Best Practice & Research Clinical Endocrinology & Metabolism xxx (xxxx) xxx

Contents lists available at ScienceDirect

Best Practice & Research Clinical Endocrinology & Metabolism

journal homepage: www.elsevier.com/locate/beem

The implications of hormone treatment for cancer risk, screening and treatment in transgender individuals

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ARTICLE INFO

Article history:
Available online xxxx

Keywords:
anus neoplasms
breast neoplasms
decision making
shared
early detection of cancer
hormones
meningioma
ovarian neoplasms
patient-centered care
prostatic neoplasms
transgender persons
uterine cervical neoplasms
uterine neoplasms

There is evidence that gender-affirming hormone treatment (GAHT) for transgender individuals modulates their risk for specific malignancies including breast and prostate cancer, and meningiomas. However, there is insufficient data to make precise risk estimates accounting for age and inherited cancer risk. As such, screening recommendations remain broad. Even less evidence exists for best practice in the management of active or historical cancers in the transgender population. Guidance is therefore mainly extrapolated from cisgender populations but with considerations of the significant benefits of GAHT in the face of any hormonal risk. Clinical experience, the multidisciplinary team and shared decision making with the patient are vital in providing person-centred care, while further research is acquired.

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https://doi.org/10.1016/j.beem.2024.101909

Please cite this article as: A.M. Berner and S.E. Atkinson, The implications of hormone treatment for cancer risk, screening and treatment in transgender individuals, Best Practice & Research Clinical Endocrinology & Metabolism, https://doi.org/10.1016/j.beem.2024.101909

Introduction

Gender-affirming hormone therapies (GAHT) alter the risk profile for benign and malignant tumours, as well as impacting their diagnosis and treatment. Much of our understanding of these effects is extrapolated from studies in cisgender individuals, though there have been a small number of studies of cancer incidence in cohorts of transgender and gender diverse (TGD) people [1–4]. These studies suffer from heterogeneity in the type and duration of GAHT, and are not able to adjust for other lifestyle risk factors (e.g. smoking, obesity) or barriers to care, which also differ by location.

Though the effects of hormonal signalling in sex-related cancers such as breast, prostate and gynaecological cancers are relatively well studied, there is emerging evidence of sex- and gender-based differences in non-sex related cancers, some of which may be hormonally driven [5]. Oestrogen, progesterone and androgen signalling contribute to both oncogenesis and immune response. The contribution of hormones, sex-chromosome and anatomy to development and treatment of cancers remains unstudied [5], and requires research inclusive of TGD participants.

Here we discuss current knowledge on the effects of hormone therapy on cancer risk and its implications for screening in TGD people. We also discuss the intersection of GAHT with cancer treatment, and the management of TGD people with hereditary cancer risk. In some cases we will extrapolate from studies in cisgender individuals but emphasise that this should be interpreted with caution until studies are carried out with TGD individuals.

Incidence

Breast cancer

Both oestrogen and progesterone signalling play a role in breast cancer development. Oestrogen stimulates proliferation of breast epithelium in postmenopausal cisgender women. Both higher circulating oestradiol levels and higher lifetime exposure to endogenous oestrogen are associated with invasive breast cancer risk [6]. Progesterone also exerts proliferative actions on breast tissue [7], although this is dependent on the relative concentration of its metabolites [8]. Higher circulating progesterone has been linked with breast cancer risk [9].

Studies in cisgender women have looked at cancer incidence following both exogenous oestrogen and progesterone [10,11]. Use of combined and oestrogen-only hormonal replacement therapy (HRT) for more than five years are both associated with increased breast cancer risk [11]. Different progestins appear to stimulate breast epithelial hyperproliferation to different degrees [12], and present different levels of risk [11].

Both genetically predicted, and measured, testosterone levels, have been positively correlated with breast cancer risk [13,14]. However, a study by the UK Biobank found this to be the case in post-menopausal cisgender women only, pointing to this effect being a result of increased aromatisation to oestrogen, which they were unable to measure in this group [14].

It therefore follows that breast cancer risk in transgender individuals will depend on the sex they were assigned at birth, any mastectomy surgery, age, and type and duration of GAHT (remembering that cyproterone is a progestogen as well as an anti-androgen). Bilateral mastectomy with male chest reconstruction may remove some or all of the breast tissue depending on the technique.

To-date, four studies have quantified breast cancer risk in cohorts of transgender individuals, and disaggregated the data according to the sex someone was assigned at birth.

The most robust of these comes from the Netherlands where de Blok and colleagues utilised linkage between the Nationwide Network and Registry of Histopathology and Cytopathology in the Netherlands (PALGA) and the gender clinic at VU University Medical Centre Amsterdam to cover breast cancer diagnoses from 1991 to 2016 [3]. It included 3489 individuals. In transgender women on GAHT, they found a lower risk compared to cisgender women (standardized incidence ratio (SIR) 0.3), though far higher than for cisgender men (SIR 46.7). Notably, these women were on cyproterone acetate or spironolactone as an anti-androgen (not gonadotropin-releasing hormone agonist (GnRHa)), alongside oestrogen therapy, unless post orchiectomy. There was also found to be a lower risk of breast cancer in transgender men on testosterone therapy compared to cisgender women (SIR 0.2) but again an elevated risk when compared to cisgender men (SIR 58.9).

