Breast Cancer Risk Among Transgender Individuals Undergoing Gender Affirming Hormone Therapy: A Systematic Review

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Abstract

Introduction: This review addresses the breast cancer risk among transgender individuals undergoing gender-affirming hormone therapy, a crucial but understudied aspect in transgender healthcare. Focusing on gender affirmation, transgender individuals often face healthcare challenges, leading to gaps in broader health concerns like cancer screening. This research, framed by Dorothea Orem's Self-Care Deficit Nursing Theory, aims to fill this gap, comparing the incidence of breast cancer in transgender populations to cisgender counterparts. **Methods:** A thorough search was conducted in MEDLINE Complete, PubMed, and CINAHL Ultimate from 2013 to 2023. Search terms included transgender, trans, breast cancer, malignancy, tumor, gender affirming therapy, hormone therapy. Studies focusing on transgender individuals undergoing hormone therapy were included, with exclusions for non-English articles and those published before 2013. **Results:** From 681 articles identified, rigorous screening led to eight studies meeting inclusion criteria. These studies offered a comprehensive view of breast cancer incidence in transgender individuals undergoing gender affirming hormone therapy. Notably, transgender women on estrogen therapy had a higher breast cancer incidence compared to cisgender men, yet lower than cisgender women, while transgender men on testosterone therapy showed similar rates to cisgender men. **Discussion:** The findings suggest a need for personalized breast cancer screening strategies tailored to transgender individuals. The review emphasizes healthcare providers' role in initiating breast health discussions and the importance of adapting clinical guidelines to transgender individuals' unique needs. Acknowledging the current literature's limitations, the review advocates for more research, policy reform, and advocacy to ensure inclusive and affirming healthcare for the transgender population.

Keywords: transgender, breast cancer, hormone therapy, risk, disparities

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Transgender individuals have reported difficulties when interfacing with the US healthcare system: 19% have reported refusal of care, 28% reported harassment, and 50% were turned off the healthcare system due to a lack of gender nonconforming providers (Seelman et al., 2017). Many transgender individuals only seek medical care as a part of gender affirmation and may avoid primary health care concerns (Seelman et al., 2017, p. 18). Patients that do seek routine health care checkups are reluctant to bring up gender incongruent health concerns (Seelman et al., 2017). Hence, transgender patients may be more reliant on their health care providers to initiate cancer screening discussions than their cis-gender counterparts. There is a lack of comprehensive understanding regarding the risk of breast cancer in transgender individuals who are undergoing gender affirming hormone therapy (GAHT). This population, while receiving hormone treatment as part of their gender transition, face uncertainties and variations in breast cancer risk assessment and management. The current state of knowledge is inconclusive, making it difficult to establish clear guidelines for breast cancer screening and prevention in transgender individuals on hormone therapy. The aim of this systematic review is to examine the complex topic of cancer risk among transgender women and men undergoing GAHT. As the transgender community continues to gain visibility and acceptance, it is essential to investigate the potential medical implications of gender affirming hormone therapy.

Background and Significance

Cancer is the leading cause of death worldwide and early detection through screening is crucial in reducing morbidity and mortality (McFarlane et al., 2018). Numerous benign and malignant tumors are influenced by sex hormones, yet it remains uncertain whether the risk of

these growths varies among transgender individuals receiving GAHT (McFarlane et al., 2018). Formal epidemiological data on transgender prevalence across different age groups is limited, but estimates suggest that approximately 0.5% to 1.3% of the population identifies as transgender, and there is a growing demand for transgender health services (McFarlane et al., 2018). To understand the impact of GAHT on cancer risk, the role of hormone therapy in transgender medicine must be understood. GAHT involves introducing exogenous hormones to align an individual's secondary sexual characteristics with their gender identity (McFarlane et al., 2018). Estrogen and anti-androgens are used in feminizing hormone therapy, whereas testosterone is administered in masculinizing hormone therapy (McFarlane et al., 2018). It is important to note that the medications used in GAHT differ from those prescribed for cisgender individuals with hormonal imbalances.

Review of the Literature

Research in transgender health has predominantly focused on HIV/AIDS and mental health, leading to considerable gaps in our understanding of the long-term effects of GAHT on breast cancer risk. This underscores a critical need for rigorous evidence to inform and improve breast cancer screening practices for transgender individuals. So far, the most robust evidence available to date has been largely derived from retrospective cohort studies conducted in the Netherlands. Once such prominent Dutch study, heralded as a milestone in transgender research, engaged a diverse cohort consisting of 2,260 transgender women and 1,229 transgender men. Among the transgender women, 15 cases of invasive breast cancer were identified. Although this incidence is lower compared to that observed in cisgender, it is significantly higher than in cisgender men (Blok et al., 2019). Similarly, among the transgender men, only four cases of invasive breast cancer were reported, lower than expected compared to cisgender women (Blok

et al., 2019). The study suggests that hormone treatment may modify breast cancer risk in transgender individuals compared to their sex assigned at birth (Blok et al., 2019). Remarkably, breast cancer diagnoses in transgender individuals were found to occur at younger ages compared to cisgender women, coupled with a relatively brief period of hormone treatment exposure before diagnosis, suggesting accelerated tumor development in certain cases (Blok et al., 2019).

A subsequent retrospective cohort study was conducted in 2021 by the same Dutch research team but this time their focus was specifically on transgender women who initiated hormone treatment between 1991 and 2018. Before the start of hormone therapy, the predominant diagnosis in these individuals was gynecomastia (Blok et al., 2021). Post-initiation of hormone treatment, however, they exhibited a wider range of pathologies, such as fibroadenomas, breast cancer, fibrosis, cysts, and infections (Blok et al., 2021). Interestingly, the ratio of benign to malignant breast lesions in transgender women was 88:12, mirroring the pattern observed in cisgender women (Blok et al., 2021). This similarity suggests that transgender women on hormone therapy might experience similar breast conditions to cisgender women. However, it's important to delve deeper into how their unique health backgrounds and the specific effects of hormone therapy on their breast health might differ from those in cisgender women. These distinctions are crucial for tailoring healthcare and screening appropriately for the transgender population.

Although data from both European studies reveal that the overall rate of breast cancer in the combined group of transgender males and females does not significantly differ from that of the general population, the precise incidence of breast cancer within the transgender community remains unclear. This ambiguity is partly due to the limited availability of comparative data on

breast cancer risk relative to cisgender counterparts. Despite these similarities in overall incidence rates, it's crucial to explore the unique risk factors that may affect transgender individuals distinctly. Factors like prolonged hormone therapy, necessary for sustained gender affirmation, along with hormonal differences that stem from one's assigned sex at birth, could result in distinctive patterns of breast cancer risk. These variances highlight the need for specialized healthcare considerations for transgender individuals. Understanding these nuances is vital for developing tailored health guidelines that address both the commonalities and the specific health needs of the transgender population.

