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Review Article

Embryologic and hormonal contributors to prostate cancer in transgender women

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Abstract: Transgender women, who were assigned male at birth but identify as women, may take several steps to merge their physical and psychological identities, including gender-affirming surgeries and hormone therapy. With the presence of the mature prostate gland there persists a risk for malignant transformation in this population. The recognition by the medical community and society at large that transgender women are at risk of developing prostate cancer has recently been supported by investigative efforts. The slowly emerging clinical evidence suggests that the disease is likely to be more aggressive than in cisgender men, with 6 of 9 published cases discussing metastasis reporting metastatic disease on presentation. Currently the overall prevalence appears low, pointing to evolving awareness, educational status, socioeconomic status, and late presentation. This commentary focuses on exploring the factors contributing to the incidence of prostate cancer and the biochemical and endocrine mechanisms that lead to aggressive prostate tumor development in transgender women.

Keywords: Transgender, prostate embryology, hormone therapy

Introduction

The term transgender refers to individuals who do not identify with the sex they were assigned at birth [1]. In the United States, it is estimated that between 0.39 and 2.7% of individuals identify as transgender [2]. Transgender women, who are assigned male at birth but identify as women, may take several steps to merge their physical, emotional and psychological identities, including gender-affirming surgeries and hormone therapy. During the male-to-female (MtF) surgical transition, patients may choose to have their penile skin inverted and undergo vaginoplasty as well as orchiectomy. During these surgeries, it is very rare that the original prostate would be removed for fear of complications such as urinary incontinence [3]. There is risk of prostate cancer for as long as the prostate remains in-situ. Factors contributing to this risk and potential preventative measures must be explored.

We must first acknowledge that the terminology used to refer to this population may be offensive to some and confusing to others. MtF is not used by some as a self-descriptor, as they do not think of themselves as having transitioned. The term transsexual has been used in the past due to the DSM's use of the diagnosis "transsexualism" prior to this being changed to "gender identity disorder" in DSM IV, and then "gender dysphoria" with DSM V [4, 5]. The term is controversial, and many find the term derogatory [https://www.lgbtqiahealtheducation.org/wp-content/uploads/Handout_7-C_Glossary_of_Gender_and_Transgender_Terms__fi.pdf]. Transgender female is a term which has been used in the medical literature, however its use is declining, and it can lead to confusion between gender identity and genetic sex.

Some prefer to be referred to as women, but we use the term transgender women (transwomen) here to refer to those assigned male at birth but who identify as female, as this is the most commonly used term in the medical literature at this time and an accepted term by the LGBTQIA + community and advocates. We acknowledge that there is no one accepted or correct term,

and that in a clinical setting, one should ask which terms are preferable.

There is some controversy as to the overall incidence of prostate cancer in transgender women, with one source stating the incidence is 0.04% in MtF patients treated with orchiectomy and exogenous estrogens. However, this estimated incidence is likely an underestimation of the true rate due to factors such as lack of screening and the majority of that cohort being under 40 years of age [3]. The average age of diagnosis of prostate cancer in the USA is 66 years [6], but the risk for development of prostate cancer begins approximately 6 weeks after conception with the expression of the SRY gene which begins male gonadal differentiation [7]. The fundamental contributing factors to a person's risk for developing prostate cancer occur as fetal development progresses, with hormones playing a role in how likely someone is to develop malignancy years later [8].

Discussions regarding the risk for prostate cancer in transgender women remain controversial. While there is evidence claiming that the risk in this population is lower than in cisgender men due to the protective effects of antiandrogen and estrogen therapy [9], other studies point to the objective evidence that in documented cases in transgender women, 100% have clinically significant cancers and 66% are metastatic at presentation [10].

These published cases of prostate cancer in transgender women, which have been further discussed by others, cite presenting symptoms of lower urinary tract symptoms, weight loss, bone pain, hematuria, abnormal digital rectal exam (DRE), and elevated prostate specific antigen (PSA) [10-21].