This superseded a previous Dutch study which carried out follow-up on 3102 individual treated at the same centre between 1975 and 2011[15], with a median follow-up of 16.1 years. This found only 2 confirmed and 1 probable case of breast cancer. Lack of linkage and follow-up outside of the centre make these figures less reliable.

Brown *et al* [16] utilised the Veterans Health administration data to estimate breast cancer incidence in transgender individuals. However, both sex assigned at birth, and gender identity was conflated in the records and individuals were often prescribed both testosterone and oestrogen during the course of follow-up, making findings unreliable. It is similarly difficult to interpret findings by Silverberg *et al* [17], as they had no data on GAHT usage. They found that the rate of breast cancer in transgender men did not differ from that of cisgender women but was higher than that of cisgender men.

Though the estimates by de Blok and colleagues [3] would seem the most reliable, they may not be comparable for those using GnRHa plus oestrogen. Though the authors state that 69 % of transgender women in this cohort received orchiectomy and that the median duration of hormone therapy was 18 years, the duration of anti-androgen is not specified, nor the rates of breast cancer in those with and without orchiectomy.

Lastly, while the reduced rates of breast cancer in transgender men compared to cisgender women were assumed to be due to male chest reconstruction, they may also be the result of testosterone therapy. Single cell sequencing of breast tissue of transgender men treated with testosterone has showed changes in gene expression and chromatin accessibility more similar to cisgender male breast tissue, and associated with reduced oestrogenic signalling [18].

Prostate cancer

Testosterone is known to drive growth of both benign and malignant prostate cancer cells [19]. However, there appears to be a non-linear relationship such that circulating testosterone levels across the normal range do not drive prostate cell growth to a greater or lesser degree, but at very low levels of circulating testosterone there is growth inhibition. This so-called 'saturation hypothesis' is backed up by a meta-analysis showing lowered prostate cancer risk in hypogonadal cisgender men [20].

Oestrogen can exert effects on prostate cancer growth either through negative feedback on the hypothalamic-pituitary axis causing anti-androgenic effects [21], or through receptors ERα and ERβ. ERα is present in prostate cancer stroma, appears to be protumourigenic and is upregulated in advanced prostate cancer and androgen deprivation [22,23]. ERβ is present in prostate epithelium and tumour stroma, and is antiproliferative [24].

Studies to-date support a reduced risk for prostate cancer in trans women on GAHT, owing to use of anti-androgens and orchiectomy, as well as the antiproliferative role of oestrogen. The Dutch used PALGA linkage with Amsterdam VUC medical records for 2281 trans women to study prostate cancer risk [4]. They found a lower risk in transgender women on GAHT compared to the Dutch cisgender male population (SIR 0.20). Age at start of GAHT likely determines risk reduction. The median age at start of GAHT for the whole cohort was 31 years compared to 47 years for the 6 prostate cancer cases. Four of these women had undergone orchiectomy also. The majority of the cohort used cyproterone acetate or spironolactone as an anti-androgen, and rates may be lower in those on GnRHa.

Gooren and colleagues [25] used cohort follow-up of transgender women treated at Amsterdam VUC from 1975–2006 to estimate prostate cancer incidence, though likely missed cases treated elsewhere. They found an overall incidence of 0.04 % but 0.13 % in those commencing GAHT at the age of 40 or over, supporting a relationship between age of starting GAHT and risk. Silverberg *et al* [17] found a much higher rate of prostate cancer but included 38 % of individuals not on GAHT. Similarly, Loria and colleagues [26] utilised the TriNetX Veterans Affairs dataset to examine prostate cancer risk in transgender women, finding an overall 2.56 fold lower risk compared to cisgender men. This study suffers from multiple methodological flaws including lack of verification, matching and accounting for duplicates [27]. It grouped the cohort according to whether they accessed oestrogen-based GAHT and gender affirming genital surgery but did not account for whether individuals used an anti-androgen, making these findings challenging to interpret [27].

Given the emerging role of ERα stimulation in prostate cancer development [28], further research is required to quantify prostate cancer risk for those taking oestrogen-only GAHT.

Gynaecological cancers

Endometrial cancer

Exposure to unopposed endogenous and exogenous oestrogens is known to increase risk of endometrial cancer in cisgender postmenopausal women, while progesterone has an anti-proliferative effect [30].

Endometrial hyperplasia *may* be premalignant. Simple hyperplasia has a < 5 % chance of developing into invasive cancer, while hyperplasia with atypia has an 8 % chance if untreated [29].

Increased serum androgens are associated with increased risk of endometrial cancer in postmenopausal cisgender women [30,31]. Cisgender women with polycystic ovarian syndrome (PCOS) also have elevated circulating androgen concentrations and demonstrate increased rates of both endometrial hyperplasia and cancer [32,33].

These observations are through to result from aromatisation of testosterone to oestrogen. However, testosterone can also be converted to dihydrotestosterone by 5-alpha reductase, which acts to suppress endometrial proliferation. The role of the androgen receptor in the endometrium remains poorly understood [34].

Despite concern, there has been no evidence of increased risk of endometrial cancer in TGD people on masculinising GAHT. Studies to-date have shown variable rates of endometrial hyperplasia but reassuringly low rates of endometrial hyperplasia with atypia, and endometrial cancer [35–39]. However, all studies have been small, and the age of hysterectomy relatively low compared to the average age of endometrial cancer diagnosis (around 60 years)[40].