As the body of research on breast health in transgender individuals continues to evolve, it is becoming increasingly apparent that clinical practice guidelines require updating to reflect transgender individuals unique risk profiles more accurately. Presently, the standard screening recommendations might not fully cater to the specific needs of transgender patients. For instance, it is appropriate that transgender men who have not undergone a bilateral mastectomy, or who have only had breast reduction, follow the breast cancer screening protocols recommended for cisgender women (Deutsch 2016). However, the lack of specific guidelines for screening transgender men who have undergone mastectomy points to a significant gap in healthcare provision. Additionally, it is recommended that screening mammography be performed every 2 years for transgender women, once the age of 50 and 5-10 years of feminizing hormone use criteria have been met (Deutsch, 2016). Even though research indicates that transgender individuals tend to receive breast cancer diagnoses at younger ages compared to cisgender women and these diagnoses often follow a relatively short period of hormone therapy (Blok et al., 2019). The studies analyzed in this systematic review underscore the need for revised guidelines that comprehensively consider the unique hormonal and surgical aspects of

transgender individuals, as well as factors like the timing and duration of hormone therapy, and relevant personal and family medical histories. This project emphasizes the importance of aligning clinical practices with the diverse needs of the transgender population for more effective breast cancer screening and prevention.

Purpose and Question

Determining the breast cancer risk associated with GAHT in transgender individuals is complex due to various factors. Firstly, age at hormone initiation, duration of hormone therapy, and personal breast cancer history, may contribute to variations in risk. Secondly, studies evaluating breast cancer risk in transgender populations are limited and often contradictory, making it challenging to draw definitive conclusions. Some studies suggest a slightly elevated risk of breast cancer, while others do not find any significant increase. Consequently, these factors beg the question: In transgender individuals receiving GAHT, how does the incidence of breast cancer and associated risk factors, such as age, hormone regimen, duration of hormone therapy, and family history, compare to cisgender women and men, over a follow-up period > 3 months? Thus, the purpose of this systematic review is to conduct a thorough analysis of current research to illuminate if there is an association between GAHT and an increased risk of breast cancer among transgender individuals.

Conceptual Framework

Dorothea Orem's Self-Care Deficit Nursing Theory provided valuable insight for both clarifying and structuring the problem, as well as organizing the data collected for this review. Dorothea Orem's theory emphasizes the importance of self-care as a fundamental component of nursing care (Hartweg & Metcalfe, 2022). According to this theory, individuals have the ability and responsibility to engage in self-care activities to maintain their health and well-being

(Hartweg & Metcalfe, 2022). However, when individuals cannot meet their self-care needs, nurses should step in to provide care and support (Hartweg & Metcalfe, 2022). In the context of this systematic review, transgender individuals, like all individuals, have self-care agency, which refers to their ability to engage in behaviors that promote their health (Hartweg & Metcalfe, 8 2022). This includes making decisions about their healthcare, including whether to take GAHT and how to manage their overall health. Transgender individuals undergoing GAHT face deficits in self-care related to cancer risk, this specifically involves factors such as cancer screening practices, lifestyle behaviors, and healthcare access. This systematic review explores how nursing interventions can assist transgender individuals in taking charge of their self-care concerning cancer risk, particularly in the context of GAHT. Through an examination of cancer risk among those undergoing GAHT, this review equips transgender individuals with essential health insights. Additionally, it indirectly raises awareness among healthcare providers about conceivable cancer risks related to GAHT, potentially influencing adjustments in their education and recommendations, further empowering their patients.

Methods

Project Design

The rationale for this systematic literature review is to address the critical gap in understanding the impact of GAHT on breast cancer risk in transgender individuals, a topic of growing importance in transgender healthcare. This project's design involves a detailed exploration of this influence, structured and guided by Dorothea Orem's Self-Care Deficit Nursing Theory framework. By applying Orem's theory, the review provides valuable insights into the interplay between GAHT, self-care practices, and breast cancer risk in this population.

This approach enhances our comprehension of a vital healthcare issue and aligns with the patient-centered care principles advocated by Orem's theory.

Search Strategy

Electronic and manual searches were completed in MEDLINE Complete, PubMed, and CINAHL Ultimate, from 2013 to 2023 using the following key terms: transgender, trans, breast cancer, malignancy, tumor, gender affirming therapy, hormone therapy. Furthermore, an ancestry search was conducted by examining the reference lists of relevant articles identified with the aim of discovering additional references.

For inclusion in this literature review, studies were considered eligible if they enrolled participants who identified as transgender, transsexual, or under another term denoting individuals with a gender identity incongruent with their assigned sex at birth, and who were seeking hormone therapy to achieve feminization or masculinization of their bodies. Included studies were nonrandomized uncontrolled, cohort studies. Such studies provide the highest quality evidence currently available in the field. Studies were included regardless of sample size. Only English language publications between 2013 and 2023 were included in this review. Given the extensive variability in hormone regimens currently available, this review encompassed all modes of hormone administration, all dosing levels, frequency of dosing, and a wide range of hormone types. European studies were also incorporated because of the scarcity of research conducted and published in the United States. The American health care systems has collected inconsistent gender identity data on their enrollees and the provision of transgender health care is most often fragmented and decentralized to individual practitioners or regional, private specialty clinics (Brown & Jones, 2015, p. 192).

The exclusion criteria for this review were studies published before 2013, those not available in English, and research not meeting the minimum quality score as per the appraisal checklist. Additionally, studies that did not focus specifically on transgender individuals undergoing hormone therapy, or those with different outcomes than cancer risk, were also excluded.

To evaluate the study quality, a Rapid Critical Appraisal Checklist was utilized. A threshold score of three or higher was established for study inclusion in the final sample. Any studies falling below the threshold were deemed ineligible for this systematic review. Given the research question's importance to transgender healthcare, the inclusion of studies meeting these quality standards is essential for effectively informing clinical practice and healthcare policy.

Selection Process

The initial step in the screening process included reviewing the titles of identified articles. Each article's title was utilized to determine its relevance to the research question. Any articles that were clearly irrelevant were excluded. After the title was reviewed, next each article's abstract was assessed for relevance to the research question and inclusion criteria. Articles that did not meet the criteria or provided insufficient information in the abstract were excluded. If there was any uncertainty, the article was included for full-text review. Articles that passed the abstract review proceeded to the full-text review stage. Here, the complete content of each article was thoroughly examined to assess its suitability for inclusion in the final sample. Articles were excluded if they did not meet the inclusion criteria (i.e., study design, population, or outcome measures). A Flow Diagram was utilized, as recommended by the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines, to visually represent the screening and selection process (See Appendix C). The article screening process was conducted by only

one independent reviewer. Zotero software was used to organize and manage the retrieved articles. This software facilitated the removal of duplicate records and assisted in tracking of the screening process. The quality appraisal of the selected studies was performed using the Rapid Critical Appraisal Questions for Cohort Studies. This tool was selected based on its appropriateness for the study designs included in this literature review. The appraisal process involved assessing various aspects of each study for validity, reliability, and applicability. The results of the quality appraisal were documented and factored into the final selection of studies for inclusion in the analysis.

