female CSH use not specified)</b>					
SHC, 2015 <sup>28</sup>	Guideline	30–69 yr, family history suggestive of hereditary breast cancer	MRI	Annual	Consider obtaining expert opinion regarding need for annual MRI
		Breast implants	Diagnostic mammography	NR	NR
THIP, 2015 <sup>5</sup>	Guideline	Developed breast tissue	NR	NR	Screening
NHS, 2013 <sup>30</sup>	Guideline	Developed breast tissue	NR	NR	Screening
ACOG, 2011 <sup>31</sup>	Position statement	NR	NR	NR	Age-appropriate screening
ES, 2009 <sup>32</sup>	Guideline	No known increased risk of breast cancer	NR	NR	Follow screening guidelines for cisgender women
<p>Note: ACOG = American College of Obstetricians and Gynecologists, 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, 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, SHC = Sherbourne Health Centre, ES = Endocrine Society, THIP = Transgender Health Information Program, TTSES = Transcend Transgender Support &amp; Education Society, VCH = Vancouver Coastal Health.</p> <p>*Cross-sex hormone use was variably termed as hormone use, feminizing hormone use, gender-affirming hormone, estrogen or progestin.</p> <p>†Or other screening test (not specified) as appropriate.</p> <p>‡Upper age limit not reported.</p> <p>§Duration not reported.</p> <p>¶Include estrogen plus progestin use for more than 5 years, family history of breast cancer, body mass index greater than 35.</p> <p>**Specific eligibility requirements not reported.</p> <p>††Cross-sex hormone regimen that includes estrogen.</p>					

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 for breast cancer as most cisgender women.<sup>10</sup> There was also agreement that CSH exposure should be considered when determining breast screening eligibility for trans women.

The topics of breast screening and the effect of CSHs on breast cancer outcomes among trans people have not been rigorously and thoroughly researched. Previous reviews on similar topics<sup>6,10,33-36</sup> have largely summarized published case reports and series on breast cancer in trans people, as well as the studies included in our 2 reviews of primary research.

### Strengths and limitations

Key strengths of our systematic reviews include comprehensive search strategies, robust citation-screening processes and the application of reputable tools for analyzing the evidence and assessing its certainty. Key limitations are due to the nature of the available evidence and methodological decisions applied throughout the reviews. Observational designs were used in all 3 studies examining the effect of CSHs on breast cancer risk,<sup>20-22</sup> and indirect comparisons were used in 2 studies.<sup>20,21</sup> Across these studies, few details were provided regarding the nature of CSH exposure, and the length of follow-up varied and, in many cases, may have been too short to reasonably observe the effect of CSHs on long-term breast cancer risk. Two studies may have also been underpowered.<sup>20,22</sup> The study on painfulness of screening is limited by its small sample, insufficient information on validity and reliability of the outcome measure, and generalizability.<sup>23</sup> The quality of the guidelines in review 3 was low. Very few documents reported the quality of the evidence on which recommendations were based or the strength of recommendations. In all 3 reviews, we searched only for evidence available in English owing to limited resources to appropriately handle evidence in other languages, which could have resulted in language bias. The search was also limited to evidence published between 1997 and 2017. Although data extraction and quality assessments were verified by a second reviewer, these tasks were not performed independently. Owing to the insufficient quantity of primary research, certain GRADE domains could not be assessed. Although the quality of included guidelines was assessed with the Appraisal of Guidelines for Research & Evaluation II instrument, we did not verify or critically appraise the evidence cited to support recommendations.

### Conclusion

Conclusions cannot be drawn from the sparse evidence of very low certainty in these 3 reviews. The 2 systematic reviews of primary research showed 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 showed that breast screening is generally recommended for trans people; however, recommendations varied. In the absence of high-

quality scientific evidence, organized screening programs will need to supplement scientific evidence with sources of contextual evidence (e.g., professional expertise and lived experience) when developing screening recommendations and policies for trans people. Furthermore, despite the limited evidence, the argument can be made that screening should be made available to trans people who meet program eligibility requirements in the same way that it is available to cisgender women. Based on our findings, it is clear that large-scale prospective, comparative, 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. Given the large sample required for such studies and the challenges with reaching trans people for research,<sup>37</sup> future research may benefit from data linkage and algorithms to improve the identification of trans people in existing population-based health databases. Alternatively, future etiologic research of sufficient sample size may include a multisite cohort study in community clinics serving trans people.

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