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SIGN OF THE TIMES: PART I

Cancer Risk and Prevention in Transgender Patients

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Transgender is an umbrella term for people whose gender identity and/or expression differs from that typically associated with the sex assigned at birth.[1] Transgender individuals may pursue hormone therapy (i.e. androgens or estrogens and anti-androgens) to induce physical characteristics consistent with their gender identity.[2] Some transgender individuals undergo one or more existing gender-affirming surgeries, including reconstructive chest surgeries, hysterectomy, and vaginoplasty, among others. Though not all transgender individuals desire hormone therapy and/or surgery, medical interventions are effective in alleviating gender dysphoria and considered medically necessary for many people.[1]

Hormone Therapy and Cancer Risk

Studies to date investigating the incidence of hormone-sensitive cancers in transgender individuals receiving hormone therapy have been predominately retrospective and limited by small cohorts, short-term follow-up, and lack of inclusion of older participants who are most likely to develop cancer. The World Professional Association for Transgender Health (WPATH) has concluded there is inconclusive or no increased risk of breast, cervical, ovarian, and endometrial cancer associated with masculinizing hormones and inconclusive or no increased risk of breast cancer associated with feminizing hormones.[1] Details are provided below and drawn from comprehensive evidence-based literature reviews of hormone therapy evaluated by WPATH.[3]

Prostate Cancer

The prostate is not removed during genital gender-affirming surgeries. The longstanding belief that low androgen environments are protective against prostate cancer development has been challenged by studies suggesting a link between depressed levels of serum testosterone and prostate cancer incidence, particularly more aggressive forms of prostate cancer.[4] Case reports demonstrate that both benign and malignant prostate tissue can grow readily in individuals on the male-to-female (MTF) spectrum in androgen-deficient states.[5]

A large study of 2,306 MTF individuals (51,173 person-years of exposure) receiving feminizing hormone therapy and bilateral orchiectomy observed an overall incidence of 0.13% of prostate cancer in individuals over age 40, compared to a 3.18% 10-year incidence for natal males age 40 to 60 in the general population.[6] Mean age of hormone initiation in this cohort was 29.3 ± 12.7 years, and mean follow-up time was 21.4 ± 8.7 years. Study limitations include probable under-diagnosis due to lack of routine prostate monitoring and the inclusion of few participants age 65 and older. Although rates of prostate cancer in MTF individuals appear to be low, there may be susceptibility to aggressive prostate cancer tumors when they do arise.[6]

Breast Cancer

MTF individuals receiving feminizing hormones experience breast cancer, yet the degree of risk relative to natal females is uncertain.[3] Factors that influence individual risk likely include duration of hormone therapy, age at hormone initiation, family history of breast cancer, obesity, and progestin use.[3] Masculinizing hormones do not appear to increase risk of breast cancer in the relative short term (30 years or less) in individuals on the FTM transgender spectrum.[3] Among a cohort of 2,307 MTF (52,370 person-years of exposure) and 795 FTM (15,974 person-years of exposure) individuals undergoing hormone therapy, incidence of breast cancer in both groups was comparable to breast cancer rates in natal males.[7]

Endometrial (Uterine) Cancer

Testosterone use may increase the risk of endometrial cancer, but evidence is limited.[3] Post-hysterectomy uteruses of FTM individuals receiving hormone therapy appear to be small with endometrial atrophy.[5] There are no long-term studies on endometrial cancer incidence among FTM individuals. Retrospective studies have not detected endometrial cancer in FTM individuals taking testosterone, though one case report has been documented.[3]

Ovarian Cancer

Testosterone use may increase the risk of ovarian cancer among FTM individuals, but evidence is limited.[3] An increase in ovarian androgen receptors has been reported after long-term testosterone administration.[5] No long-term studies have investigated ovarian cancer incidence among FTM individuals. There are three case reports of ovarian cancer in FTM patients on hormone therapy.[5]

Cervical Cancer

There is no evidence linking testosterone and cervical cancer in either FTM individuals or natal females. Testosterone use can cause atrophy of the cervical epithelium, which may mimic dysplasia on Pap tests and increase risk of both unsatisfactory and minimally abnormal cytology results.[3]

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Other Hormone-sensitive Tumors

There are several case reports of pituitary tumors after long-term estrogen use in MTF individuals, though prolactinomas have not been identified in large cohort studies.[5] Using estrogen for more than 10 years or at higher-than-recommended doses may increase risk of prolactinoma.[3] The Endocrine Society recommends prolactin monitoring in MTF individuals and radiologic examination of the pituitary if prolactin levels persistently rise despite stable or reduced estrogen levels.[5] There are no reports of other common estrogen-related growth factor tumors, such as focal nodular hyperplasia, hemangioma, or angiomyolipoma.

Cancer-related Mortality

Asscheman et al. determined causes of mortality in a cohort of 966 MTF (8,678 person-years of exposure) and 365 FTM (6,866 person-years of exposure) individuals on hormone therapy with a mean age of 31.4 and 26.1 years at hormone initiation, respectively. The observed number of deaths in the study cohort was compared to the expected number derived from mortality data of the general population, stratified by age and natal sex. The total cancer mortality rate was not increased in either the MTF or FTM group.[8] However, no firm conclusions can be drawn for FTM individuals age 65 to 79 in particular due to cohort size limitations.[8]

Additional studies that examine cancer outcomes specifically are needed to ascertain whether disparities in stage at diagnosis and receipt of oncologic care exist. Valuable data regarding comparative cancer incidence and stage at diagnosis could be obtained if cancer registries mandated collection of gender identity data.

