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Cancer in Transgender People: Evidence and Methodological Considerations

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Transgender people comprise a diverse group of individuals whose gender identity or expression differs from that originally assigned to them at birth. Some, but not all, transgender people elect to undergo medical gender affirmation, which may include therapy with cross-sex hormones and/or surgical change of the genitalia and other sex characteristics. As cross-sex hormones administered for the purposes of gender affirmation may be delivered at high doses and over a period of decades, the carcinogenicity of hormonal therapy in transgender people is an area of considerable concern. In addition, concerns about cancer risk in transgender patients have been linked to sexually transmitted infections, increased exposure to well-known risk factors such as smoking and alcohol use, and the lack of adequate access to screening. Several publications have identified cancer as an important priority in transgender health research and called for large-scale studies. The goals of this article are to summarize the evidence on factors that may differentially affect cancer risk in transgender people, assess the relevant cancer surveillance and epidemiologic data available to date, and offer an overview of possible methodological considerations for future studies investigating cancer incidence and mortality in this population.

cancer; hormones; transgender

Abbreviations: CI, confidence interval; DHT, dihydrotestosterone; ENIGI, European Network for the Investigation of Gender Incongruence; HPV, human papillomavirus; PCOS, polycystic ovary syndrome; PIR, proportional incidence ratio; PSA, prostate-specific antigen; SEER, Surveillance, Epidemiology, and End Results; VA, Veteran Affairs.

INTRODUCTION

Transgender people comprise a diverse group of individuals whose gender identity or expression differs from that originally assigned to them at birth (1). Biological sex is determined on the basis of the appearance of genitals, chromosomal and hormonal makeup, and secondary sex characteristics, whereas gender refers to an individual's sense of maleness, femaleness, neither, or both (1, 2). Although transgender people may not self-identify on the basis of binary definitions (3), a person whose gender identity differs from a male sex assignment at birth is often referred to as male-to-female, transfeminine, or transwoman, and a person whose gender identity differs from a female sex assignment at birth is often referred to as a female-to-male, transmasculine, or transman (4, 5).

Some, but not all, transgender people may seek medical treatment to affirm their gender identity. In some cases, this is done to alleviate gender dysphoria, which is a diagnostic term that describes a "strong and persistent distress with physical sex characteristics or ascribed social gender role that is incongruent with persistent gender identity" (6, p. 117).

The gender affirmation treatment includes 4 types of interventions: 1) changes in social expression of gender to achieve consistency with gender identity, 2) therapy with cross-sex hormones to achieve desired masculinization or feminization, 3) surgical change of the genitalia and/or other sex characteristics, and 4) psychotherapy to further explore gender identity, improve body image, and promote resilience (7). The goal of psychotherapeutic, endocrine, or surgical therapy is lasting personal comfort with the gendered self in order to maximize overall well-being (8).

The current literature indicates that transgender people face a disproportional burden of adverse health outcomes (9). In 2011, the Institute of Medicine (10) released a report on the health of lesbian, gay, bisexual, and transgender persons. The report specifically emphasized the importance of transgender health research to better understand the needs of this population.

Although the body of literature addressing transgender health issues has been growing exponentially (11), to date most available studies primarily focused on substance use and abuse, sexual health and sexually transmitted infections, and, to a lesser extent, mental health problems (12). By contrast, limited data are available on the incidence of chronic age-related conditions, including cancer.

Whereas cancer among transgender people is listed among research priorities (10), most of the concerns pertaining to the occurrence and outcomes of malignant tumors in this population are based on anecdotal evidence or on the general considerations of possible disease mechanisms (13–18). The high quality empirical data assessing cancer incidence and mortality among transgender people are lacking primarily because of an absence of large-scale prospective studies of this population (19). Before large-scale prospective studies of cancer among transgender people are initiated, it is important to conduct a systematic evaluation of the possible biological mechanisms by which transgender status may influence carcinogenesis and review the information that is available to date.

In this article, we first review the possible risk factors that may differentially affect cancer risk in transgender people. We then provide an overview of the available cancer surveillance data pertaining to this population. We complete an evaluation of the available evidence by reviewing the limited epidemiologic data addressing this issue. Finally, in the Discussion section, we offer an overview of possible methodological approaches to investigating cancer incidence and mortality among transgender people.

METHODS

Review of the literature

We conducted the initial literature search of the PubMed electronic database using the following combinations of general text keywords and Medical Subject Headings (MeSH) terms: "cancer transgender" ("neoplasms"(MeSH Terms) *OR* "neoplasms"(All Fields) *OR* "cancer"(All Fields)) *AND* ("transgendered persons"(MeSH Terms) *OR* ("transgendered"(All Fields) *AND* "persons"(All Fields)) *OR* "transgendered persons"(All Fields) *OR* "transgender"(All Fields)) and "cancer transsexual" ("neoplasms"(MeSH Terms) *OR* "neoplasms"(All Fields) *OR* "cancer"(All Fields)) *OR* transsexual (All Fields)) with "cancer transgender" and "cancer transsexual" resulting in 65 and 64 results, respectively. Out of the 129 articles initially identified, 15 duplicates were removed, 30 were removed after reviewing the title as the result of lack of relevance, and 6 were unavailable. The remaining 78 articles were printed and reviewed. Of those, 34 relevant studies were selected: 28 case reports, 5 epidemiologic studies, and 1 article that included both. Secondary references of retrieved articles and recent reviews were examined to identify publications not captured by the electronic search. Eight case reports and 5 epidemiologic studies were added on the basis of manual search, resulting in 47 studies for review: 36 case reports, 10 epidemiologic studies, and 1 publication that included both.

Case reports were included in the review if they described cancer in a transgender person who had initiated surgical or hormonal gender affirmation therapy. Eligibility criteria for epidemiologic studies included any quantitative assessment of cancer occurrence (incidence or prevalence) in a defined population of transgender people.

Information obtained from each eligible case report included primary tumor site, geographical location, type of gender affirmation therapy received, and various additional aspects of the case including details of treatment and histological features. Epidemiologic studies were described with respect to the source and location of the population, sample sizes of transmen and transwomen, and measures of cancer occurrence (e.g., incidence or mortality), by site in transgender people overall and compared with the reference populations.