Increasing numbers of TGD elect to retain their uterus due to abolition of mandated surgery for legal gender change, shifting cultural attitudes and desire for pregnancy [41]. More studies are needed to evaluate the risk of endometrial hyperplasia with atypia, and cancer, in older TGD people on testosterone.

Ovarian cancer

Ovarian tumours may develop from epithelium, stroma or germ cells. The most common type of ovarian carcinoma, high grade serous (HGSOC) actually originates from the fallopian tube epithelium. *In vitro* studies have shown that testosterone increases migration and invasion of fallopian tube cells but whether such effects are relevant in humans is undetermined [42].

Pooled analysis of case-control studies involving cisgender women has shown that circulating serum testosterone was positively associated with a risk of epithelial ovarian cancers (OR = 1.12, 95 % CI 1.02–1.24) but that this was driven by an association with endometroid and mucinous, not serous or clear cell, subtypes [43].

There is no evidence to suggest increased rates of ovarian cancer in transgender men on GAHT. Nash and colleagues used the American Association of Central Cancer Registries (NAACCR) database to examine cancer cases for transgender individuals between 1995–2013 [1]. They found a lower rate of ovarian cancer compared to cisgender women, but were unable to determine the sex assigned at birth for individuals or whether they had accessed GAHT or salpingo-oophorectomy.

Cervical cancer

Exogenous oestrogen exposure via oral contraceptives and pregnancy has been associated with development of cervical cancer in cisgender women [44,45]. Cervical cancer is almost exclusively the result of persistent infection with high risk human papillomavirus (hrHPV). Endogenous oestradiol levels have also been linked to HPV persistence [46] and pre-clinical studies support its role in driving progression from premalignant lesions to invasive cervical cancer [47].

Although in cisgender women raised serum testosterone levels have been linked to cervical premalignant lesions and cancer, this is again thought to be due to its aromatisation to oestrogen [45,48].

As for endometrial cancer and ovarian cancer, there is no evidence of an increased risk of cervical cancer in transgender men. Nash and colleagues [1] found a reduced incidence of cervical cancer in all transgender individuals compared to cisgender women.

Anal cancer

Anal cancer is caused by persistent infection with hrHPV in 90 % of cases [49]. There are clear differences in incidence between cisgender men and women, which may be the result of behaviour as well as biology.

Anal cancer incidence is related to anal intercourse, age at sexual debut, number of sexual partners, and condomless sex, all of which affect HPV acquisition [50,51]. It is also increased in those with human immunodeficiency virus (HIV), as immunosuppression increases HPV persistence and reduces endogenous tumour-immune response. Anal cancer rates are 20 times higher in HIV positive individuals compared to the general population [52].

There is a higher incidence of anal cancer in cisgender women compared to cisgender men in Caucasian populations but this is reversed in black populations in the United States, as well as in Western Africa [53]. This is postulated to be the result of differing rates of HIV infection and effective treatment.

In cisgender women, anal HPV infection may be due to autoinoculation of HPV from the cervix to the anus or anal intercourse [54]. Therefore the presence of a vagina or cervix may provide a reservoir for anal HPV infection, though cisgender women appear to clear it more effectively from the anus, resulting in the lower rate of anal compared to cervical cancer [55].

Free testosterone has been associated with increased hrHPV prevalence but not pre-malignancy or malignancy in men who have sex with men (MSM), but total testosterone and estradiol were associated with lower odds of both [56,57].

Studies utilising US cancer databases found increased rates of anal cancer in transgender compared to cisgender populations [1,2] but were unable to disaggregate by sex assigned at birth, GAHT use or HIV co-infection.

Studies of anal hrHPV prevalence in transgender women have found figures ranging from 19–89 % depending on geographical location and rate of HIV co-infection [58–60]. Further studies are required to investigate the role of hormones in anal hrHPV persistence and cancer development.

Meningioma

Meningiomas are benign brain tumours that develop from the meningeal tissues that cover the brain and spinal cord [61]. They are generally slow growing and do not metastasise, but may cause devastating and long term sequelae due to mass effect. They are diagnosed more commonly in women.

By immunohistochemistry, 40 % of meningiomas are oestrogen receptor positive and 80 % are progesterone receptor positive [62,63]. The United States Nurses' Health Study found an increased risk of meningioma with exogenous and endogenous oestrogen and progesterone in cisgender women [64].

Cyproterone acetate acts as a progestin and there is a known association between its long-term use and meningioma in both cisgender and transgender individuals [65,66]. Between 1 and 10 in 10,000 people taking cyproterone develop meningioma, and that risk is dose-dependent [65].

In a Dutch cohort of 2555 trans women and 1373 trans men, the incidence of meningiomas in transgender women was four times higher than for cisgender women, and twelve times higher than for cisgender men [66]. In all eight cases of meningioma, individuals had remained on cyproterone, even post-orchiectomy. The median duration of GAHT was 166 months (range 59–477 months) [66].

The European Medicines Agency published guidance in February 2020 restricting use of cyproterone at doses higher than 10 mg [67]. However, a number of individuals remain on long-term cyproterone having commenced this prior to the guidance or are self-medicating.