This discrepancy in the published literature demonstrates a clinical need for clarification on the risks that transgender women face regarding prostate cancer. High-grade, aggressive disease in the documented cases may occur secondary to hormonal treatment and other psychosocial factors that transgender women face. One may also argue that it may be a product of observation bias, if only patients experiencing symptoms - and therefore likely having more aggressive cancer - choose to seek care. For example, in our own institution, we recently identified two transgender women with prostate cancer, both with low-risk localized disease, (average PSA 1.4 ng/ml, ISUP 1), thus demonstrating a greater potential level of heterogeneity in disease within the population.

In this commentary, we explore the risks in developing aggressive prostate cancer in transgender women, with the overarching goal of increasing awareness and decreasing preventable negative health outcomes. Our goal is to further understand the interplay of early-life factors, hormone therapy, mental health, and transgender relationships to society and healthcare and their combined role in the development of prostate cancer in transgender women.

Prostate cancer epidemiology and pathophysiology

Prostate cancer remains one of the most common malignancies, affecting one in eight men over the course of their lives [https://www.cancer.org/cancer/prostate-cancer/about/key-statistics.html]. The prostate is an androgen-stimulated organ, requiring testosterone to optimally produce and secrete its alkaline contribution to seminal fluid [6]. Cancer of the prostate may occur when the normal glandular tissue cells which comprise it become mutated, causing glandular proliferation and creating a nodule [6, 22]. This tumor may remain within or close to the surrounding prostatic tissue or metastasize to the bone or lymph nodes [6].

The vast majority of prostate cancer cases at diagnosis are identified as localized disease, usually exists without symptoms. In these cases, abnormal DRE and PSA may provide the first signs that cancer is present as well as opportunity for early intervention [23]. Prostate cancer may present with nonspecific lower urinary tract symptoms such as nocturia, hematuria, dysuria and sexual dysfunction [24, 25]. The rate of metastatic disease at presentation ranges from 6.3%-8% [26]. In addition, approximately 15% of patients with localized disease at presentation, and treated with curative intent, progress to metastatic disease [27]. Patients with metastatic prostate cancer may present with bone pain, typically in their vertebrae, pelvic region, ribs, or proximal femur, hematuria, erectile dysfunction, weight loss, urinary retention or urinary incontinence and weakness amongst many others [28].

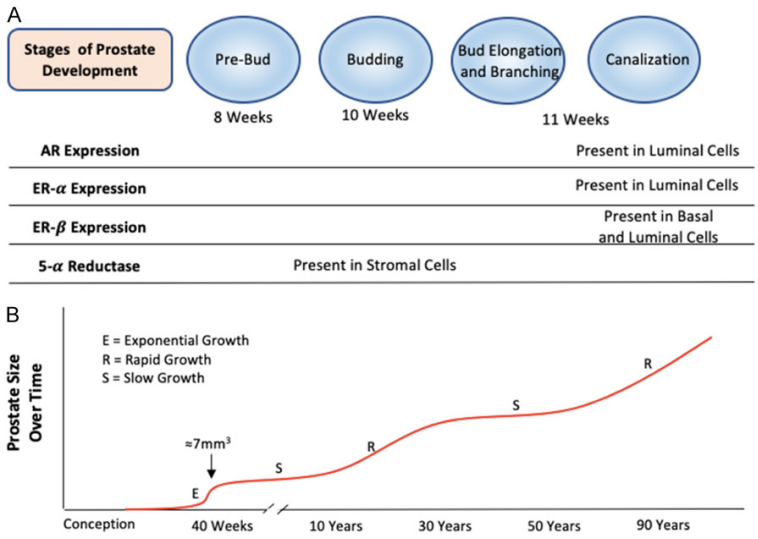

Figure 1. (A) Timeline of the expression of androgen receptors, estrogen receptors, and 5-α reductase in the fetal prostate and (B) Generalized timeline of prostate size from conception until death including separate growth phases [8, 37, 38].