To more fully understand the important research questions related to cancer epidemiology in transgender people, we supplemented the systematic review of cancer case reports and epidemiologic studies with additional searches of the literature on the known and hypothesized cancer risk factors that may disproportionately affect this population. Separate searches were conducted by using PubMed and Web of Science electronic databases for studies evaluating the prevalence of risk factors of interest and the potential mechanisms by which exposure to these factors may affect cancer risk in transgender people.

Analysis of cancer surveillance data

Although population-based data on cancer incidence among transgender people are not available, some information can be obtained from the US National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database. At present, the SEER program includes 18 registries covering approximately 30% of the US population (20).

Although the variable "sex" in SEER data typically includes only the 2 categories "male" and "female," the variable also allows inclusion of categories "other (hermaphrodite)" and "transsexual." It is not clear if the latter category is used consistently; however, it allows assessing the frequency and site distribution of cancer cases among transsexual patients reported to SEER. For the purposes of the present review, we used data from the SEER 18-registry data set for the years 1973–2013 to select all patients whose variable "sex" was categorized as "transsexual." Each case was characterized with respect to primary site, tumor histology, patient's age, and year of diagnosis. To assess if the observed distributions of primary sites differ from those in the general population of cancer cases, we calculated proportional incidence ratios and the corresponding 95% confidence intervals. For a given cancer site, a proportional incidence ratio estimate is obtained by dividing the observed cancer cases in the transsexual group by the expected number, which is based on the site-, age-, and diagnosis year-specific proportions in the total SEER sample. During this period, the transsexual category did not distinguish between transmen and transwomen. For this reason, we calculated the proportional incidence ratio using the expected cases obtained separately from data on nontransgender males and females.

CANCER RISK FACTORS AND CASE REPORTS

Human papillomavirus infections

Human papillomavirus (HPV) has been implicated in the etiology of anal, oropharyngeal, and penile cancers among

nontransgender men and in cervical, anal, vulvar, and vaginal cancers among nontransgender women (21). Among over 40 types of HPV, at least 13 are considered high risk with respect to their carcinogenic potential (22).

Studies evaluating the prevalence of HPV or related conditions focused primarily on the examination of anal mucosa in transwomen. The endpoints of interest in these studies included detectable HPV DNA in anal swabs, presence of anogenital warts, or results of cytological examination. For example, a study of 111 transgender sex workers in Argentina found HPV DNA in 97% of anal mucosa samples. High-risk carcinogenic genotypes were detected in 83% of the participants, and 71% were coinfected with 2 or more HPV genotypes (23). In another study conducted among transwomen in Lima, Peru, visible anogenital warts were detected in 22% of the participants (24). Two recent studies examined the prevalence of anal squamous intraepithelial lesions by using Papanicolau (Pap) smears. These 2 studies reported the prevalence of anal squamous intraepithelial lesions to be around 56% and 42% among transwomen in India and Thailand, respectively (25, 26).

A number of studies of both transgender and nontransgender people indicate that HPV and HPV-related anal squamous intraepithelial lesions are more common in human immunodeficiency virus-infected individuals (22, 27, 28). Human immunodeficiency virus infections are common among transgender people, particularly transwomen who have some of the highest laboratory-confirmed prevalence estimates in the world (29). For all of the above reasons, HPV-related cancers are expected to occur more frequently in transgender people than in the general population (30).

The case reports of presumably or potentially HPV-related malignancies in transgender patients who received gender affirmation therapy include anal and neovaginal cancers in transwomen and cervical and vaginal cancers in transmen (17, 31–35). Of special consideration with respect to neovaginal cancers is the use of heterotopic penile skin, which may be at higher risk for HPV-induced squamous cell carcinoma. A recent study of 54 transwomen who underwent vaginoplasty and were followed up at a clinic in Amsterdam examined neovaginal swabs for the presence of high-risk HPV DNA. Of 28 sexually active study participants, 6 (20%) tested positive for neovaginal high-risk HPV (36). It has been suggested that complications of vaginoplasty, including chronic laceration and inflammation, may increase the risk of malignancy (32).

Possible effects of cross-sex hormones

The aim of typical hormonal treatment for transwomen is to decrease blood testosterone to physiological female concentrations (30–100 ng/dL) through antiandrogens (or surgical castration) and to achieve normal female but not supraphysiological levels (<400 pg/mL) of estradiol through estrogen therapy. The corresponding goal of hormonal gender affirmation in transmen is to reach testosterone levels of the normal male, which range between 300 and 1,000 ng/dL (37).

Cases of presumably hormone-related malignancies in transwomen diagnosed after the initiation of medical or surgical gender affirmation include carcinomas of the breast and prostate, prolactinomas, and meningiomas (16, 38–63). In transmen, published case reports describe cancers of the breast, ovaries, cervix, vagina, and endometrium (17, 18, 34, 35, 44, 45, 64–68).

In the next few sections, we will discuss the hypothesized effects of cross-sex hormones by cancer site and provide examples of published case reports among transgender patients who underwent hormonal or surgical gender affirmation (Tables 1 and 2).

Prostate cancer in transwomen. The prostate is not removed during gender affirmation surgery. Whereas androgen deprivation through antiandrogens or orchiectomy is expected to protect against prostate cancer (69), the role of exogenous estrogen and its action on estrogen receptors α and β also needs to be considered. Recent literature indicates that estrogen receptor α stimulates prostate carcinogenesis, while estrogen receptor β appears to exert an antineoplastic effect, although studies suggest that different estrogen receptor β isoforms may have different and sometimes opposing modes of action (70–72). Estrogen receptors are not the only target of estrogen; it has been shown that 17β-estradiol can bind to androgen receptors with the assistance of coactivators or androgen receptor mutations that result in 17β-estradiol hypersensitivity (73, 74).

It is possible that prostate cancers in transwomen are more aggressive because these malignancies develop despite low levels of testosterone and high levels of estrogen (38). All reported cases of prostate cancer among transwomen who underwent gender affirmation had orchiectomy, and all were receiving hormonal therapy. All but 1 of those cases received hormonal therapy for at least 10 years prior to diagnosis. Although most reported cases of prostate cancer in transwomen presented with high prostate-specific antigen (PSA) levels, a feature of more aggressive disease, it should be kept in mind that almost all of these cases were symptomatic or at least had a palpable prostate lesion at diagnosis. It is, therefore, expected that PSA levels in these cases were higher than the levels typically observed in the general population of prostate cancer patients (75).