Synthesis Method

For this research project, an Evidence Synthesis Table was employed as a systematic and organized method for extracting pertinent information from the selected articles (see Appendix A). This table served as a central repository for key data elements, incorporating essential information from each study, including the author's name, publication year, research framework, and study design. Additionally, a brief summary of the study's objectives, sample and setting details, methodology, findings, and limitations were also documented to provide a comprehensive context. To analyze the data and arrive at overarching themes, studies were systematically categorized based on reported outcomes. Whenever multiple studies presented data on identical outcomes, a collective analysis was conducted to synthesize these findings. Additionally, subgroup analyses were undertaken to address observed inconsistencies, identifying instances where certain studies diverged significantly from the majority. This involved a careful examination of the study outcomes, methodologies, and population characteristics. By comparing and contrasting these elements, recurring themes and unique

insights were identified that emerged across the body of research, which also facilitated the understanding of gaps in the current research landscape.

Results

Search Results

A comprehensive search incorporating terms such as transgender, trans, breast cancer, malignancy, tumor, gender affirming therapy, hormone therapy, yielded 681 potential articles from various databases, including MEDLINE Complete, PubMed, and CINAHL Ultimate. After removing duplicates, 576 unique articles remained. These articles were subjected to initial screening based on titles and abstracts. During the initial screening, 528 articles were excluded as they did not meet the inclusion criteria. Additionally, six articles could not be accessed from the database, rendering them unavailable for review. The remaining 42 articles underwent full-text assessment to determine their eligibility for inclusion in the systematic review. Upon further examination of the full-text articles, an additional 24 studies were excluded for the following reasons: irrelevant outcome measures, lack of transgender-specific data, and insufficient methodological rigor. Fifteen articles had outcome measures that did not align with the specific research question or focus of the study. Another 10 articles were found to have considerable methodological issues that would have undermined the quality and reliability of this review's findings. Furthermore, nine of the articles, while addressing broader topics, lacked specific data or insights pertinent to the transgender population, a vital aspect for this review. Finally, eight studies were included in the systematic review, as they met the predefined criteria for relevance, data quality, and study design. These studies were then subjected to data extraction and synthesis for the final analysis. The flow chart, (See Appendix B), illustrates the stepwise process of study selection. In summary, the systematic search and screening process resulted in the inclusion of

eight relevant studies that will be analyzed to address the clinical question regarding the relationship between gender-affirming hormone therapy and breast cancer risk among transgender individuals.

Characteristics of Studies

This systematic review encompasses eight distinct studies, a total of 20,344 participants—13,744 transgender women and 6,600 transgender men—each study contributed valuable insights into the complex relationship between transgender individuals and their risk of breast cancer or associated morbidities. These studies collectively employ diverse research methodologies, encompassing a wide range of study designs, purposes, and sample sizes, thereby offering a comprehensive understanding of the subject matter. Notably, retrospective cohort studies, including Brown (2015) and Gooren (2013), utilized extensive datasets to investigate transgender populations over extended periods. In addition, cross-sectional studies such as Baker (2021) and Wierckx (2013) provided valuable insights into breast morphology and related morbidities during cross-sex hormone therapy. Sample sizes across the studies exhibit significant variation. Blok (2019) and Silverberg (2017) conducted retrospective cohort studies on large scales, encompassing thousands of transgender individuals, offering substantial statistical power. Conversely, Baker (2021) and Wolters (2023) adopted smaller cohorts, focusing on specific aspects of breast tissue characteristics and histopathological findings. The studies' research purposes also diverge, reflecting different objectives within the broader context of transgender breast cancer risk. Some studies, such as Blok (2019) and Brown (2015), aimed to compare breast cancer rates in transgender individuals to cisgender populations, seeking to quantify the potential risk differential. Conversely, Baker (2021) and Wolters (2023) focused on evaluating breast morphology and histopathological differences during hormone therapy, contributing to a

nuanced understanding of breast tissue alterations. Furthermore, each study brings a unique perspective to the review. For instance, Blok (2021) delves into the outcomes of breast biopsies in transgender women, offering insights into clinical practices and potential diagnostic challenges. Gooren (2013) explored the alignment of breast cancer risk with gender identity in transgender individuals receiving hormone therapy. The study specifically investigated how hormone treatments, such as androgen deprivation and estrogen administration in transgender women and testosterone for transgender men, influenced the development of breast cancer.

In summary, this systematic review comprised a heterogeneous group of studies, each contributing to a nuanced understanding of the relationship between GAHT and breast cancer risk among transgender individuals. The diversity in study designs, purposes, sample sizes, and focus areas allowed for a comprehensive synthesis of evidence to address the clinical question at hand. The synthesis table (See Appendix A) included in this literature review provides a concise summary of key findings from these studies, aiding in the interpretation and application of their results.

Synthesis Across Studies

The studies included in this systematic review focused on evaluating the incidence of breast cancer in transgender individuals receiving GAHT and compared it to cisgender men and women in the general population. Several themes emerged from the findings of these studies. First, with regard to transgender women (MTF) receiving estrogen therapy, there was a consistent trend across the studies. Blok et al. (2019) reported that MTF individuals had a 46-fold higher breast cancer incidence compared to cisgender men but lower rates than cisgender women. Gooren et al. (2013) found that the incidence rate in MTF cohorts was 4.1 per 100,000 person-years. These findings suggest that transgender women on estrogen therapy may have a

higher breast cancer risk compared to cisgender men but remain at a lower risk than cisgender women.

Second, transgender men (FTM) receiving testosterone therapy showed different patterns. Blok et al. (2019) reported that FTM individuals had a breast cancer incidence rate similar to that of cisgender men, but significantly lower than the expected rate in cisgender women. This indicates that FTM individuals on testosterone therapy may not have an elevated risk of breast cancer comparable to cisgender women.