Importance of Cancer Prevention

Transgender individuals are at risk for cancer and thus require preventive screening appropriate to their anatomy as well as prompt evaluation of associated symptoms. Patient education regarding screening needs is critical, particularly in contexts that are not self-evident (e.g. post-supracervical hysterectomy). To guide screening for anatomical structures that may be affected by hormone therapy, clinicians should consult national evidence-based guidelines as well as available transgender primary care protocols when considering the effects of hormone therapy and surgery on baseline risk, as summarized in Table 1. Cited recommendations have been developed by clinical experts and professional organizations based on published literature and clinical experience where data are scarce or nonexistent.[2]

Conclusion

Provision of life-saving cancer screenings to gender minorities necessitates awareness of transgender-specific health needs and sensitivity to the barriers that manifest from historical stigmatization of the transgender community. Dissemination of information is an important step in enabling competent care provision. However, evidence for current screening guidelines is incomplete. Further study is critical to better understand the long-term impact of hormone therapy on cancer risk and improve health outcomes among transgender individuals.

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Table 1. Cancer Screening Recommendations

Reference	Prostate[a,b]	Breast[c]	Endometrial	Cervical[e]
ACOG (2011)	Follow guidelines for natal males.	• MTF individuals: Follow guidelines for natal females. • FTM individuals: Follow guidelines for natal females, unless post-mastectomy.	____	• MTF individuals: Routine Pap tests may be indicated if neocervix created from the glans penis. • FTM individuals: Follow guidelines for natal females unless cervix removed.
Endocrine Society (2009)	Follow guidelines for natal males.	• MTF individuals: Follow guidelines for natal females if no increased risk of breast cancer. • FTM individuals: Follow guidelines for natal females, post-mastectomy.	____	____
Center of Excellence for Transgender Health, UCSF (2011)	Perform digital rectal exams (DRE) in all MTF individuals. Only consider PSA screening in high-risk patients.	• MTF individuals: Mammograhy in patients age >50 with additional risk factors. • FTM individuals: Mammography per guidelines, for natal females unless post-mastectomy. Consider mammography if only reduction occurred. Annual chest wall/axillary exam.	Evaluate spontaneous vaginal bleeding in absence of mitigating factor per guidelines for post-menopausal natal females. Consider hysterectomy if fertility is not an issue, patient age >40, and health will not be adversely affected by surgery.	• MTF individuals: Visual inspection of neovagina with speculum. • FTM individuals: Follow guidelines for natal females, unless cervix removed. Perform annual Pap of vaginal cuff following total hysterectomy if history of high-grade cervical dysplasia. After 3 normal tests, continue Pap every 2-3 years.
Feldman & Goldberg (2006)	Perform DRE as recommended for natal males in all MTF individuals. Consider PSA screening in patients age 45+ with additional risks.	• MTF individuals: Yearly screening mammography for patients age 50+ with estrogen use for 5+ years. Consider earlier screening if additional risk factors. Consider annual clinician breast exam.[d] • FTM individuals: Follow screening for natal females, unless post-mastectomy. Yearly chest wall and axillary exams post-mastectomy.	Fully evaluate dysfunctional vaginal bleeding with uninterrupted testosterone therapy, especially in amenorrheic patients. If prolonged bleeding, evaluate endometrium with trans-vaginal ultrasound and/or endometrial biopsy, especially if patient age >35. Consider total hysterectomy if fertility not an issue, patient age >40, and health will not be adversely affected by surgery.	• MTF individuals: Follow guidelines for natal females if neocervix created from glans penis. Consider regular vaginal Pap if history of genital warts, especially in immunocompromised patients. • FTM individuals: Follow guidelines for natal females, unless cervix removed. Perform annual Pap of vaginal cuff following total hysterectomy if history of high-grade tests, continue Pap every 2-3 years. Authors support Pap deferral if low risk for HPV transmission.
Gorton, Buth, & Spade (2005)	____	FTM individuals: Follow guidelines for natal females, unless post-mastectomy. with endometrial biopsy and generally an ultrasound to rule-out cancer.	Evaluate any bleeding in amenorrheic patient with uninterrupted androgen therapy.	FTM individuals: Follow guidelines for natal females, unless cervix removed.

[a] PSA levels may be low in an androgen-deficient setting, even in the presence of prostate cancer.
[b] In vaginoplasty, the neovagina is positioned posterior to the prostate, which may make digital palpitation difficult. DRE should still be used, as no standardized protocol for prostate evaluation by digital vaginal exam exists.
[c] Breast implants may impair mammography accuracy. The technician should be informed if present, so special techniques can be utilized.
[d] Drawn from Feldman & Safer (2009) which included updated recommendations by same author.
[e] The majority of FTM individuals do not undergo genital gender-affirming surgery, or undergo hysterectomy later in life, and therefore retain a cervix for a substantial portion of their lives.