Breast cancer in transwomen. High-dose exogenous cross-sex estrogens and androgen antagonists stimulate the formation of breast lobules, ducts, and acini histologically identical to those of biological females (43). Exogenous estrogen binds to the estrogen receptor in the breast tissue and is hypothesized to stimulate carcinogenesis via increased cell proliferation, decreased apoptosis, and elevated production of oxidative metabolites that result in DNA damage (76, 77). Higher serum levels of endogenous estradiol have been associated with higher breast cancer risk in nontransgender natal males (78), lending further support to the hypothesis that transwomen may be at increased risk of breast cancer due to hormonal therapy.

Risk associated with progesterone use may require particular attention. Data from several studies indicate that the risk of breast cancer in postmenopausal women receiving hormone replacement therapy may differ depending on inclusion of progesterone in the hormone replacement formulations (79–81).

Table 1. Summary of Published Cancer Case Reports on Transwomen Who Underwent Hormonal or Surgical Gender Affirmation Therapy

Cancer Site or Tumor Type	No. of Cases	Location(s)	Age, years	Gender Affirmation Status	Comments	References
Anus	1	Italy	63	Neovaginal construction using penile components; no reported HT use	Diagnosed 24 years after gender affirmation surgery	33
Neovagina	2	Australia, Switzerland	42–53	2/2 cases had neovaginal construction, and 1/2 reported HT use.	1 case confirmed as HPV induced, and the other negative for p16 immunohistochemistry suggesting no HPV	31, 32
Prostate	6	United States, United Kingdom, Netherlands	60–78	6/6 cases had orchiectomy and HT.	5/6 cases diagnosed at least 10 years after HT initiation	38–42, 63
Breast	15	United States, United Kingdom, Netherlands, Germany, New Zealand, Thailand	30–65	15/15 cases had HT, 6/15 cases had silicone injections or mammoplasty, and 1/15 had an unspecified surgery.	0/2 cases *BRCA1* (+), 0/2 cases *BRCA2* (+), 6/12 cases ER (+), 5/11 cases PR (+), 2/6 cases *HER2*/*ERBB2* (+), 0/1 AR (+), 3/15 cases triple negative for ER/PR/*HER2*	43–53
Meningioma	4	France, Italy, Spain, United States	28–48	4/4 cases had HT, 3/4 included cyproterone acetate, and 1/4 received orchiectomy.	3/4 cases diagnosed within first 10 years of HT initiation	54–57
Prolactinoma	8	Netherlands, Brazil, Canada, Spain	26–69	8/8 cases had HT, and 4/8 included cyproterone acetate.	2/8 cases diagnosed within 1 year of HT initiation; the rest (6/8) developed >10 years after initiation	16, 58–62

Abbreviations: AR, androgen receptor; *BRCA1* and *BRCA2*, breast cancer susceptibility genes, type 1 and type 2; ER, estrogen receptor; *ERBB2*, erb-b2 receptor tyrosine kinase 2 gene; *HER2*, human epidermal growth factor receptor type 2 gene; HPV, human papillomavirus; HT, hormone therapy; PR, progesterone receptor; +, positive.

Another factor that may affect breast cancer risk in transwomen is a relatively low level of testosterone. Mechanistic evidence indicates that testosterone inhibits proliferation and stimulates apoptosis in breast epithelium (82, 83). Analyses of observational data from the Women's Health Initiative study also showed that rates of estrogen receptor-negative breast cancer are inversely associated with circulating testosterone levels (80). For these reasons, it is possible that antiandrogen therapy in transwomen can increase breast cancer risk, particularly for estrogen receptor-negative disease.

The current literature includes 15 reported cases of breast cancer in transwomen who received estrogen therapy (43–53). Most reported cases were relatively young, with some patients presenting in their early 30s.

Meningioma in transwomen. Female sex hormones may also play a role in the pathogenesis of meningiomas. This hypothesis is based on the observations that meningiomas

Table 2. Summary of Published Cancer Case Reports in Transmen Who Underwent Hormonal or Surgical Gender Affirmation Therapy

Cancer Site	No. of Cases	Location(s)	Age, years	Gender Affirmation Status	Comments	References
Vagina	1	Germany	60	Hysterectomy and phalloplasty	HPV positive; diagnosed 18 years after SRS	35
Cervix	2	United States, Czech Republic	38–54	2/2 cases had HT, and 1 case had mastectomy.	Both cases were diagnosed less than 10 years after HT.	17, 34
Breast	7	Netherlands, United States, Serbia, United Kingdom	27–53	4/7 cases had mastectomy, and 7/7 cases had HT.	0/2 cases *BRCA1* (+), 0/2 cases *BRCA2* (+), 5/7 cases ER (+), 4/7 cases PR (+), 3/5 cases *HER2* (+). Cases diagnosed between 1 and 13 years after HT	44, 45, 64–66
Ovary	3	Netherlands, United States	38–46	3/3 cases had HT, 1/3 cases had hysterectomy and phalloplasty, and 3/3 cases had mastectomy.	2/2 cases were VEGF (+), 2/2 cases were EGFR (+), 1/1 case was ER (+), 1/1 case was PR (+), 1/1 case was AR (+). Cases were diagnosed 1–28 years after HT.	18, 67
Endometrium	1	United States	51	Received HT	Case was diagnosed less than 10 years after HT.	17

Abbreviations: AR, androgen receptor; *BRCA1* and *BRCA2*, breast cancer susceptibility genes, type 1 and type 2; EGFR, epidermal growth factor receptor; ER, estrogen receptor; *HER2*, human epidermal growth factor receptor type 2 gene; HPV, human papillomavirus; HT, hormone therapy; PR, progesterone receptor; SRS, sex reassignment surgery; VEGF, vascular endothelial growth factor; +, positive.

are more common in women than in men, appear to change in size during the luteal phase of the menstrual cycle and pregnancy, are associated with the use of oral contraceptives and hormone replacement therapy, and tend to co-occur with breast cancer (84, 85). Most meningiomas express progesterone receptors, whereas estrogen receptors are found in only one-third of tumors. For this reason, it is has been suggested that progesterone, especially in large doses, may be implicated in the etiology of meningioma among transwomen (57). Of particular interest in these cases is the use of cyproterone acetate compound that acts as both a progesterone agonist and an antiandrogen (55). Although commonly prescribed in Europe, it is not available in the United States (7).