In addition to these overarching themes, some studies provided unique insights. Wierckx et al. (2013) assessed the short- and long-term cardiovascular- and cancer-related morbidities during cross sex hormone (CSH) therapy and found relatively low morbidity rates during CSH therapy, particularly in transgender men. Silverberg et al. (2017) examined cancer incidence in a cohort of transgender people and found that transgender males have a breast cancer risk 82 times higher than cisgender males, but no increase compared to matched cisgender females. While the individual studies varied in terms of design, sample size, and methodology, consistently indicated an increase in breast cancer risk associated with GAHT in transgender individuals. The findings collectively suggested that transgender women on estrogen therapy may have an increased risk of breast cancer compared to cisgender men but not as high as cisgender women. Conversely, transgender men on testosterone therapy do not appear to have an elevated risk comparable to cisgender women.

Guided by Dorothea Orem's Self-Care Deficit Nursing Theory, the conceptual framework of this review examines the impact of hormone therapy on breast cancer risk, providing a lens through which to interpret these findings. It highlights the complex interplay between gender-

affirming hormone therapy, hormone exposure, and breast cancer incidence in transgender individuals.

In summary, the synthesis across studies underscores the significance of considering hormone therapy as a potential factor influencing breast cancer risk in transgender populations. These findings enhance our comprehension of the multifaceted relationship between hormone therapy and breast cancer risk, which can guide healthcare decisions and inform guidelines for transgender individuals pursuing gender-affirming care.

Discussion

The aim of this systemic review is to examine the incidence of breast cancer among transgender individuals receiving GAHT in comparison to cisgender men and women in the general population. Eight studies were systematically analyzed that provided valuable insights into this complex relationship. The overarching findings revealed distinct patterns based on gender identity and hormone therapy. Specifically, transgender women receiving estrogen therapy appeared to have an increased risk of breast cancer compared to cisgender men but remained at a lower risk than cisgender women. On the other hand, transgender men undergoing testosterone therapy did not show an elevated breast cancer risk comparable to cisgender women. These findings align with the conceptual framework utilized in this review, Orem's Self-Care Theory, which helped interpret the results by emphasizing the importance of hormone exposure as a self-care action and its potential implications for health outcomes.

The synthesis of these studies' findings has provided valuable insights into the breast cancer risk landscape for transgender individuals undergoing GAHT. The results shed light on the nuanced relationship between hormone therapy and breast cancer incidence, addressing the primary question of whether there is an increased risk of breast cancer among transgender

persons receiving GAHT. The evidence suggests that transgender women, in their journey towards gender affirmation, may face a heightened risk of breast cancer when exposed to estrogen therapy. However, it is crucial to note that this risk remains slightly lower than that observed in cisgender women. This conclusion aligns with our first aim, which sought to evaluate the incidence of breast cancer in transgender individuals compared to cisgender counterparts. It also underscores the necessity of considering transgender-specific healthcare needs and tailoring breast cancer screening and prevention strategies accordingly. Moreover, our findings regarding transgender men undergoing testosterone therapy contribute to the second aim of this review, which aimed to assess the breast cancer risk among transgender male individuals. Notably, the literature synthesis indicates that this cohort does not appear to bear an elevated risk of breast cancer comparable to cisgender women. While these conclusions align with some existing literature, they underscore the importance of personalized healthcare plans for transgender individuals based on their unique hormonal and gender identity journeys. Orem's Self-Care Theory aptly supports the interpretation of these results by emphasizing the role of individuals in managing their health and well-being, which includes the decision to undergo hormone therapy and the potential consequences for health outcomes. Overall, this systematic review contributes to our understanding of the complex interplay between hormone therapy and breast cancer risk in transgender populations, offering valuable guidance for healthcare providers and policymakers in addressing the unique healthcare needs of transgender individuals.

Recommendations From Findings

The findings of this synthesis review provide valuable insights that can be applied to similar clinical settings and research projects involving transgender healthcare. The consistent theme across multiple studies, show that when comparing the general transgender population

undergoing GAHT to the general cisgender population, there isn't a significant increase in breast cancer incidence. However, distinct differences are evident when making more specific comparisons. Transgender women on estrogen therapy have an almost 50% higher risk of developing breast cancer than cisgender men. Yet, this risk for transgender women does not surpass the breast cancer risk faced by cisgender women. For transgender men on testosterone therapy, the studies show a lower breast cancer risk when compared cisgender women.

These results suggest that gender-affirming hormone therapy, a crucial component of transgender care, does not appear to pose a substantial additional risk of breast cancer. Therefore, clinicians and researchers in transgender healthcare can be reassured about the safety of this intervention, and this knowledge can guide the development of evidence-based guidelines for transgender care.

While the majority of findings aligned with our expectations and the conceptual framework (Orem's self-care theory), it is essential to address the unexpected result of a relatively low breast cancer incidence rate among transgender population undergoing GAHT. One possible explanation for this unexpected finding could be the relatively young age of the study populations in several included studies. Breast cancer risk tends to increase with age, and the limited follow-up duration in some studies might not have captured long-term cancer risk accurately. Further research is warranted to explore the relationship between transgender status, GAHT, and breast cancer risk across diverse age groups and for longer periods.

Based on the evidence synthesized in this review, the following strategies are recommended to improve clinical practice for healthcare providers working with transgender patients. Regular breast cancer screening is advisable. While the absolute risk of breast cancer among transgender individuals on GAHT appears low for the population as a whole; regular

breast cancer screening as recommended for cisgender women is advisable for transgender women. Conversely, since transgender men on testosterone therapy do not show a significant increase in breast cancer risk compared to women, it may be more appropriate to align their screening guidelines with those of cisgender men. Still, healthcare providers should also develop and implement tailored breast health education programs for transgender patients undergoing GAHT. These programs should focus on breast self-examinations, awareness of breast changes, and the importance of reporting any unusual symptoms promptly. Empowering transgender individuals with knowledge and self-monitoring skills can promote proactive health behaviors and early detection, aligning with the principles of patient self-care emphasized in Orem's self-care theory. This approach ensures that transgender patients are actively engaged in their breast health and overall well-being. These recommendations aim to enhance the quality of care provided to transgender individuals and foster ongoing research efforts to refine our understanding of transgender health outcomes.

Limitations

The findings of this systematic review are subject to several limitations that should be considered when interpreting the results. Firstly, the limited availability of high-quality evidence on the topic poses a significant constraint. The included studies exhibited variations in study design, sample size, and methodological rigor, making it challenging to draw definitive conclusions. The majority of the studies in this review were observational in nature, which inherently carries a risk of bias and limits the establishment of causal relationships. The lack of randomized controlled trials (RCTs) or intervention studies focusing on GAHT and its association with breast cancer incidence is a notable limitation. To address this limitation, future

research efforts should prioritize the conduct of well-designed RCTs to provide more robust evidence.