In practice, cyproterone is best used only for two weeks to prevent the testosterone surge associated with the start of GnRH analogue. For those already on cyproterone, there should be shared decision making with the patient about switching to an alternative anti-androgen.

Population screening

Here we discuss where there are additional cancer screening considerations due to GAHT use or other aspects of transition. These apply to those without increased cancer predisposition by virtue of family history or a confirmed genetic variant. National call and recall systems may call people automatically for screening for sex-associated cancers depending on how their sex or gender is registered, and bespoke referrals may be required.

Breast cancer

TGD who were assigned male at birth

The Endocrine Society and the World Professional Association for Transgender Health (WPATH) both recommend following the same local screening guidelines for cisgender women in the case of TGD on oestrogen therapy [68,69]. UCSF Transgender Care and Treatment Guidelines [70] recommend not commencing mammographic screening in TGD who were assigned male at birth until they have been on oestrogen therapy for 5 years, and not earlier than age 50, due to the risks of over-screening in the context of short duration of oestrogen therapy. This is only a consensus recommendation and may alter where population screening begins younger.

de Blok and colleagues found cases of breast cancer in trans women only after 7 years of hormone therapy [3] but of 15 cases of invasive breast cancer, 9 were diagnosed in the 30–50 years age group, with 6 over 50 years [3].

Dense breasts are a risk factor for breast cancer and were found in 60 % of trans women in one study [15]. Some screening programmes are now introducing ultrasound screening at younger ages for those with dense breasts [71] which may be relevant for this population.

The Radiological Society of North America (RSNA) have produced guidelines for breast imaging in transgender people [72]. They note that a minority of transgender women undergo breast augmentation by injection of particles or soft-tissue fillers that can make mammography less sensitive and recommend contrast-enhanced MRI for this subgroup [72].

TGD who were assigned female at birth

WPATH recommend that TGD people who were assigned female at birth and who have not had bilateral mastectomy and male chest reconstruction, should follow local screening guidelines for cisgender women [69].

RSNA guidelines note that “in transgender men who have undergone top surgery and chest contouring, no reliable evidence exists for screening” and recommend clinical and physical examination, and discussion with clinician where appropriate [72].

Cervical cancer

The Endocrine Society and WPATH both recommend screening for cervical cancer as per local guidelines for TGD with a cervix [68,69].

Transgender men and non-binary people (TMNB) with a cervix experience multiple barriers to screening, including dysphoria from the procedure and information materials, failure to be called when registered with a male gender marker and vaginal atrophy from testosterone resulting in discomfort with the speculum examination required [73].

As a result, TMNB with a cervix have been found to have lower rates of attending cervical cancer screening and are less up-to-date than cisgender women [74,75].

Vaginal atrophy on testosterone therapy can lead to a higher rate of inadequate cytology compared to cisgender patients [76] though this is now somewhat mitigated by the advent of primary hrHPV testing in many cervical cancer screening programmes.

Organ-based screening recommendations for hrHPV-related cancers in sexual and gender minorities [77] recommend a number of measures to assist in speculum examination including pre-treatment with low-dose topical oestrogen, muscle relaxants or analgesia. Self-insertion of the speculum and longer appointments can also help.

Newer screening methods such as self-collecting vaginal swabs and urine sampling for hrHPV are more acceptable to the TGD community [78,79] but are not yet in widespread use.

Higher levels of testosterone can lead to cervical atrophy or transitional cell metaplasia [36,80–82] which can mimic intermediate and high grade premalignant lesions (cervical intraepithelial neoplasia (CIN) 2–3) at colposcopy. This could result in unnecessary biopsy or excision procedures.

Cervical cancer rates are already falling in countries with widespread use of the hrHPV vaccine [83] and those unvaccinated should be encouraged to take part in catch up programmes.

Anal cancer

The International Anal Neoplasia Society's consensus guidelines for anal cancer screening [99] recommend screening for transgender women from age 35 years with HIV and from age 45 years without HIV. Acceptable screening methods include anal cytology, hrHPV testing and hrHPV-cytology co-testing and there are thresholds for onward referral for high resolution anoscopy + /- biopsy. How individual countries will choose to implement these guidelines remains to be seen.

The guideline recommends the same screening for transgender women as for men who have sex with men (MSM) [84]. Recommendations for transgender women are based on anal cancer incidence data from MSM alone, as incidence data does not exist for this group. There are no recommendations for transgender men specifically [99]. Assumptions about anatomy and sexual behaviour may result in under or over screening.

Endometrial cancer

WPATH recommend using the "same local screening guidelines (including the recommendation not to screen) developed for cisgender women at average and elevated risk for developing ovarian or endometrial cancer in their care of transgender and gender diverse people who have the same risks." [69] No population screening programme exists for endometrial cancers [85]. The only high-risk group where screening may be considered are individuals with Lynch syndrome, but here evidence remains inconclusive [86]. Cisgender women with PCOS are not screened. However, some practitioners continue to screen TMNB people.

Screening in cisgender women consists of transvaginal ultrasound scanning + /- endometrial sampling [86]. This is often unacceptable for TMNB people, so pelvic ultrasound has been recommended. This is less sensitive and the normal endometrial thickness not well defined.