According to the NCI, the median age for the development of prostate cancer in the United States is 66 years [29]. For transgender individuals, however, age of surgical transition is usually much younger - 29.5 in the United States [30]. With this difference between the age of transition and median age of prostate cancer diagnosis, it can be gathered that physiological processes may be altered years before any pathology becomes apparent, changing the risk of developing this hormonally regulated cancer in this hormonally distinct population. Our manuscript aims to longitudinally profile the risk of prostate cancer in transgender women.

Early-life factors contributing to prostate cancer development

Prostate cancer is a hormonally regulated disease which affects chromosomally XY individuals. However, not all genetic males are at risk for prostate cancer. Studies have shown that anatomic males born with a 5-α reductase (5αR) deficiency (testicular feminization syndrome) will not develop prostate cancer [31]. Other early-life factors including hormone exposures also have the ability to affect lifetime risk for disease. Exploiting the embryological development and sexual differentiation of genetic males may help explain the effects that pre-pubertal vs. post-pubertal hormone therapy may have on transgender women and their likelihood of developing aggressive prostate tumors.

Embryology and sexual differentiation

Embryological differentiation of anatomical males begins between 6 and 8 weeks of gestational age with activation of the SRY gene located on the Y chromosome, which initiates a genetic cascade that leads to the development of the testes [32]. In the absence of the SRY gene, the expression of the DAX1 gene on the X chromosome prevents male differentiation and ovarian hormones later cause the female reproductive tract to mature [33]. After about 7-8 weeks of human gestation, the developed testes begin secreting testosterone and anti-Mullerian hormone (AMH) to continue development of the male reproductive tract and cause degradation of the would-be female internal reproductive tract, or the Mullerian duct [33].

The physiological development of the human prostate occurs in six stages; namely, the pre-bud urogenital sinus (8-9 weeks of gestation), prostatic epithelial budding from urogenital sinus epithelium (10-11 weeks), bud elongation and branching (11 weeks onwards), canalization of epithelial cords (11 weeks onwards), differentiation of luminal and basal epithelium (11 weeks onwards), and secretory cytodifferentiation (late second and third trimesters), **Figure 1** [8]. Even at the early pre-bud stage, luminal and basal prostatic epithelial cells are present, although not yet well-differentiated [34]. Androgen receptors within the prostatic stroma, which are expressed starting at 11.5 weeks of gestational age, help mediate the morphogenesis of the prostate and are required for every step of prostate development starting from budding [35]. The conversion of testosterone to dihydrotestosterone (DHT) by 5αR in the rudimentary prostate is integral to normal prostate and external genitalia develop-

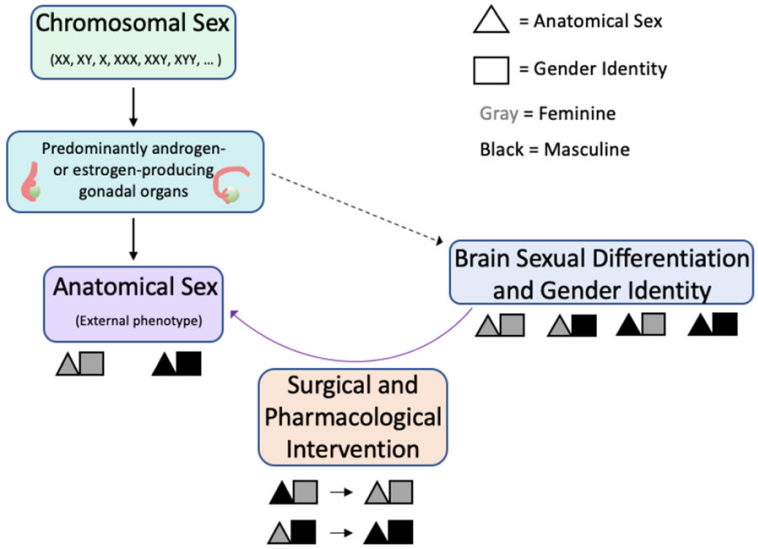

Figure 2. Simplified schematic depicting the relationship between gender identity and anatomical sex. Chromosomal sex determines gonadal sex, and gonads release hormones which help develop anatomical sex. Brain sexual differentiation (potentially including gender identity) is also affected by hormones produced in the gonads, but as a process takes place later than and somewhat independently from anatomical sex differentiation, providing a possible source of discrepancy between gender identity and physical sex. If this occurs, surgical and pharmacological intervention may be used to alter physical characteristics to create a body that aligns with psychological gender identity.