Of the 4 reported cases of meningioma among transwomen (54–57), 3 (54, 55, 57) were diagnosed in patients who received cyproterone acetate prior to diagnosis. In 1 patient, who presented with 2 tumors, 1 lesion was markedly decreased in size and the other lesion was no longer evident 10 months after cyproterone acetate was discontinued (55).

Prolactinoma in transwomen. Prolactinomas are the most common pituitary tumors that tend to be relatively small, slow growing, and diagnosed predominantly in women (86, 87). Estrogens have been reported to induce prolactin synthesis and release, and their use has been linked to both hyperprolactinemia and prolactinoma risk (58). Progesterone is also thought to play a role in prolactinoma development as indicated by the evidence that these tumors express both estrogen and progesterone receptors; however, the latter pathway is not well understood (88).

Current literature includes 8 case reports of prolactinoma in transwomen treated with hormonal therapy (16, 58–62). In 4 cases, hormonal therapy included cyproterone acetate, and all patients presented with highly elevated prolactin levels.

Breast cancer in transmen. The role of testosterone in breast cancer is not clear. Some studies have suggested that testosterone may reduce proliferation and increase apoptosis by decreasing the expression of estrogen receptor in breast epithelium (82, 83). On the other hand, an increased risk of breast cancer has been reported with increased serum testosterone levels in both pre- and postmenopausal women (89–91). One possible explanation for these discrepancies is the fate of the testosterone and whether it is aromatized to estrogen or metabolized to dihydrotestosterone (DHT).

There were 7 reported cases of breast cancer in transmen who received gender affirmation therapy (44, 45, 64–66). All 7 cases received testosterone therapy, and 4 underwent a mastectomy prior to diagnosis.

Cervical cancer in transmen. Although carcinogenicity of HPV infections is well established (21), the relationship between cervical cancer and testosterone is unclear. In premenopausal women, free, but not total, testosterone was associated with a greater risk of invasive cervical carcinoma, while among postmenopausal women, a positive association was observed for total, but not free, testosterone (92). How these observations apply to transmen is not known.

The current literature includes 2 case reports of cervical cancer in transmen (17, 34). Both cancers were diagnosed in the context of planned gender affirmation surgery. In the first case, a carcinoma in situ was discovered postoperatively (34), and in the second case, invasive cervical cancer was identified during the preoperative work-up (17). Only 1 of the 2 cases had Papanicolaou smear examinations prior to diagnosis (34).

Endometrial cancer in transmen. Testosterone can be converted to DHT by 5α-reductase or to estradiol by aromatase. Although DHT has been shown to have antiproliferative effects on endometrial cancer cells, aromatase may decrease DHT production by depleting testosterone and increasing estrogen levels, which may stimulate proliferation of the endometrial epithelium (93). In addition, both testosterone and DHT interact with endometrial epidermal growth factor receptor (94). This information aligns with observational epidemiologic studies that suggest an association between endometrial cancer and total higher testosterone levels in postmenopausal women (95, 96).

Another consideration is the relationship between polycystic ovary syndrome (PCOS) and endometrial cancer. PCOS patients have thicker endometrium, possibly due to the effect of androgens on the endometrial epidermal growth factor receptor (94). Endometrial cancer risk is greater in women with PCOS (94, 97, 98). One study showed that 80% of transmen had histological characteristics of PCOS after at least 6 months of testosterone therapy (99). By contrast, another study reported hyperplasia of the ovarian cortex without PCOS morphology in transmen treated with testosterone; this study involved fewer participants but a longer follow-up (100).

To date, there is only 1 reported case of endometrial cancer in a transman receiving testosterone therapy. The cancer was diagnosed 7 years after initiation of hormonal treatment (17). It is possible that endometrial cancer risk in transmen receiving testosterone is decreased because of complete atrophy of the endometrium. On the other hand, endometrial cancer in a transman receiving testosterone may be missed because of a lack of early signs such as abnormal bleeding.

Ovarian cancer in transmen. The previously discussed effects of androgen on endometrial carcinogenesis may also play a role in the etiology of ovarian cancer (67, 94). Endometrial epidermal growth factor receptor is commonly found in ovarian cancer cells, and its expression has been associated with poor prognosis (101). It is important to keep in mind that many transmen in Europe undergo an oophorectomy within 12–18 months of initiation of hormonal treatment. For this reason, elevated ovarian cancer risk may not be as evident in this population (102).

Three cases of ovarian cancer in transmen undergoing gender affirmation are reported in the literature. All 3 cases received testosterone therapy, 1 had a hysterectomy and a phalloplasty, and all 3 underwent a mastectomy (18, 67). Only 2 cases were tested for the endometrial epidermal growth factor receptor and in both cases the results were positive (67).

Other cancer risk factors

People receiving gender affirmation therapy may present with a unique set of health issues, but they also require routine primary and preventive care (103). Although large-scale

nationally representative data are lacking, there is evidence that transgender people are disproportionately exposed to common modifiable cancer risk factors including smoking, obesity, and lack of or inadequate cancer screening. For example, a recent cross-sectional survey conducted through collaboration with community-based agencies across the United States (104) reported that the prevalence of current smoking among older (over the age of 50 years) transgender participants was 15% compared with just under 9% in nontransgender respondents of similar age. Lack of physical activity was observed in 23% and 15% of transgender and nontransgender survey respondents, respectively, and the corresponding prevalence estimates for obesity were 40% and 25%.

An important concern in transgender health is access to transgender-specific and general care (105). A survey in Massachusetts demonstrated that 14% of transgender and only 6% of nontransgender respondents reported having no health insurance (106). Even among transgender persons with health insurance, experiences with discrimination in a health-care setting were reported in 38% of responders (107). Another factor that may act as a barrier to health care is poor understanding of transgender health issues among medical professionals. For example, in a recent survey of transgender people, 62% of transmen and 51% of transwomen indicated they had "to teach their providers about transgender people" (108, p. 1010).