Secondly, the quality appraisal ratings of the articles included in this systematic review revealed that some studies had methodological shortcomings. These limitations included issues related to sample selection, potential confounding variables, and data reporting. Such limitations in the primary studies could introduce biases into the synthesis of evidence. To improve upon this limitation, future studies should adhere to rigorous research methodologies and provide transparent reporting of methods and results. Additionally, the development of standardized protocols and criteria for data collection and analysis within the field would enhance the quality of research on this topic.

Furthermore, the limited number of articles directly addressing the research question posed another challenge. Despite an exhaustive search strategy, the relatively small pool of relevant studies suggests that this is still an emerging area of research. Consequently, the generalizability of the findings to a broader population may be limited. To mitigate this limitation, researchers should prioritize investigating the relationship between GAHT and breast cancer risk. Collaboration across institutions and the establishment of research networks may facilitate the accumulation of larger and more diverse datasets, allowing for more comprehensive analyses and increasing the external validity of future research.

In summary, while this systematic review provides valuable insights into the current state of evidence on the relationship between gender-affirming hormone therapy and breast cancer risk among transgender individuals, it is crucial to acknowledge the inherent limitations. Addressing these limitations through the promotion of high-quality research, standardized methodologies,

and increased research efforts will contribute to a more comprehensive understanding of this complex and clinically relevant issue.

Conclusions and Implications

The key takeaway for advanced practice nurses and other healthcare facilities from this review is the importance of considering breast health in transgender individuals undergoing GAHT. While the absolute risk of breast cancer in this population remains low, healthcare providers should remain vigilant, conduct regular breast examinations, and promote breast health awareness among transgender patients. This review highlights the need for tailored breast care guidelines that account for the unique characteristics and needs of transgender individuals.

Addressing the issue of breast cancer risk in transgender individuals receiving GAHT demands a comprehensive and multifaceted approach, encompassing various key components. To gain deeper insights into the relationship between GAHT and breast cancer risk, further research endeavors are imperative. As previously stated, this entails conducting meticulously designed prospective cohort studies or even RCTs thoughtfully tailored to transgender populations. These studies should involve larger and more diverse sample sizes, extending over more extended periods, thereby yielding more robust and comprehensive evidence. Moreover, research should delve into the diverse impact of distinct hormone regimens, routes of administration, and dosages to mitigate breast cancer risks. Collaborative efforts among healthcare institutions and researchers hold the key to bridging the current gap in high-quality evidence in this domain.

Healthcare institutions should take the initiative to launch quality improvement (QI) projects, specifically designed to enhance the delivery of breast healthcare services to transgender individuals. This involves the meticulous development and implementation of

comprehensive breast care guidelines, thoughtfully tailored to address the unique needs of this population. These guidelines should encompass recommendations for effective risk assessment, well-timed screening intervals, and appropriate diagnostic procedures. Additionally, QI projects can strategically concentrate on augmenting the cultural competence of healthcare providers to ensure transgender patients receive care that aligns with their gender identity, fostering an environment of sensitivity and affirmation.

Policymakers and healthcare organizations should join forces in formulating and enforcing policies and guidelines that explicitly acknowledge and address the distinctive breast health requirements of transgender individuals. This entails advocating for comprehensive insurance coverage encompassing essential breast health services, such as mammograms and breast ultrasounds, to guarantee equitable access to transgender patients. Furthermore, these policies should encompass gender-affirming care access and coverage, safeguarding that transgender individuals can avail themselves of essential services without encountering discrimination. Collaborative efforts with LGBTQ+ advocacy groups are pivotal to navigating this landscape successfully.

Equipping transgender individuals with the knowledge and understanding they need regarding their breast health is of paramount importance. Healthcare providers should proactively engage in patient education efforts, serving to inform transgender patients about their potential breast cancer risk. Additionally, patients should be apprised of the significance of adhering to regular breast examinations and the tangible benefits of early detection. The active involvement of transgender advocacy groups can play a pivotal role in disseminating critical information and championing equitable access to healthcare services.

In summary, the holistic approach to addressing breast cancer risk in transgender populations necessitates the concerted efforts of diverse stakeholders across various domains, including research, quality improvement, policy reform, and advocacy. Collaboration among healthcare professionals, researchers, policymakers, and advocacy groups serves as the cornerstone of endeavors to enhance breast health outcomes, ensuring that transgender individuals receive healthcare services that are inclusive and affirming of their gender identities.

References

Baker, G. M., Guzmán-Arocho, Y. D., Bret-Mounet, V. C., Torous, V. F., Schnitt, S. J., Tobias, A. M., Bartlett, R. A., Fein-Zachary, V., Collins, L. C., Wulf, G. M., & Heng, Y. J. (2021). Testosterone therapy and breast histopathological features in transgender individuals. *Modern Pathology*, *34*(1), 85–94. https://doi.org/10.1038/s41379-020- 006759

Blok, C. J., Wiepjes, C. M., Nota, N. M., Klaartje, V., Adank, M. A., Dreijerink, K. M., & den Heijer, M. (2019). Breast cancer risk in transgender people receiving hormone treatment: Nationwide cohort study in the Netherlands. *BMJ-British Medical Journal, 365*. https://doi.org/10.1136/bmj.l1652

Blok, C. J., Dijkman, B. A., Wiepjes, C. M., Konings, I. R., Dreijerink, K. M., Barbe, E., & den Heijer, M. (2021). Frequency and outcomes of benign breast biopsies in trans women: A nationwide cohort study. *The Breast, 57*, 118-122. https://doi.org/10.1016/j.breast.2021.03.007

Brown, G. R., & Jones, K. T. (2015). Incidence of breast cancer in a cohort of 5,135 transgender individuals. *Breast Cancer Research and Treatment, 149*(1), 191–198. https://doi.org/10.1007/s10549-014-3213-2

Deutsch, M. B. (2016, June 17). Breast cancer screening in transgender men. UCSF Transgender Care. https://transcare.ucsf.edu/guidelines/breast-cancer-men

Deutsch, M. B. (2016, June 17). Screening for breast cancer in transgender women. UCSF Transgender Care. https://transcare.ucsf.edu/guidelines/breast-cancer-women

Gooren, L. J., van Trotsenburg, M. A. A., Giltay, E. J., & van Diest, P. J. (2013). Breast cancer development in transsexual subjects receiving cross-sex hormone treatment. *The Journal of Sexual Medicine, 10*(12), 3129–3134. https://doi.org/10.1111/jsm.12319

Hartweg, D. L., & Metcalfe, S. A. (2022). Orem's self-care deficit nursing theory: *Relevance and need for refinement. Nursing Science Quarterly, 35*(1), 70-76. https://doi.org/10.1177/08943184211051369

McFarlane, T., Zajac, J. D., & Cheung, A. S. (2018). Gender-affirming hormone therapy and the risk of sex hormone-dependent tumours in transgender individuals—A systematic review. *Clinical Endocrinology, 89*, 700-711. https://doi.org/10.1111/cen.13835