ment [8]. DHT formation occurs in the urogenital sinus, urogenital tubercle, and urogenital swellings during sexual differentiation and in the Wolffian duct, DHT formation does not occur until after differentiation has already occurred [36]. Androgen levels after birth and prior to puberty are low, keeping the prostate at a small size - approximately 7 mm^3 at 40 weeks of gestation followed by a period of slow growth until the age of 10 [37, 38]. The increase in androgens seen at puberty allows the prostate to grow to its full adult size (**Figure 1**) [38].

Estrogen receptors are also present in the prostate. Maternally originating estrogens promote squamous metaplasia of prostatic epithelium [39]. Estrogen receptor α (ER-α) has been detected in luminal cells and stroma at 19 weeks of gestation, while estrogen receptor β (ER-β) has been detected at 13 weeks in solid prostatic epithelial cords, and then later in the epithelium of canalized prostatic ducts [35]. While ER-β is the dominant estrogen receptor affecting fetal prostate growth (potentially working together with androgens to promote cell expansion throughout early gestation and limiting prostate growth later on), the ER-α contributes to the development of the prostate gland postnatally [35].

Temporally, sexual differentiation of the reproductive tract occurs prior to sexual differentiation of the brain, suggesting that these two processes may occur independently of one another (**Figure 2**) [40]. Brain sexual differentiation in humans is dependent on the surge in testosterone circulation that occurs between the second and sixth months of pregnancy. High levels of testosterone during these sensitive time periods are thought to be responsible for phenotypic and neurological development of the brain in males, likely including gender identity [33]. Some evidence suggests that there may be a genetic and hormonal component to gender dysphoria [33].

Overall, for transgender women who have not initiated gender-affirming surgery or hormone therapy, the risk for prostate cancer remains equal to that of cisgender men, due to the complete sexual masculinization of their reproductive organs [21]. While this risk may change upon starting therapy, there is not yet any evidence to suggest differences in embryology alone between transgender women and cisgender men which would account for differences in prostate cancer risk.

Hormone therapy and its relation to prostate cancer development

Anti-androgen therapy: There is a significant overlap between drugs used in feminizing hormone therapy for transgender women and those used in patients with prostate cancer (summarized in **Table 1**). Anti-androgen therapy is one of the major components of hormone therapy for transgender women as an adjuvant to estrogen therapy. Drugs include gonadotro-

Table 1. Summary of drugs used in feminizing hormone therapy and prostate cancer therapy

Ref.	Generic Drug Name	Common Brand Names	Mechanism of Action	Feminizing Effects	Effects in Prostate Cancer	Dose in Feminizing Therapy	Dose in Prostate Cancer
[41, 62-64]	Leuprolide	Lupron, Eligard, Lupron Depot, Viadur	GnRH agonist	Decreased serum testosterone, softening of masculine appearance	Medical castration with decreased size of prostate, seminal vesicles, and testicles	3.75-7.5 mg IM monthly	7.5 mg IM monthly
[41, 65, 66]	Histrelin implant	Supprelin LA, Vantas	GnRH agonist	Inhibition of hypothalamic-pituitary-gonadal axis, decreased serum testosterone	Medical castration, suppression of LH and PSA	50 mg implanted annually	50 mg implanted annually
[41, 67-69]	Spironolactone	CaroSpir, Aldactone	AR blocker	Decreased male-pattern hair, breast development and feminization, lack of erections	Preventative against development of cancer	100-400 mg PO daily	25 mg PO daily
[41, 68, 70]	Finasteride	Propecia, Propecia Pro-Pak, Proscar	5αR inhibitor	Treatment of male-pattern baldness	Preventative against development of cancer	1-5 mg PO daily	5 mg PO daily