UCSF guidelines and multiple reviews recommend against routine screening but suggest prompt investigation of abnormal vaginal bleeding [70,87,88].

Future prospective research should examine the development of endometrial hyperplasia and cancer in TMNB people.

Prostate cancer

The Endocrine Society recommend that TGD with prostates follow the same prostate cancer screening recommendations as cisgender men [68,69], though WPATH Standards of Care Version 8 makes no specific recommendation [69].

Screening guidelines vary by country due to the difficult risk-benefit balance of screening, as many prostate cancers are indolent and not life-limiting. Screening typically utilises prostate-specific antigen (PSA) which is androgen-regulated and produced by both prostate epithelial cells and stroma. Sensitivity of PSA in detecting prostate cancer in cisgender men ranges from 61–100 %, but specificity is poor, ranging from 5–74 % [89,90].

The risk-benefit balance is further complicated in TGD people due to lowering of PSA by anti-androgen therapy (population-specific normal range), lower rates of prostate cancer, and the potential for dysphoria in the diagnostic pathway [91].

Three studies have measured PSA pre- and post-commencement of GAHT that included an anti-androgen in healthy transgender women [92–94]. Mean PSA at 4 months ranged from 0.032 ng/ml to 0.177 ng/ml, at 12 months was 0.015 ng/ml and at 9 years was 0.1 mg/L across these studies [92–94].

Gooren et al [25] suggested 1 ng/ml as a referral threshold for prostate cancer investigation in transgender women. This is lower than the 4 ng/ml used in the general cisgender male population, but higher than that used in hypogonadal cisgender men (0.65 ng/ml) [95].

Work is ongoing to determine a normal reference range for PSA in TGD people with a prostate on GAHT. Until then the threshold of 0.65 ng/ml is suggested.

Factors that may influence the risk-benefit discussion further include family history of prostate (or breast or ovarian) cancer, and Afro-Caribbean ethnicity [96,97].

Abnormal PSA levels may prompt prostate MRI and biopsy. The prostate may appear smaller post-GAHT which may further complicate interpretation [98].

In cisgender men, multiparametric MRI (mpMRI) was better able to delineate low-grade cancers from benign regions in those on 5-α reductase inhibitors compared to those who were not [99]. This suggests

mpMRI will be particularly useful in TGD on feminising hormone therapy being screened or investigated for prostate cancer [98].

Implications of GAHT in following a cancer diagnosis

There are *potential* adverse effects of GAHT with regard to drug-drug interactions, thrombosis risk and hormone-sensitive malignancies. However, these are often extrapolated from studies in cisgender populations only, or pre-clinical studies.

Where clear evidence of risk exists (e.g. oestrogen for a trans women with an oestrogen-receptor positive breast cancer), that must be weighed against psychological and physiological benefits of GAHT, alongside stage of malignancy and treatment intent. In all cases there should be shared decision making with the patient and all their healthcare professionals through a multidisciplinary team (MDT) approach, acknowledging the extent and strength of the evidence. Clinicians should consider if they would inhibit hormones for a cisgender person in the same circumstances. The rapidity of drug approval and guidelines evolution in oncology makes the involvement of the tumour-type specialist key but they may not have a working knowledge of gender affirming care.

Specialist services are emerging to assist with these decisions. For example, the UK Cancer and Transition Service [100] is a national virtual clinic and MDT meeting which aims to integrate gender-affirming and oncological care.

General considerations

Drug Interactions on chemotherapy

Drug interactions, particularly those metabolised by the Cytochrome P450 (CYP) family of enzymes, affect the metabolism of oestrogen and progestins [101–103], leading to changes in previously stable serum levels. Potential interactions should be checked in a formulary or with a specialist pharmacist. Where interactions are predicted, more frequent monitoring may be indicated, at least during the initial phase of a new treatment.

Electrolyte imbalances are also common following cytotoxic chemotherapy. Spironolactone may be better substituted for an alternative anti-androgen following discussion with the individual.

Estimating kidney function for chemotherapy dosing

Some chemotherapies (e.g. Carboplatin) are dosed using glomerular filtration rate (GFR). Creatinine is used to estimate GFR using the Cockcroft-Gault equation, which has a sex-specific constant.

TGD on masculinising hormone therapy exhibit a rise in serum creatinine within 6–12 months of commencing testosterone, due to an increase in muscle mass [104,105]. TGD on feminising hormone therapy experience the opposite [104,105].

The constant used in the formula should be determined by length of GAHT (more or less than 6 months) and degree of change in muscle mass. Particular attention is needed if an individual commences GAHT while undergoing chemotherapy. If necessary, an accurate measurement of GFR can be taken by ^{51}Cr-EDTA Clearance.

Altered liver function

Increases in liver enzymes have been observed at initiation of both oestrogen and testosterone GAHT with uncertain clinical significance [106,107]. Changes to liver function in TGD people with cancer outside of this period are more likely to be a complication of cancer or anti-cancer therapy and it is rarely necessary to stop GAHT. An exception to this is cyproterone acetate, which can cause liver injury on initiation or contribute to liver injury from another cause [108]. An alternative anti-androgen should be considered in these cases.

As CYP enzymes are responsible for GAHT metabolism [101–103], serum levels should be checked in cases of severe liver function derangement.