Seelman, K. L., Colón-Diaz, M. J., LeCroix, R. H., Xavier-Brier, M., & Kattari, L. (2017). Transgender noninclusive healthcare and delaying care because of fear: Connections to 13 general health and mental health among transgender adults. *Transgender Health, 2*(1), 17-28. https://doi.org/10.1089/trgh.2016.0024

Silverberg, M. J., Nash, R., Becerra-Culqui, T. A., Cromwell, L., Getahun, D., Hunkeler, E. M., Lash, T. L., Millman, A., Quinn, V. P., Robinson, B., Roblin, D. W., Slovis, J., Vin Tangpricha, & Goodman, M. (2017). Cohort study of cancer risk among insured transgender people. *Annals of Epidemiology, 27*(8), 499–501. https://doi.org/10.1016/j.annepidem.2017.07.007

Wierckx, K., Elaut, E., Declercq, E., Heylens, G., De Cuypere, G., Taes, Y., Kaufman, J. M., & T'Sjoen, G. (2013). Prevalence of cardiovascular disease and cancer during cross-sex

hormone therapy in a large cohort of trans persons: a case–control study. European *Journal of Endocrinology, 169*(4), 471–478. https://doi.org/10.1530/eje-13-0493

Wolters, E. A., Rabe, K. E., Siegel, L., Butts, J., & Klein, M. (2022). Histopathologic features of breast tissue from transgender men and their associations with androgen therapy. *American Journal of Clinical Pathology, 159*(1), 43–52. https://doi.org/10.1093/ajcp/aqac12

Appendix A

Table 1

Evidence Synthesis Table

Author	Purpose	Frame-work	Design	Sample/ Setting	Methods	Findings	Quality Appraisal/ Limitations	Conclusions/ Application
Baker, 2021	To evaluate if and how long it took for TT to modulate breast morphology in TG males and masculine centered GNCIs.	NA	Observational cross-sectional study	Total subjects: 447; 367 received TT, 79 did not, 1 excluded due to unknown TT status; duration of TT for 43 patients unknown; most frequent route of administration IM testosterone enanthate/ cypionate (314/367; 85.6%), followed by transdermal gel, patch, or cream (29/367; 7.9%), and subcutaneous pellet (5/367; 1.4%); route of administration for 19 subjects unknown (5.2%); majority young, white non-Hispanic, identifying as TG male; 36 subjects had history of breast or ovarian cancer; surgeries	Chest-contouring specimens collected in quadrants; additional sections taken: If nipple/skin present or gross lesions/atypia identified; H&E stained slides reviewed: various histopathological features assessed; Features included: lobular atrophy, stromal composition, ectatic ducts, inflammation, and other characteristics, e.g., gynecomastoid change, cysts, apocrine metaplasia, atypical lesions like flat epithelial atypia, and ductal	11/446 atypical lesions (ADH, ALH, DCIS); all patients with atypical lesions received TT; 7 ADH cases received TT 10.1 to 34.9 months, three had family history; 2 ALH cases: one received TT for 12.1 months, no family history; duration unknown for the other; 1 case had both ADH and ALH, received TT for 64.1 months, family history of breast cancer, 1 DCIS case received TT 61.4 months, strong	QA: 6/10; small sample size; majority of study cohorts young age; 12-month duration of TT treatment; some subjects missing data about duration of TT treatment; no standardized protocols for sampling breast tissue; comparative challenges related to study design, control groups, and TT duration.	Atypical lesions and DCIS were detected in 11 subjects receiving TT; overall findings do not suggest a substantial increase in the risk of clinically significant breast lesions or carcinoma solely due to TT; does not include hormone therapy in transgender females, cannot comprehensively address breast cancer risk in the entire transgender population

Author	Purpose	Frame-work	Design	Sample/ Setting	Methods	Findings	Quality Appraisal/ Limitations	Conclusions/ Application
				performed between 2013 and 2019 at Beth Israel Deaconess Medical Center Boston	carcinoma in situ; compared histopathological findings to TG males and GNCIs who did and did not receive TT; R version 3.4.0 for all analyses; significance level p<0.05	family history of breast cancer		
Blok, 2019	To investigate the incidence and characteristics of breast cancer in transgender people in the Netherlands; compare with the general Dutch population.	NA	Retrospective nationwide cohort study	2260 adult TG women (median age at start of treatment 31y); 1229 adult TG men (median age at start of treatment 23y); gender clinic of the VU University Medical Centre Amsterdam; btwn 1972 and January 2016	Exclusion criteria: no hormone treatment, unknown start date, age < 18, regret about transition; Utilization of PALGA for breast cancer diagnosis data; exclusion of visits prior to 1991 (start of PALGA); Data collection: age at start of hormone treatment, treatment type, gender-affirming surgery, medical history; linked to PALGA and Statistics Netherlands for breast cancer diagnosis, histology,	TG women 18 cases of breast cancer (15 invasive and 3 non-invasive; median duration of GAHT 18 years, range 7-37 years; median age at diagnosis was 50; Most case ductal origin, 83% estrogen and 67% progesterone receptor positive; 8.3% HER2 positive. TG men 4 cases of invasive breast cancer; no cases of noninvasive breast cancer; median duration	QA: 7/10; retrospective design; no consideration for different types of GAHT or other breast cancer risk factors (family history, BMI, alcohol/tobacco use); Study participants with breast cancer, treatment not elsewhere; limited data on treatment type and outcomes.	Risk of breast cancer in TG persons as a group comparable to risk in cisgender men; increased risk in TG women compared to cisgender men; Most tumors in TG women are of type sensitive to estrogen; a younger age at time of breast cancer diagnosis in TG people compared with cisgender women; exposure to hormone treatment before breast cancer diagnosis relatively short in TG women; median of 18 years, suggesting rapid development of breast tumors in a subset of people.