pin-releasing hormone (GnRH) agonists, androgen receptor blockers such as spironolactone, and 5αR inhibitors, although 5αR inhibitors are not used as first-line therapy in transgender women [41, 42]. GnRH agonists prevent the release of luteinizing hormone (LH) from the anterior pituitary gland via negative feedback on the hypothalamic-pituitary-gonadal axis and therefore inhibit the release of testosterone from the testes (**Figure 3**). Spironolactone, a diuretic, also acts as a nonspecific androgen receptor blocker. 5αR inhibitors prevent the conversion of testosterone to DHT, which is a stronger, more potent form of testosterone that is implicated in the pathological growth of the prostate. In transgender women, these drugs prevent progression of secondary male sex characteristics, while in prostate cancer patients they prevent progression of prostate growth [43].

Prostate cancer development is driven by activation of the androgen receptor (AR)/androgen axis signaling pathway, so surgical or chemical castration (using androgen-deprivation therapy (ADT)) is a first-line treatment for patients with locally advanced disease [44]. The inhibition of androgens blocks activation of AR signaling and subsequently impairs prostate tumor growth. However, in some patients, treatment with ADT can lead to the development of a more aggressive, therapy-resistant form of prostate cancer that no longer requires the presence of androgens [45]. This more aggressive form of cancer, called castration-resistant prostate cancer (CRPC), has several potential mechanisms including amplification in number and sensitivity of androgen receptors, promiscuous AR mutations, production of androgens within the tumor itself, and AR activation independent of the presence of androgens [46]. Mechanisms including the overexpression of proto-oncogene c-myc, PI3K/mTOR pathway, RAS/MAPK pathway, and Wnt/*β*-catenin signaling are all related to CRPC and can occur in the environment of androgen deprivation [47]. These mechanisms could provide a pathway whereby transgender women on ADT develop aggressive forms of prostate cancer.

Estrogen therapy: In the normal prostate gland, stem cells and early progenitor cells (in addition to AR), express ER-*α*, ER-*β*, and G protein-coupled receptor 30 (GPCR30) [48]. These receptor subtypes have distinct roles in prostate cancer, with ER-*α* having stimulatory effects, ER-*β* having inhibitory effects, and G protein-coupled estrogen receptor (GPER) having a combination of both [48]. According to Mishra et al., prostate cancer mouse models have shown that ER-*α* is associated with epithelial-mesenchymal transition (EMT) and osteoblastic bone formation [49]. ER-*β*, on the other hand, is expressed less in localized malignant prostate lesions than in benign lesions, suggesting a protective effect of these receptors from prostate cancer [50]. Even in the presence of ER-*α* agonists, it was demonstrated in rat models that giving ER-*β* agonists prevented the development of prostatic intraepithelial neoplasia (PIN), a precursor to prostate cancer [51].