Thrombosis

Active cancer and chemotherapy are known risk factors for venous thromboembolism (VTE), as is feminising GAHT. VTE rates for TGD people on feminising GAHT are lowest using transdermal oestrogen

formulations and there should be shared decision making about a switch for individuals on oral oestrogens who have a concurrent cancer diagnosis and/or are on chemotherapy.

In high risk individuals (e.g. uncontrolled myeloma, patients at risk of superior vena cava obstruction, previous VTE), there should be shared decision making about a reduction in dose.

Though rarely prescribed routinely, individuals self-medicating may access conjugated oestrogens or ethinyl oestradiol, which are the highest risk [109,110]. These individuals should be supported in a switch to a lower risk preparation.

Continuing to prescribe a preparation and dose which has a slightly higher risk of VTE may be preferable to withdrawing a prescription and leading an individual to self-medicate unmonitored.

In cases of high VTE risk (e.g. due to cancer type, tumour location, anti-cancer therapy or historic VTE), clinicians should consider prophylactic low molecular weight heparin to enable patients to safely continue GAHT. Linalidomide is of particularly high risk for VTE with combined oestrogen and progesterone GAHT [111].

Development of a VTE should prompt anticoagulation as for any patient. There should be shared decision making about dose reduction or interruption of GAHT in cases of extensive or recurrent VTE, acknowledging the benefits and harms of all options [112].

Studies suggest that the rate of VTE in TGD on masculinising GAHT is comparable to cisgender hypogonadal men using testosterone [113]. Studies in cisgender men have shown a slightly increased VTE risk in the first 6 months of testosterone [114]. Clinical vigilance for VTE is therefore advised within this period, with the option to use prophylactic anticoagulation in high-risk individuals.

Breast cancer

TGD who were assigned male at birth

ER positive breast cancer in TGD people presents a challenge for those currently on, or wishing to access, feminising GAHT.

In the adjuvant setting, the recommendation in cisgender women is for oestrogen blockade either with tamoxifen or aromatase inhibitor (AI) (+/- GnRHa), depending on menopausal status and stage, for 5–10 years [115]. Chemotherapy may be given neoadjuvantly or adjuvantly but in high risk ER positive HER2 receptor negative disease, a CDK4/6 inhibitor is recommended alongside an AI (+/- GnRHa) [115].

In cisgender men, adjuvant treatment is similar to that for lower risk premenopausal cisgender women. Oestrogen blockade is with tamoxifen (as 20 % of the oestradiol comes from the testes) but where a CDK4/6 is indicated, it must be combined with an aromatase inhibitor and GnRHa [115].

The approach for TGD individuals who were assigned male at birth depends on the acceptability of stopping oestrogen. For those who feel able to stop, management should be as for cisgender men. For those who do not, there is little point in use of tamoxifen. Oestrogen should be reduced to the lowest dose possible. An AI could be used to partially lower circulating oestradiol levels, providing side effects are acceptable. Where the individual meets the criteria for adjuvant CDK4/6, co-prescription of AI may be required by the license to enable access, as benefit of CDK4/6 monotherapy without AI has only been shown in the metastatic setting.

First-line treatment in ER positive metastatic breast cancer in cisgender patients is also via CDK4/6 inhibitor alongside AI or Fulvestrant (an oestrogen receptor antagonist), along with GnRHa in the case of men or premenopausal cisgender women [116]. As in adjuvant management, this creates a dilemma for those who feel unable to stop oestrogen. Palliative treatment for ER positive breast cancer can result in life-expectancy in the order of years, and the patient should weigh this against the impact on quality of life from stopping oestrogen therapy. Patients may wish to proceed directly to chemotherapy. These decisions should be made with the support of the MDT.

TGD who were assigned female at birth

ER positivity also impacts breast cancer management for TGD people who were assigned female at birth accessing masculinising hormone therapy.

Literature suggests that oestradiol levels in TGD accessing masculinising hormone therapy are rarely suppressed to cisgender male levels with testosterone alone [3]. Little data exists on oestradiol levels for those on concurrent GnRHa.

Current evidence would suggest that TGD people who were assigned female at birth with breast cancer, should receive adjuvant management as for cisgender women of equivalent menopausal status. However, given the potential for testosterone to be aromatised to oestrogen, oestrogen levels should be monitored for those on AI. In these cases, testosterone gel is also preferred to avoid excess aromatisation due to fluctuating high levels. For this reason tamoxifen may be a preferrable strategy, especially in those post-hysterectomy (avoiding the increased risk of endometrial cancer).

The same principles apply in the metastatic setting. Here CDK4/6 treatment necessitates co-prescription of an AI [116]. If serum oestradiol levels are not suppressed on AI, Fulvestrant can be used as an alternative endocrine therapy. [116]. However, Fulvestrant can interfere with commonly used assays for serum oestradiol, resulting in falsely raised levels, making them uninterpretable [117].

The androgen receptor (AR) is an emerging therapeutic target in breast cancer. It is expressed in 70–90 % of ER positive HER2 negative tumours, 60 % of ER positive and HER2 positive tumours, and 20–50 % of "triple negative tumours" [118].