Author	Purpose	Frame-work	Design	Sample/ Setting	Methods	Findings	Quality Appraisal/ Limitations	Conclusions/ Application
					and mortality data - Analysis: STATA statistical software version 14.1; OpenEpi version 3.01	of GAHT, 15 years, range 2-17 years; diagnosed at median age of 47; 3 cases of ductal origin; 2 cases estrogen and progesterone receptor positive, 1 case HER2 positive; 1 case androgen receptor positive		
Blok, 2021	To examine the frequency and outcomes of breast biopsies in a large cohort of TG women.	NA	Retrospective cohort study	2616 total participants; exclusions: <18 years old, testosterone users, unknown treatment start dates; study focus: TG women who began hormone treatment after 1990; Center of Expertise on Gender Dysphoria at Amsterdam University Medical Center, Netherlands	Eligible participants' data collected: age at hormone treatment start, gender-affirming surgery, mean BMI during follow-up, medical history; Breast pathology diagnoses obtained from PALGA database; Statistical analysis: Baseline data presented as mean (SD) for normally distributed; median (IQR) for non-normally distributed; breast lesions shown as	126 diagnosed breast lesions; 21 TG women had a breast lesion before start of GAHT, 53 after start of GAHT; breast lesion biopsies at median 20 years (IQR 16-22) post hormone treatment start; Common lesions identified after GAHT: fibroadenomas, invasive breast cancer, fibrosis, cysts, infections; benign versus	QA:4/10; retrospective design; breast biopsies performed at other hospitals; inconsistent documentation of reason for breast biopsies; data regarding other medication usage missing/incomplete; incomplete clinical data in PALGA database	No elevated breast cancer risk in TG women; biopsy indications and outcomes in trans women paralleled those in cis women; reasonable to follow breast care guidelines as developed for cis women.

Author	Purpose	Frame-work	Design	Sample/ Setting	Methods	Findings	Quality Appraisal/ Limitations	Conclusions/ Application
					diagnoses (percentage); treatment duration calculated from hormone treatment start to first breast lesion, study end, or death; STATA v15.1 used for analyses	malignant lesions ratio, after the start of GAHT 88:12		
Brown, 2015	To assess hormone therapy exposure; examine breast cancer incidence in a large North American TG population; compare findings with European studies	NA	Retrospective cohort study	5,135 TG veterans; US VHA	Analyzed breast cancer incidence in a cohort of US TG veterans; examined EHR data from 1996-2013 based on ICD-9 codes; compared TG veteran breast cancer rates to the general American population.	10 breast cancer cases; 7 FtM, 2 MtF, 1 natal male with transvestic fetishism; incidence rate of breast cancer 20.0 per 100,000 patient-years of VHA treatment; expected rate was 14.8 per 100,000 patient-years; 52% had at least one hormone therapy prescription; overall SIR observed versus expected cases of confirmed breast cancer was 1.36 per 100,000 (95 % CI 0.03–5.57).	QA:3/10; possibility hormone therapy obtained outside VHA sources; cohort size possibly too small and/or duration of follow-up too short; average cohort age 55, may be too young to detect cancers that may appear with longer-term follow-up; TG leaving VHA care before diagnosis; inconsistent hormone prescriptions until 2011 national directive; Conflation of "sex" and "gender" in data sets from other	Differences between expected cases and the observed cases were not statistically significant. So, there was no significant impact of hormone therapy on breast cancer rates in this sample. Hormone therapy in TG veterans show no increase in breast cancer incidence greater than general population; findings consistent with European studies.

Author	Purpose	Frame-work	Design	Sample/ Setting	Methods	Findings	Quality Appraisal/ Limitations	Conclusions/ Application
							systems; retrospective study design	
Gooren, 2013	To investigate breast cancer occurrence in a large cohort of Dutch TG individuals; assess whether breast cancer risk aligns with birth sex or new gender identity.	NA	Retrospective cohort study	2,307 MtF TG persons undergoing androgen deprivation and estrogen administration; 795 FtM TG persons receiving testosterone; 18-80 years of age; exposure to CSH 5 to >30 years; University Medical Center in Amsterdam.	Incidence of breast cancer rates calculated per 100,000 patient years; Byar method used to calculate the 95% CI for FtM small number of cases; for comparison expected incidence of breast cancer calculated based on Dutch incidence numbers for men and women.	Incidence rate MtF cohort 4.1 per 100,000 person-years; FtM subjects incidence rate 5.9 per 100,000 person-years; MtF TG persons breast cancer patterns more akin to males; FtM TG persons patterns more akin to males as well.	QA: 5/10; retrospective study design; no control group; relatively long follow up for some participants; short follow up period for others, <6 years; small cohort of FtM TG persons; limited generalizability.	Low incidence rate in TG women, two cases identified, similar to what would be expected in biologically assigned males; TG male low incidence rate of breast cancer, one case identified, similar to what would be expected in biologically assigned males; regardless of assigned sex at birth or gender-affirming hormone therapy, may not have a significantly elevated risk of breast cancer.
Silverberg, 2017	To examine cancer incidence in a cohort of transgender people, enrolled in three large integrated health care systems	NA	Retrospective cohort study	2791 TG females and 2098 TG male participants; mean age TG female and TG males 39 and 32 years, respectively; Three Kaiser Permanente sites (Georgia, Northern California, and Southern California)	TG status identified via medical records review; 10 males and 10 females with no evidence of TG status matched for comparison; cancer cases among cohorts identified via health plan associated cancer registry; all types of cancers assessed; Cancer incidence rates and 95% CI	Overall cancer incidence the same when comparing TG female and TG male subjects with their matched reference groups; TG male subjects' higher rates of breast cancer relative to male referents; no increase	QA: 5/10; small sample size; few events related to young mean age of the sample; lack of direct causality btwn androgen therapy and breast cancer risk.	Identifies specific cancer risk patterns in TG males and TG females compared to male and female referents. Findings provide valuable insight into the unique cancer risks associated with transgender identities and hormone therapy.

Author	Purpose	Frame-work	Design	Sample/ Setting	Methods	Findings	Quality Appraisal/ Limitations	Conclusions/ Application
					based on Poisson distribution; HR and 95% CI comparing cancer risk in TG males and TG females with matched reference cohorts obtained from Cox regression models; data analysis using SAS software version 9.4	compared with matched female cohort		
Wierckx, 2013	To evaluate the short- and long-term cardiovascular- and cancer-related morbidities during CSH therapy in a large sample of TG persons	NA	Cross-sectional study	Compared 214 TG women; 138 TG men with an age- and gender-matched control population (1–3 matching); CSH therapy average 7.4 years; assessed physical health and possible treatment related adverse events using questionnaires; Center for Sexology and Gender Problems at the Ghent University Hospital (Ghent, Belgium) between 1986 and June 2012	Age-matched female and male control groups to compare cardiovascular disease- and cancer-related morbidity data; randomly selected control group, 3 men and 3 women for each subject; All data were gathered via face-to-face computer assisted personal interviewing and/or computer-assisted self-interviewing; Data were analyzed using the PASW software, v.19 (SPSS, Inc.).	11 TG women venous thrombosis, pulmonary embolism; 3 cases of acute MI; 5 TG TIA or CVD; cancer in TG persons similar or lower to control men and women; 3 cases of colon carcinoma, 2 cases of melanoma, 1 case of lymphoma in TG women; TG men experienced 0 cases of cancer; no cases of breast cancer	QA. selection bias, 54% response rate; small sample size; many women in control group used hormone therapy, possible underestimation in observed differences in morbidity rates in TG persons and the control population	Morbidity rate during cross-sex hormone therapy was relatively low, especially in TG men; rates of cancer were similar compared with the control men and women.