All of the above factors contribute to delayed or inadequate health care and, specifically, to a lack of adherence to recommended cancer screening. A recent evaluation of medical records from a community health center that provides care to underserved populations, including gender and sexual minorities, examined adherence to mammography screening guidelines. Adherence was defined as having 1 or more mammograms during the preceding 2-year interval (109). Among nontransgender females included in the study, 73% were considered screening adherent. This proportion was significantly higher than the corresponding proportions observed among transwomen (55%) and transmen without a history of mastectomy (50%).

Another review of medical records at the same institution focused on Papanicolaou smears (110). The up-to-date Papanicolaou smear screening was found in 74% of nontransgender female patients and 64% of transmen. After controlling for patient- and provider-related factors, transmen had a 37% lower odds of being up-to-date compared with nontransgender females.

A separate analysis of the records from the same clinic focused on the proportion of "inadequate" Papanicolaou smears, defined as tests that could not be evaluated by the laboratory because of a lack of sufficient cells or obscuring factors (111). Compared with nontransgender female patients, transmen were more likely to have an inadequate Papanicolaou test (1.3% vs. 11%). The difference remained similar in magnitude and statistically significant after adjustment for age, race, and body mass index.

CANCER SURVEILLANCE DATA

To date, SEER data include a total of 354 transsexual cancer patients. The earliest case was documented in 1978, and the majority of cases (70%) were reported in the most recent decade (2004–2013), which is expected as the program coverage greatly expanded after 2001.

With respect to the most common primary sites, the top 5 malignancies were carcinomas of the lung and bronchus ($n = 35$), anal cancers ($n = 32$), non-Hodgkin lymphomas ($n = 31$), Kaposi sarcomas ($n = 29$), and cancers of the colon and rectum ($n = 25$). Table 3 contains the summary results of

Table 3. Proportional Incidence Ratios by Site of Primary Cancer in Transgender People Compared With Natal Males and Females in the Reference Population, Surveillance Epidemiology and End Results Data

Site of Primary Cancer or Type of Cancer	Observed Transgender Cases, no.	Comparison With Nontransgender Males		Comparison With Nontransgender Females	
		PIR[a]	95% CI[b]	PIR[a]	95% CI[b]
Anus	32	9.71	6.64, 13.71	19.79	13.54, 27.94
Base of tongue, pharynx	10	1.59	0.76, 2.93	8.92	4.28, 16.41
Breast	20	26.71	16.31, 41.24	0.16	0.10, 0.25
Colorectum	25	0.77	0.50, 1.14	1.11	0.72, 1.63
Kaposi sarcoma	29	4.65	3.11, 6.68	445.71	298.50, 640.10
Kidney and renal pelvis	12	0.84	0.43, 1.46	1.89	0.98, 3.30
Liver and intrahepatic bile duct	14	1.65	0.90, 2.77	6.30	3.45, 10.57
Lung and bronchus	35	1.13	0.78, 1.57	1.49	1.04, 2.08
Melanoma	8	0.25	0.11, 0.49	0.34	0.15, 0.67
Non-Hodgkin lymphoma	31	1.61	1.09, 2.28	3.13	2.13, 4.44
Pituitary	6	1.80	0.66, 3.93	1.83	0.67, 3.99
Urinary bladder	13	0.97	0.51, 1.65	3.41	1.82, 5.84

Abbreviations: CI, confidence interval; PIR, proportional incidence ratio.
[a] Adjusted for year of diagnosis and age at diagnosis.
[b] Calculated by using Poisson approximation.

proportional incidence ratio analyses for cancer sites with at least 6 cases. By use of nontransgender females as the reference category, significantly elevated proportional incidence ratios were observed for Kaposi sarcoma (proportional incidence ratio (PIR) = 446, 95% confidence interval (CI): 299, 640), anal cancer (PIR = 20, 95% CI: 14, 28), base of tongue/pharyngeal cancer (PIR = 9, 95% CI: 4, 16), liver/bile duct cancer (PIR = 6, 95% CI: 3, 11), urinary bladder cancer (PIR = 3, 95% CI: 2, 6), and non-Hodgkin lymphoma (PIR = 3, 95% CI 2, 4.5). Relative to nontransgender males, significantly elevated proportional incidence ratios were observed for breast cancer (PIR = 27, 95% CI: 16, 41), anal cancer (PIR = 10, 95% CI: 7, 14), Kaposi sarcoma (PIR = 5, 95% CI: 3, 7), and non-Hodgkin lymphoma (PIR = 1.6, 95% CI: 1, 2). Significantly lower-than-expected numbers of cases were observed for breast cancer relative to females (PIR = 0.2, 95% CI; 0.1, 0.3) and melanoma relative to either sex (both PIRs = 0.3).

REVIEW OF PUBLISHED EPIDEMIOLOGIC DATA

To date, 11 published articles assessed cancer incidence or mortality in transgender persons (Table 4). These articles were published over a period of more than 25 years (1989–2016) and examined 4 different populations. Five articles were based on a cohort of patients who received hormonal therapy at the Free University Hospital in Amsterdam, Netherlands (45, 69, 102, 112, 113). One study assessed mortality in the Swedish transgender population (114). Two articles were published using clinical data from the Ghent University Hospital in Belgium (115, 116). In the United States, 3 studies assessed cancer-related morbidity and mortality among transgender people identified in the US Department of Veterans Affairs (VA) national health system (117–119). The next sections of this review describe cancer-related findings for each of these study populations.

Dutch cohort

The earliest epidemiologic report describing the Dutch cohort was published in 1989 and included all 303 transwomen and 122 transmen seen in the outpatient department of Free University Hospital between 1972 and 1986 (112). Most transwomen were treated with oral ethinyl estradiol and cyproterone acetate, although some of them also elected to receive high-dose estrogen injections outside of the study clinic. Transmen received long-acting injections (every 2 weeks) or daily oral doses of testosterone. The median ages at the initiation of hormone treatment were 32 years (range, 16–67 years) and 25 years (range, 16–54 years) in transwomen and transmen, respectively. The duration of hormone therapy (and apparently follow-up) ranged from 6 months to more than 13 years with no cases of cancer reported at the time of publication.