In vitro and in vivo models have demonstrated that AR acts as a tumour suppressor in ER positive breast tumours from cisgender women, antagonising the effect of oestrogen [119]. Studies using selective AR modulators in AR positive ER positive breast cancers have shown efficacy in early phase studies [120]. These findings suggest that in AR positive ER positive breast cancers, testosterone can be safely continued, with the adjustments to endocrine therapy noted above. A switch to a gel may be preferable in case of clinical concern and the need to stop abruptly.

However, in ER negative breast cancers, evidence points to a possible protumourigenic role for AR, with its stimulation able to activate both oestrogen- and androgen-responsive oncogenic pathways [118]. This area requires further study. There should be shared decision making about stopping or lowering dosages of testosterone in ER negative breast cancer. Of note, androgen-blockade is not part of standard management for breast cancer in cisgender men, apart from in the metastatic setting when treatment options have been exhausted [121].

Prostate cancer

Treatment of prostate cancer depends on whether it is localised or metastatic. Localised cancers are classed according to risk level (very low to high) according to PSA level, biopsy and imaging results. There are additional diagnostic considerations for TGD people post-vaginoplasty which are beyond the scope of this chapter and discussed elsewhere [98,122].

Low and very-low risk patients are generally advised towards active surveillance, while intermediate or high risk patients are offered radical prostatectomy or radiotherapy, with or without androgen deprivation therapy (ADT) [123].

TGD people with a prostate may already be on a GnRHa for GAHT, with constitutes ADT. In cases where individuals have been on GnRHa for long periods, clinicians may be concerned that the cancer is already "castrate-resistant" due to prolonged anti-androgen exposure, and thus more likely to exhibit rapid progression. However there are no studies to-date that have directly evaluated this.

Studies in cisgender men with low risk prostate cancer have shown that immediate and delayed (within 12 months) surgery or radiation have similar outcomes [124]. This suggests that active surveillance is a safe option in TGD people with prostates who have very-low or low risk disease [98]. As PSA is lowered by GAHT, an individualised monitoring plan and thresholds should be agreed between clinical teams.

A period of ADT alone may allow time for vaginoplasty with later radical treatment to allow individuals their preferred genital surgery [98,122].

Where individuals are not already on a GnRHa, this may be offered neodjuvantly or adjuvantly in moderate or high risk disease, as for cisgender men [123]. For those not already on GnRHa, it is often acceptable as an anti-androgen for TGD people but may not always be tolerable. Chemotherapy may also be offered adjuvantly in high risk disease and there should probably be a low threshold for this in those who have already been on long-term GnRHa.

Localised disease may be classed as castrate-resistant if testosterone is suppressed below 1.7nmol/l and there are three consecutive rises in PSA 1 week apart, resulting in two 50 % increases over the nadir, and PSA > 2 ng/ml [125]. Androgen receptor inhibitors may be indicated for TGD people with castrate-resistant localised prostate cancer following long-term GnRHa, and GnRHa can be continued as GAHT.

Metastatic disease may also be hormone-sensitive or castrate-resistant. In cisgender men, ADT is commenced in hormone naïve patients and in those already on ADT, this is continued [123]. The addition of chemotherapy + /- androgen receptor inhibitor to ADT significantly prolongs survival in high-volume even in hormone-sensitive disease [126,127].

In castrate-resistant disease, chemotherapy or androgen receptor inhibitors may be used alongside ADT [123]. These treatments need not differ for TGD people with prostates.

There is no current evidence for harm of continuing oestrogen therapy regardless of disease stage. In fact, recent evidence has shown benefit and safety of transdermal oestradiol in hormone-sensitive prostate cancer in cisgender men [128].

One US study [2] using a national cancer database indicated a poorer survival from prostate cancer in transgender people, potentially due to castrate-resistant disease.

Meningioma

Where meningioma occurs in patients on cyproterone, this should be stopped, with the offer of an alternative anti-androgen. Where resection or biopsy has been performed, ER and progesterone receptors should be tested, to support informed consent discussions about GAHT. However, in vitro work has shown that these receptors are not always functional [129].

A retrospective study of cisgender women with incidental meningiomas with and without oestrogen-based HRT, showed a lower growth-rate and progression-free survival in the HRT group [130]. This suggests that oestrogen-therapy is likely to be safe in TGD people with meningiomas provided there is careful imaging follow-up.

Desmoid tumours

Desmoid tumours are rare tumours derived from connective tissue containing fibroblasts and occur in 10–30 % of people with familial adenomatosis polyposis coli [131]. They express ERβ in up to 90 % of cases [132], and may be oestrogen driven. However, they do not always respond to anti-oestrogen therapy in cisgender women, and can remain stable or spontaneously regress in the presence of oestrogen. Surgical removal can prompt regrowth at the original tumour site [131]. This presents a challenge in the TGD person on, or due to commence, feminising hormone therapy.

Management of desmoid tumours in TGD people on oestrogen should involve a MDT including surgeons and endocrinologists. The risks of growth should be discussed with the individual. If they are happy to accept this, they should be on the lowest tolerable dose of oestrogen and monitored with regular imaging [133].

Gonadal failure after stem cell transplant or gonadectomy in the course of treatment

Gonadal failure is common after both autologous and allogenic stem cell transplantation due to the high doses of myeloablative chemotherapy [134]. These procedures are common in haematological cancers and germ cell tumours.