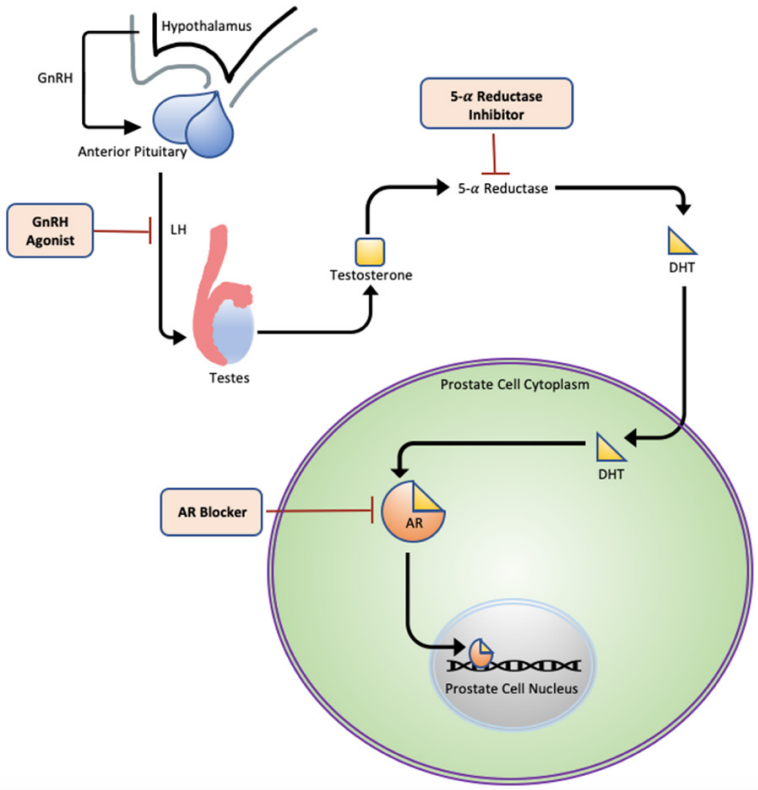

Figure 3. Schematic diagram of the androgen pathway and the drugs common to prostate cancer treatment and feminizing hormone therapy. GnRH agonists work by using negative feedback to prevent the anterior pituitary from releasing LH, thereby preventing the testes from producing testosterone. R inhibitors prevent the transformation of testosterone to DHT, thereby, reducing the ability for the AR to bind to its preferred ligand. AR blockers directly inhibit the AR, preventing the DHT-AR complex from forming and translocating to the nucleus to activate proliferative transcription factors.

When discussing estrogen compounds themselves as opposed to their receptors, it is significant to note that estrogen and testosterone work together synergistically in the development of prostate cancer. Bosland et al. demonstrated that the combination of 17β-estradiol and testosterone in Noble rats was correlated to a prostate cancer incidence of 90-100%, while chronic administration of low-dose testosterone alone was associated with prostate cancer in only 35-40% of cases [52]. Oral, transdermal, and parenteral estradiol are major components of hormone therapy for transgender women [41], implicating that this exogenous estradiol in combination with existing testosterone levels may play a role in prostate cancer development in this population.

Because hormone therapy in transgender women may be initiated at any age, the possibility of preexisting cancerous tissue transitioning to more aggressive forms later on must be considered. In malignant prostatic tissue, there are much lower levels of ER-β expression compared to normal tissue [53]. 17β-Estradiol has been shown to have relatively equal affinity to both ER-α and ER-β [54]. In transgender women being treated with estradiol, if cancer was already present prior to the initiation of gender-affirming hormone therapy, the disproportionately high levels of ER-α at therapy initiation could help explain an accelerated path to more aggressive, high-grade disease considering the proliferative effects of ER-α discussed previously.

Other biological factors: Gender-affirming hormone therapy in transgender women has other effects that may contribute to prostate cancer risk in this population. Feminizing hormones lead to an increase in body fat and a decrease in lean body mass, and Suppakitjanusant et al. demonstrated that body mass index (BMI) in transgender women tends to increase for the first two years following the initiation of therapy [55]. With this increase in body fat percentage, higher levels of adipose tissue correspond to higher levels of aromatase (the enzyme responsible for the conversion of testosterone to 17β-estradiol). While more research is necessary to elucidate a distinct mechanism by which obesity may be causative for prostate cancer, the correlation between increased obesity and prostate cancer incidence and aggression implicates another link between feminizing hormone therapy and prostate cancer risk [48].

The relationship between fat distribution and prostate cancer risk cannot be overlooked. Choi et al. demonstrated that waist circumference is a significant indicator of how well BMI predicts the risk of prostate cancer develop-

ment. When waist circumference category was greater, the stronger the linear relationship between BMI and waist circumference was [56]. When undergoing feminizing hormone therapy, transgender women experience changes to their fat distribution. A study by Klaver et al. demonstrated that after initiating hormone therapy, while a more feminine fat distribution with a lower waist-to-hip ratio is achieved with a 34% overall increase in fat in the gynoid region, an increase in fat in the android region is also observed with an increase of 18% [57]. These changes in BMI, body fat percentage, and fat distribution may have associations with prostate cancer risk and aggression in transgender women and is an area for further study.