The next follow-up of the same cohort with the addition of new members was published in 1997 and included a total 816 transwomen and 293 transmen who contributed 7,734 and 2,418 person-years, respectively (102). By the end of follow-up, a total of 7 cancer-related deaths were observed among transwomen. Three of those deaths were caused by lung cancer, and the remaining deaths were due to gastric carcinoma, leukemia, meningioma, and glioblastoma. The overall cancer-related standardized mortality ratio was 0.46 with a 95% confidence interval from 0.20 to 0.91. Only 1 cancer death (due to carcinoma of the colon) was reported among transmen.

By July 2007, the Amsterdam cohort had grown to include 966 transwomen and 365 transmen (113). The average treatment duration was 19 years with the total follow-up of 18,678 and 6,866 person-years for transwomen and transmen, respectively. In more recent years, the hormonal treatment underwent a few modifications. After an elevated risk of venous thrombosis was found to be related to ethinyl estradiol use, the hormonal therapy for transwomen changed to transdermal estrogen or oral estradiol valerate. Management of transmen remained largely unchanged, although the daily dose of oral testosterone undecanoate (if preferred over biweekly injections) was increased from 120–160 mg to 160–240 mg. A total of 28 cancer deaths were observed in transwomen for a standardized mortality ratio of 0.98 (95% CI: 0.88, 1.08). As in the previous follow-up, the most common cause of cancer-related death was carcinoma of the lung ($n = 13$) (standardized mortality ratio = 1.35, 95% CI: 1.14, 1.58). The number of observed cancers of the digestive tract ($n = 3$) was lower than expected (standardized mortality ratio = 0.42, 95% CI: 0.28, 0.60). The corresponding standardized mortality ratio estimates for hematological malignancies and brain cancers were 2.58 (95% CI: 1.97, 3.30) and 1.59 (95% CI: 0.95, 2.46), respectively.

Survival analyses compared transwomen with continuous hormone therapy with those with no history of hormone therapy or those who used hormones in the past. For all cancer deaths combined, the hazard ratios were 0.99 (95% CI: 0.46, 2.12) in the crude analyses, 1.24 (95% CI: 0.57, 2.67) after controlling for age and smoking, and 1.35 (95% CI: 0.60, 3.10) in the more fully adjusted model that also included the year hormone therapy was initiated (to account for the change in protocol). Only 5 cancer deaths were observed in transmen (standardized mortality ratio = 0.99, 95% CI: 0.65, 1.44). The site-specific standardized mortality ratios were difficult to interpret because of the small numbers of cases and wide confidence intervals.

Although earlier publications focused primarily on cancer mortality, more recent analyses sought to examine the incidence of 2 specific hormone-related malignancies: breast cancer and prostate cancer (45, 69). Little can be concluded from these studies because of small sample sizes and lack of systematic case ascertainment. Only 1 case of prostate cancer was reported among 2,307 transwomen followed for a total of 51,173 person-years. It is notable, however, that the study cohort was relatively young with the mean age at baseline of 29 years and an average follow-up of 21 years. The single prostate cancer case in this study presented with advanced metastatic disease and a PSA of 1,710 ng/mL and survived only 3 years after diagnosis.

In a similar analysis for breast cancer limited to transgender persons with greater than 5 years of hormonal treatment (45), the incidence rate among transwomen was higher, but not significantly different from that of nontransgender natal males (4.1 vs. 1.2 per 100,000 person-years). For transmen, the incidence rate was lower than that of nontransgender natal females (5.9 vs. 155 per 100,000 person-years).

Table 4. Summary of Epidemiologic Studies That Evaluated Cancer Endpoints Among Transgender People

Study Population	First Author, Year (Reference No.)	Sample Sizes	Measures	Cancer Site or Type	Result and Comparison[a]	95% CI
Dutch cohort of transgender patients treated with cross-sex hormones at a specialized clinic in Amsterdam, Netherlands	Asscheman, 1989 (112)	303 transwomen	Incidence and mortality	None		
		122 transmen		None		
	van Kesteren, 1997 (102)	816 transwomen	SMR	All sites ($n = 7$)	0.5[b]	0.2, 0.9
				Lung ($n = 3$)	0.5[b]	0.1, 1.4
				Stomach ($n = 1$)		
				Leukemia ($n = 1$)		
				Meningioma ($n = 1$)		
				Glioblastoma ($n = 1$)		
			Incidence	Prostate ($n = 1$)		
		293 transmen	Mortality	Colon ($n = 1$)		
	Asscheman, 2011 (113)	966 transwomen	SMR	All sites ($n = 28$)	1.0[b]	0.9, 1.1
				Lung ($n = 13$)	1.4[b]	1.1, 1.6
				Hematological ($n = 6$)	2.6[b]	2.0, 3.3
				Gastrointestinal tract ($n = 3$)	0.4[b]	0.3, 0.6
				Brain ($n = 2$)	1.6[b]	1.0, 2.5
				Kidney ($n = 1$)		
				Melanoma ($n = 1$)		
				Bone ($n = 1$)		
				Prostate ($n = 1$)		
		596 ethinyl estrogen users	Mortality HR	All sites ($n = 17$)	1.4[c]	0.6, 3.0
		365 transmen	SMR	All sites ($n = 5$)	1.0[d]	0.7, 1.4
				Gastrointestinal tract ($n = 2$)	2.4[d]	0.9, 5.2
				Lung ($n = 1$)		
				Hematological ($n = 1$)		
				Sarcoma ($n = 1$)		
	Gooren, 2013 (45)	2,307 transwomen	Incidence	Breast ($n = 2$)	4.1[e]	
		795 transmen		Breast ($n = 1$)		
	Gooren, 2014 (69)	2,306 transwomen	Incidence	Prostate ($n = 1$)		
Swedish national cohort of persons with documented official gender change and surgical affirmation	Dhejne, 2011 (114)	324 transgender persons (133 transmen, 191 transwomen combined)	Mortality HR	All sites ($n = 8$)	2.1[f]	1.0, 4.6
				Lung ($n = 3$)		
				Tongue ($n = 1$)		
				Pharynx ($n = 1$)		
				Pancreas ($n = 1$)		
				Liver ($n = 1$)		
				Unspecified ($n = 1$)		
Belgian clinic patients treated at a specialized clinic in Ghent, Belgium	Wierckx, 2012 (115)	50 transwomen	Prevalence	None		
		50 transmen		Prolactinoma ($n = 1$)[g]		
	Wierckx, 2013 (116)	214 transwomen	Prevalence	All sites ($n = 6$)	28[h]	
					28[i]	
				Colon ($n = 3$)		
				Melanoma ($n = 2$)		
				Lymphoma ($n = 1$)		
		138 transmen		None		