In cases where individuals have not commenced GAHT prior to gonadal failure, hormone replacement therapy with the hormones associated with the individual's sex-assigned at birth may induce greater dysphoria and distress. Prompt hormone therapy may be required to alleviate physiological symptoms of hypogonadism and protecting bone health.

Careful liaison between the teams involved will hopefully minimise time from gonadal failure to GAHT. Where GAHT is not appropriate or levels insufficient, calcium, vitamin D and bisphosphonates should be used to protect bone health.

Similar circumstances may arise where a cancer diagnosis necessitates gonadectomy prior to GAHT, e.g. in gynaecological malignancy or immunotherapy-induced hypopituitarism.

Implications of GAHT in genetic cancer predisposition

More widespread genetic testing means that more TGD individuals are being diagnosed with high risk genetic variants that predispose them to cancer. Of particular concern are variants in *BRCA1* and *BRCA2* genes, which predispose individuals to cancers such as breast and prostate.

Suspicion or confirmation of hereditary cancer risk should not be a barrier to accessing GAHT [135]. Addition of GAHT is not considered to confer much in the way of additional increased cancer risk

[133,135], though there is not robust data on cancer risk for TGD with these mutations and estimates are extrapolated from studies in cisgender individuals.

Review by clinical genetics enables better informed consent for risk-reducing surgeries and screening. Consensus guidance exists to assist clinicians involved in referrals and care [133,135,136] and are clear that individuals should not feel pressured into genetic testing in order to access GAHT.

TGD people who were assigned male at birth with confirmed or suspected *BRCA* mutations need particular counselling. Development of a greater volume of breast tissue on oestrogen-containing GAHT may push lifetime breast cancer risk from 1–10 % closer to 45–85 % depending on age. Individuals should be informed of this before commencing GAHT and a prompt referral to clinical genetics discussed.

Summary

We are just beginning to build a robust evidence for the sequelae of GAHT for cancer risk, screening and management. Retrospective data suggests that GAHT confers an increased risk of breast cancer and reduced risk of prostate cancer in TGD people who were assigned male at birth. Long-term high dose cyproterone carries risk for meningioma. There is reduced risk of breast cancer in TGD people who were assigned female at birth which may be the result of both GAHT and surgery. However, we require longer term cohort studies to provide better risk estimates by age and type of GAHT used, that will inform evidence-based screening guidelines. Hormones are postulated to play a role in HPV-related cancers such as cervical and anal cancers but this requires further study. There is no proven increase in endometrial cancer risk in TGD people on testosterone and requires prospective study. Screening is not advised but unexplained vaginal bleeding should prompt investigation. In active cancer, GAHT has implications for thrombosis risk, drug interactions and renal function estimation. Evidence for best practice in hormonally driven cancers in TGD people is lacking and requires extrapolation from work in cisgender populations. Where there is evidence of risk (e.g. for TGD people on oestrogen with ER positive breast cancers) there should be shared decision making about stopping hormonal therapy. Other scenarios may require adjustments to the standard treatment algorithm, for example TGD people on testosterone with ER positive breast cancer and TGD people who develop prostate cancer after long-term GnRH analogue.

Research agenda

- Generate robust incidence statistics for cancer in transgender individuals and how this is influenced by GAHT.
- Determine risk of endometrial hyperplasia and cancer in older TMNB on testosterone who choose to retain their uterus.
- Establish normal PSA reference ranges for TGD people with a prostate on GAHT and/or post orchiectomy to enable better prostate cancer diagnosis and monitoring.
- Determine the risk of prostate cancer for TGD people with a prostate on oestrogen-based GAHT alone or in combination with GnRHa, especially those commencing at young ages.
- Explore the effects of oestrogen-based GAHT in active prostate cancer in TGD.
- Explore the effects of testosterone-based GAHT in AR positive breast cancers in TGD.
- Inclusion of transgender individuals in studies examining sex-based difference in non-sex related cancers.
- Explore the role of sex hormones in HPV acquisition, persistence and cancer development at different body sites in transgender populations.

Practice points

- TGD people who were assigned male at birth commencing feminising GAHT should be counselled on the increased risk of breast cancer, and reduced but remaining risk of prostate cancer.

- TGD people who were assigned male at birth on feminising GAHT should follow local screening recommendations for cisgender women.
- TGD people who were assigned female at birth commencing GAHT should be counselled on the decreased but residual risk of breast cancer, and reduced but remaining risk of prostate cancer.
- TGD people who were assigned female at birth should access breast and cervical screening as per local recommendations while these organs are in situ. Following bilateral mastectomy and male chest reconstruction they should self-examine any remaining breast tissue.
- Long term high dose cyproterone confers a risk of meningioma and TGD people should be counselled on a potential switch to an alternative anti-androgen or a reduced dose.
- Management of hormonally driven cancers in TGD on GAHT should consider both the risks and the benefits of hormone therapy and involve shared decision making with the patient and the wider MDT.
- TGD people at inherited cancer risk should be offered a review by clinical genetics services to enable better informed consent for risk-reducing surgeries and screening.

Funding

This work has not received specific funding. AMB is funded by an NIHR Academic Clinical Lectureship.

Declaration of Competing Interest

AMB has received honoraria for non-promotional education on cancer care in transgender patients from Pfizer, Lilly and Astellas, and a fellowship grant to employ staff for the UK Cancer and Transition Service from Gilead. SA declares no conflicts of interest.

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