Psychosocial factors contributing to prostate cancer in transgender women

Transgender women face marginalization in several spheres, and their own dissonance between born body and gender identity plays a large role in their mental health, as has been well-documented in literature over the past several decades. Reisner et al. demonstrated that up to 64% of transgender women have depression using the Center for Epidemiologic Studies Depression Scale [58]. Between 22 and 43% of transgender people across North America and Europe report at least one suicide attempt [59]. Transgender women have a 1.8x higher standardized mortality ratio (SMR) than cisgender men (95% CI 1.6-2.0x), and 2.8x (95% CI 2.5-3x) higher SMR than cisgender women [60]. The Virginia Transgender Health Initiative Study found that while a 60% majority of transgender individuals report having a primary care provider, only 43% report being out as transgender to their PCP, and almost 27% report some kind of healthcare-related discrimination. The study also found that 21% of participants had not received more than a high school level education [61]. With poor mental health outcomes, fear of discrimination from healthcare providers, low health literacy, and desire to move away from potentially dysphoric experiences, it is likely that transgender women are not being screened as often as they should be for prostate cancer - another potential contributor for why cancers found in this population may be relatively later in their course.

Interpersonal and systematic relationships can be highly impactful to health and how people receive care, and transgender individuals exemplify this association. In 2019, transgender people accounted for 2% of new HIV cases. Among transgender adults and adolescents, 93% of these new HIV cases were among transgender women [http://www.cdc.gov/hiv/library/reports/hiv-surveillance.html]. The Virginia Transgender Health Initiative Study found that 23% of respondents had a lifetime problem with tobacco usage, 23% had a past or current problem with alcohol abuse, and 6% had a lifetime history of injection drug use [61]. The same study showed that 38% of participants were living at or below Virginia's poverty line, which was $16,999 annually at the time of the study. It was also found that 29% did not have health insurance [61]. With societal stigma and lack of acceptance comes a disconnect between transgender people and the environment that surrounds them. Negative experiences within personal circles as well as larger institutions like government and healthcare create a difficult arena for transgender women to navigate their care and practice healthy, preventative behaviors that could lower their risk for diseases such as prostate cancer.

Conclusions and future directions

The only published estimate of prostate cancer incidence in transgender women treated with orchiectomy and exogenous estrogens is low (0.04%), and it is likely an underestimation [3]. Multiple factors contribute to this including the relatively young age of patients in this study, lower life expectancy for transgender women, as well as poor access for prostate cancer screening and health disparities experienced by transgender women.

The incidence of prostate cancer correlates with increasing age, and as many of the modifiable factors contributing to lower life expectancy in transgender women are addressed, an increasing number of transgender women may present with prostate cancer. Further work is needed before a consensus can be reached on whether to screen and/or monitor all transgender women for prostate cancer after MtF transition, however there is a strong rationale to use PSA, digital rectal examination, and MRI to assess risk prior to initiating MtF transition.

Understanding the unique hormonal milieu which the prostate in the transgender woman is exposed to may offer insights to the diagnosis and management of indolent and advanced prostate cancer. Further epidemiological and basic science studies are required to establish a definitive measure of disease incidence, prevalence, and severity upon presentation in transgender women (as opposed to cisgender men).

Disclosure of conflict of interest

None.

Abbreviations

5αR, 5-α reductase; ADT, Androgen-deprivation therapy; AMH, Anti-Mullerian hormone; AR, Androgen receptor; BMI, Body mass index; CRPC, Castration-resistant prostate cancer; DRE, Digital rectal exam; EMT, Epithelial-mesenchymal transition; ER, Estrogen receptor; GnRH, Gonadotropin-releasing hormone; GPCR30, G protein-coupled receptor 30; GPER, G protein-coupled estrogen receptor; LH, Luteinizing hormone; MtF, Male-to-female; PCP, Primary care provider; PSA, Prostate specific antigen; SMR, Standardized mortality ratio; SRY, Sex-determining region Y.

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