Author	Purpose	Frame-work	Design	Sample/ Setting	Methods	Findings	Quality Appraisal/ Limitations	Conclusions/ Application
					Statistical significance was set at P>0.05, and all tests were two-tailed; morbidity comparison btwn groups adjusted for age			
Wolters, 2023	To assess the histopathologic features of breast tissue in TG males undergoing gender-affirming bilateral mastectomies in relation to androgen therapy.	NA	Observational retrospective cohort study	374 TG bilateral mastectomy cases reviewed from 2017 to 2020; of those 314 patients received preoperative androgen therapy; compared with 127 cases of cisgender females undergoing elective breast reduction; University of Minnesota Medical Center from January 2017 through August 2020	Two reviewers examined tissue slides for composition, lobules, and atrophy; compared data using different statistical tests; looked at associations between findings and hormone therapy duration in TG men; significance threshold of P < 0.05; R version 3.6.3 or higher was used for all analyses.	Specimens from TG males on androgen therapy had more fibrous tissue, decreased lobular density, and more atrophic lobules than from cisgender females; findings related to the length of androgen therapy; Atypia was more prevalent in the cisgender group than in the TG males on androgen therapy; All cases of atypia in the	QA: 7/10 potential influence of age and BMI, no statistical adjustment for these factors; limited generalizability; lack of longitudinal data; no adjustment for multiple comparisons	Four cases of atypia were found among TG individuals; Atypia was more prevalent in the cisgender group than in the TG individuals on androgen group; provides valuable information about breast tissue characteristics in TG individuals on androgen therapy, it does not directly address the question of increased breast cancer risk; did not provide direct comparison to the expected rates in the general population.

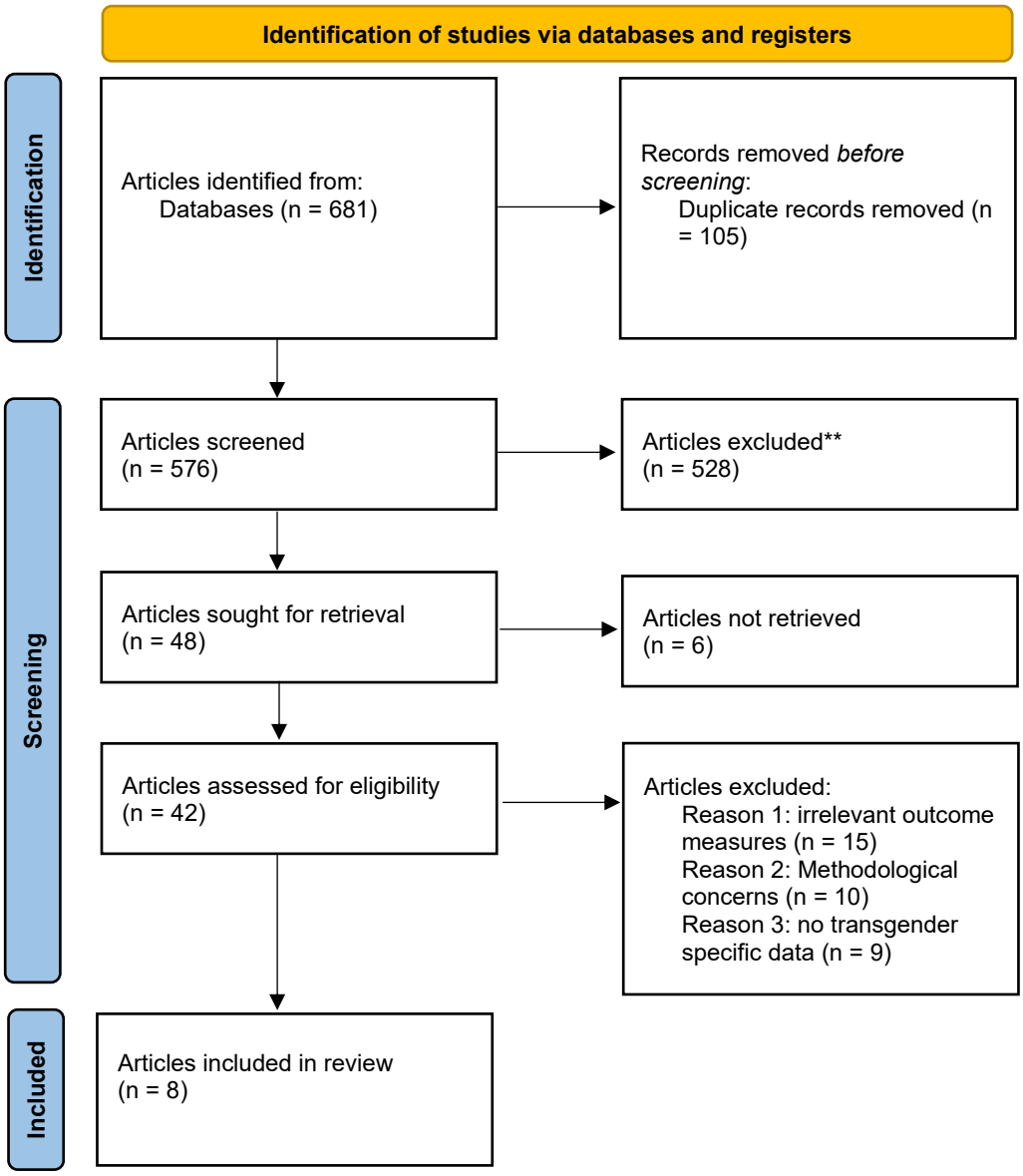
Author	Purpose	Frame-work	Design	Sample/ Setting	Methods	Findings	Quality Appraisal/ Limitations	Conclusions/ Application
						TG male group had normal imaging and gross findings.		

Abbreviations (*in alphabetical order*): ADH=atypical ductal hyperplasia; ALH=atypical lobular hyperplasia; BMI=body mass index; Btwn=between; CI- confidence interval; CSH=cross sex hormones; DCIS=ductal carcinoma in situ; EHR=electronic health record; FtM=female to male; GNCI=gender non-conforming individuals (natal female); H&E= Hematoxylin and Eosin; HR= hazard ratios; HER2=human epidermal growth factor 2; ICD-9CM=international classification of diseases ninth revision; IM=intramuscular; MI=myocardial infarction; MtF=male to female; PALGA= Nationwide Network and Registry of Histopathology and Cytopathology in the Netherlands; SIR= standardized incidence ratio TG=transgender; TT=testosterone; US=United States; VHA=Veterans Health Administration; y=years

Appendix B

Figure 1

PRISMA Flowchart



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