Table continues

Table 4. Continued

Study Population	First Author, Year (Reference No.)	Sample Sizes	Measures	Cancer Site or Type	Result and Comparison[a]	95% CI
US veterans' cohort of persons with at least 1 diagnostic code indicative of transgender status	Blosnich, 2014 (117)	3,327 transgender persons	Proportional mortality	All sites ($n = 65$)	21[j]	
	Brown, 2015 (118)	3,556 "men"	SIR	Breast ($n = 3$)	33.3[b]	21.9, 45.2
					0.7[d]	0.03, 5.6
		1,579 "women"		Breast ($n = 7$)	77.8[b]	59.0, 94.0
					1.6[d]	0.2, 7.2
	Brown, 2016 (119)	5,135 transgender veterans	Lifetime POR	Breast ($n = 33$)	0.3[f]	0.2, 0.5
				Prostate ($n = 190$)	1.4[f]	1.2, 1.7

Abbreviations: CI, confidence interval; HR, hazard ratio; POR, prevalence odds ratio; SIR, standardized incidence ratio; SMR, standardized mortality ratio.

[a] Reported only for sites with 2 or more cases.
[b] General population males.
[c] Nonusers.
[d] General population females.
[e] Per 100,00 person-years versus 1.2 in general population males.
[f] Matched controls.
[g] Diagnosed before initiation of hormone therapy.
[h] Per 1,000 versus 21.9 in general population males.
[i] Per 1,000 versus 24.9 in general population females.
[j] Result expressed as percentage versus 23.6% in general population.

Swedish cohort

A 2011 retrospective cohort study assessed cancer mortality among Swedish transgender people from 1973 to 2003 (114). The National Board of Health and Welfare assigns all Swedish residents a registration number, where the ninth digit identifies gender. Sex reassignment surgery and legal sex status changes must be approved by the Board that assigns the new sex in the registration number. The link between the old and newly assigned number is maintained, making it possible to identify transgender individuals and follow them over time. A total of 324 cohort members (191 transwomen and 133 transmen) were birth-year matched with 10 nontransgender controls of each sex.

The average follow-up time in this study was 11.4 years. There were 8 deaths due to neoplasms with a cancer mortality rate of 2.2 (95% CI: 1.1, 4.3) per 1,000 person-years. Relative to nontransgender cohort members, the hazard ratio for cancer deaths among transgender cohort members was 2.1 (95% CI: 1.0, 4.6). Malignancies among transgender persons included 3 lung cancers, a tongue cancer, a pharyngeal cancer, a pancreatic cancer, a liver cancer, and a cancer of unknown origin. The cancer data were not presented separately for transmen and transwomen.

Belgian cross-sectional studies

Two cross-sectional studies examined the prevalence of cancer in transgender patients who received gender affirmation care at the Ghent University Hospital. The earlier of the 2 studies (115) recruited 50 transwomen and 50 transmen who underwent genital surgery and received, on average, 10 years of hormonal treatment. Participants were sent questionnaires that asked about their medical history, and positive responses were validated by a medical chart review. The average age at the time of the study was 43 years for transwomen and 37 years for transmen. No malignancies were reported in this population.

In the second cross-sectional study (116), 214 transwomen and 138 transmen who had at least 3 months of cross-sex hormone therapy between 1986 and 2012 were each age matched to 6 controls, 3 nontransgender males and 3 nontransgender females. The study participants were on hormone therapy for an average of 7.4 years. There were 6 cases of cancer during follow-up in transwomen (3 colon cancers, 2 melanomas, and 1 lymphoma). The prevalence of self-reported cancer in transwomen was not significantly different from the corresponding estimates for nontransgender males and females. There were no cancer cases in transmen.

US veterans studies

Three studies examined the morbidity and mortality of transgender US veterans (117–119). Eligibility was determined by *International Classification of Diseases, Ninth Revision*, codes for transvestic fetishism (code 302.3), transsexualism (code 302.5), gender identity disorder not otherwise specified (code 302.6), and gender identity disorder in adolescents or adults (code 302.85).

The first VA study (117) examined all-cause and suicide-related mortality, but it did not provide information on mortality rates due to cancer. Instead, the authors calculated the proportion of cancer-related deaths among all deaths reported in transgender veterans and compared it with the corresponding crude proportion based on all deaths in the US

population. The 2 proportions were similar, 21% versus 23.6%, respectively.

A more recent study assessed breast cancer incidence among 5,135 transgender veterans (118). The cohort members were categorized as "female" or "male" on the basis of the demographic variable in the Vital Status Files, but this variable may reflect either natal sex or gender identity. For this reason, it is possible that some of the participants categorized as "female" were transwomen and some of the "male" patients were transmen. Cross-sex hormone use was ascertained from prescription documentation for 2,645 veterans.

Three cases of breast cancer were reported among cohort members categorized as "male," and 7 cases were found among "females." The standardized incidence ratio comparing observed breast cancer cases in male transgender veterans compared with the expected numbers in natal males based on the SEER data was 33.3 (95% CI: 21.9, 45.2). The corresponding standardized incidence ratio relative to natal females was 0.70 (95% CI: 0.03, 5.57). None of the 3 cases had hormone prescriptions from the VA.

Seven cases of breast cancer among "female" transgender veterans were reported. Two of those were receiving estrogen, and 1 was receiving testosterone. The observed number of cases was comparable to that expected among the natal females (standardized incidence ratio = 1.6, 95% CI: 0.24, 7.22) and was greater than that expected for natal males (standardized incidence ratio = 77.8, 95% CI: 59.0, 94.0).

The most recent VA study compared the medical and/or mental health status of the same 5,135 transgender veterans with the corresponding data among 15,405 nontransgender veterans matched on documented gender, race, birth year, and geographical region (119). Analyses compared lifetime prevalence of various conditions in transgender and nontransgender veterans by calculating odds ratios adjusted for marital status, religious affiliation, and enrollment priority group. Only 2 of the reported results were cancer related. The prevalence odds ratio estimates for breast and prostate cancer were 0.34 (95% CI: 0.24, 0.50) and 1.42 (95% CI: 1.29, 1.58), respectively. These results are difficult to interpret because the natal sex distributions in the transgender and comparison groups may have been different, despite attempts to match for gender.

DISCUSSION

Cancer risk is considered an area of priority in transgender research. Important areas of uncertainty include the risk of breast neoplasms and the need for breast cancer screening in transwomen receiving estrogens and in transmen who underwent masculinizing chest surgeries and/or received treatment with androgens (7, 120). Other relevant research questions of primary importance include optimal screening protocols for breast cancer and endometrial and ovarian neoplasms in persons exposed to androgens, estrogen-related prolactinoma incidence and progression, and PSA levels as well as both risk and prognosis of prostate cancer after estrogen exposure and/or orchiectomy (121, 122).

Based on the available evidence, the concerns about cancer in transgender populations, albeit biologically plausible, are neither adequately supported nor convincingly alleviated because of a lack of well-designed epidemiologic studies. This lack of high-quality data is acknowledged in the current guidelines issued by various professional organizations (7, 120, 122). For example, the Center of Excellence for Transgender Health at the University of California, San Francisco, uses the GRADE scoring system (123) in assessing quality of evidence to support the most current *Guidelines for the Primary and Gender-Affirming Care of Transgender and Gender Nonbinary People* (120). It is notable that most recommendations related to cancer risk and prevention in these guidelines were based on expert opinions, and the supporting evidence was categorized as "weak."

Despite a recognized lack of conclusive data, a few observations from the available published literature are warranted. The limited surveillance data show that the distributions of cancer sites in transgender patients may differ from those in nontransgender patients. These differences are attributable primarily to overrepresentation of malignancies linked to human immunodeficiency virus and HPV infections, most notably Kaposi sarcoma and anal carcinoma.

The differences in hormone-related cancers are difficult to discern without higher quality epidemiologic data. The main limitation of the existing data is the very small size of the available studies and the very few events of interest. This limitation is particularly evident in European studies. The studies of US veterans, the largest to date, are probably still underpowered to adequately estimate cancer incidence among transgender people. Although the VA studies made an important contribution to the better understanding of various health issues among transgender veterans, their main limitation with respect to addressing cancer-related questions is a lack of reliable natal sex and gender identity information. Moreover, the treatment information in the studies of transgender veterans is limited to gender affirmation therapy received through VA.

These limitations notwithstanding, the available studies offer useful methodological insights that may inform future research of cancer in transgender populations. For example, future VA studies may be enhanced by supplementing the existing data with additional codes for sex-specific diagnoses (e.g., benign prostatic hyperplasia or PCOS), procedures (e.g., hysterectomy or transurethral resection of the prostate), or laboratory tests (e.g., PSA or Papanicolaou smear). In addition, future VA-based studies would benefit from the recent Veterans Health Administration directives that mandated the provision of requested gender affirmation therapy (124). These changes in policy mean that, in the future, much of the transgender care will be delivered at the VA and should be captured by the VA data systems.

In contrast to the VA studies, the data collected by Dutch and Belgian research groups include detailed natal sex, gender identity, and treatment information. The main limitation of these single clinic-based studies is low statistical power, which renders them inadequate for analyzing rare events such as cancer. These limitations can be overcome by coordinating data collection across multiple clinical sites as was done recently through the establishment of the European Network for the Investigation of Gender Incongruence (ENIGI). The ENIGI collaboration started at 4 clinical centers in

Amsterdam, Netherlands; Ghent, Belgium; Hamburg, Germany; and Oslo, Norway (125, 126). More recently, ENIGI was expanded by including a fifth center in Florence, Italy (127). The ENIGI collaboration now uses the same diagnostic and psychological assessment battery and a common hormone treatment protocol. This enhances the comparable collection of data and biological samples and will enable a wide range of studies evaluating treatment effectiveness and health outcomes. So far, the ENIGI endocrine data collection protocol enrolled 333 transwomen and 343 transmen (127), but the work is ongoing.

Although also limited by a small sample size, the Swedish cohort (114) illustrates another methodological option for future studies. The availability of a national system of capturing changes in gender (128) allows extending the existing data to include additional years and perhaps involving other countries with similar national registration systems. Previous successful efforts of pooling national data across several Scandinavian counties (129, 130) may offer a model for future transgender health studies.

In the United States, efforts are underway to assemble a cohort of transgender people enrolled in integrated healthcare delivery systems (131, 132). Many such systems use electronic medical records systems that share similarly structured databases with identical variable names, formats, and specifications across sites (133). Consequently, the data collection methods applicable at 1 site can be disseminated to health systems across the United States as evidenced in the creation of various research consortia, such as the Health Care Systems Research Network (134), the Mental Health Research Network (135), and the Cancer Research Network (136). The existing research networks are already supporting transgender health research at selected sites (137). The ongoing studies can be scaled to include up to 18 integrated health systems serving as many as 20 million US residents.

Efficient population-based research depends on routine and systematic collection of critical data elements. With respect to studies of transgender and gender nonconforming populations, the most important data element is gender identity. A recent directive from the US Department of Health and Human Services recommended that electronic medical record systems should find a way to record a patient's sexual orientation and gender identity in a structured way with standardized data. The directive specifically does not require that a provider collect this information but states only that the electronic medical records should enable the provider to do so (138). Until collection of data on gender identity becomes routine, studies will continue relying on surveys and information from medical records.

From the epidemiology perspective, the current review offers limited information about the risk and prognosis of cancer among transgender people. In the absence of rich, population-based data, we considered case reports; however, the utility of these case reports even for the purpose of hypothesis generation remains questionable. It is also important to acknowledge that transgender people represent a heterogeneous population group. It is expected that cancer risks, hormone use, and prevalence of nonhormonal risk factors may vary widely across the gender identity spectrum.

In summary, although published studies do not offer sufficient information about the risk of cancer in transgender people, the available data may help to formulate important hypotheses and inform future research. The required methodological features of the studies addressing this issue include, at a minimum, a large sample size and long follow-up, accurate ascertainment of natal sex and gender identity, and detailed data on treatment. Although it is likely that no single study will fulfill all of these criteria, there may be opportunities for pooling data and coordinating efforts across research centers.

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