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Implications of hormonal carcinogenesis for transgender and gender-diverse people undergoing gender-affirming hormone therapy: an up-to-date review

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ABSTRACT

Transgender and gender-diverse (TGD) individuals face an elevated risk of cancer in comparison with the general population. This increased risk is primarily attributed to an imbalanced exposure to modifiable risk factors and a limited adherence to cancer screening programmes, stemming from historical social and economic marginalisation. Consequently, these factors contribute to poorer clinical outcomes in terms of cancer diagnosis and mortality. A focal point of interest is the potential carcinogenic effect of gender-affirming hormone therapy (GAHT). It is crucial to recognise that GAHT serves as an essential, life-saving treatment for TGD individuals. Therefore, if a demonstrated direct correlation between GAHT and elevated cancer risk emerges, essential shared decision-making discussions should occur between oncology practitioners and patients. This narrative review aims to collect and discuss evidence regarding potential correlations between GAHT and the most prevalent tumours known to be influenced by sex hormones. The objective is to comprehend how these potential carcinogenic effects impact health and inform health interventions for TGD individuals. Unfortunately, the scarcity of epidemiological data on cancer incidence in the TGD population persists due to the absence of sexual orientation and gender identity data collection in cancer centres. Consequently, in most cases, establishing a positive or negative correlation between GAHT and cancer risk remains speculative. There is an urgent need for concerted efforts from researchers and clinicians worldwide to overcome barriers and enhance cancer prevention and care in this specific population.

INTRODUCTION

The latest global estimates indicate that a proportion ranging between 1% and 6% of the general population aged 16–74 years identifies as transgender, gender non-conforming, gender fluid or does not feel that their identity is represented by gender binarism.[1] Yet, such a proportion is rapidly growing, especially among adolescents and young adults.[2]

Transgender and gender-diverse (TGD) individuals—the phrase that we will use in this paper to be as comprehensive as possible (table 1)—face a higher risk of cancer compared with cisgender individuals.[3] The increased risk is attributed primarily to an imbalanced exposure to modifiable risk factors, including smoking, alcohol consumption, obesity and sexually transmitted infections. Second, there is limited adherence to cancer screening programmes due to the historical social and economic marginalisation.[4] Finally, widely insufficient knowledge of TGD health issues among healthcare providers has been demonstrated.[5–8] These factors lead to worse clinical outcomes in terms of cancer diagnosis and mortality.[9]

TGD individuals may decide to undergo feminising or masculinising gender-affirming hormone therapy (GAHT), which is variably consisting of exogenous oestrogens, antiandrogens, androgens and gonadotropin-releasing hormone agonists. Moreover, there is a recent trend in using selective oestrogen receptor (ER) modulators among non-binary individuals assigned male at birth who seek an androgynous appearance without the development of breast tissue.[10] GAHT regimens might vary according to the local guidelines and the specific needs of recipients, as indicated by the World Professional Association for Transgender Health (table 2).[11] Several researchers have raised the question of whether GAHT might increase the risk of certain types of cancer.[12 13] However, only few, and mostly retrospective, epidemiological

Table 1 Gender terminology (modified from WPATH Standards of Care 8.0)

Gender identity	The internal, personal sense of being male, female, non-binary, having a different gender identity or having no gender
Transgender	Individuals whose gender identity and/or gender expression does not match with societal expectations determined by their assigned sex at birth.
Cisgender	Individuals whose gender identity conforms to societal expectations determined by their assigned sex at birth.
Gender diverse	A broad term employed to describe individuals whose gender identity and/or gender expression diverge from societal expectations or norms. This category includes terms like non-binary, gender fluid, gender queer, gender neutral, agender, X-gender and various others.
Non-binary	It refers to individuals with gender identities that fall outside the traditional gender binary. Those with non-binary gender identities might identify as a blend of both male and female, fluctuate between identifying as male and female, identify as a gender distinct from male or female, or as lacking a gender altogether. Non-binary individuals may opt for pronouns such as they/them/theirs in place of he/him/his or she/her/hers
Gender binarism	The categorisation of gender into two distinct forms, namely masculine and feminine, often influenced by societal structures, cultural beliefs or a combination of both.
Gender fluid	An individual who embraces a flexible or adaptable approach to the concept of gender identity and expression. This may involve identifying as one gender, multiple genders or no gender at all.
Gender incongruence	A diagnostic term identified in the 11th Revision of the International Classification of Diseases, describing an individual's enduring and marked experience of incongruity between their gender identity and the sex assigned to them at birth.
Gender dysphoria	A clinically significant distress arising from the perceived incongruence between an individual's gender identity and the sex assigned to them at birth. This term is also a diagnostic classification in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition. It's important to note that not all transgender and gender-diverse individuals necessarily experience gender dysphoria.
Gender affirmation	It denotes the acknowledgement or validation of an individual's gender identity. This concept typically encompasses social, psychological, medical and legal dimensions.

WPATH, World Professional Association for Transgender Health.

data on cancer risk in TGD population are available due to the chronic lack of gender identity data collection in clinical records and within clinical trials.[14 15] Therefore, in most cases, the causative role of GAHT in cancer occurrence is merely speculative.

With this narrative review, we aimed at collecting and discussing evidence about the possible correlations between GAHT and the most common tumours known to be sex hormone driven (figure 1) to understand how these possible carcinogenic effects impact on health or inform health interventions in TGD people (table 3). Each paragraph of the manuscript is further subdivided into three parts. The first part delves into the biological background of the potential hormonal effects on the target organ. The second part reviews clinical data among the general population, while the last part explores available clinical data specific to the transgender population. The main clinical studies focusing on transgender population undergoing GAHT are summarised in online supplemental table 1.

RESULTS

Oestrogens and breast cancer

Biological background. Two essential mechanisms through which oestrogens act as cancer promoters and carcinogens have been extensively described. The first mechanism, known as the classic oestrogen-signalling pathway, involves the stimulation of tissue growth through receptor-mediated hormonal activity.[16] Upon binding to nuclear ERs, the oestradiol-ER complex activates cell proliferation, with an increased number of errors during DNA replication. The second mechanism involves genotoxic effects induced by elevated mutation rates through cytochrome P450-mediated mutagenic metabolites.[17] In detail, oestradiol can be metabolised to quinone derivatives by NAD(P)H and P450 reductase. This metabolic process generates reactive oxygen species that may cause DNA strand breaks and oxidation of DNA bases.

Clinical data in general population. Both epidemiological and randomised clinical trials demonstrate an increased breast cancer (BC) risk with hormone-replacement therapy (HRT) containing conjugated equine estrone with or without medroxyprogesterone acetate.[18–20] A 1997 meta-analysis, including 52 705 women with BC and 108 411 healthy women, found an increased BC risk in HRT users, positively correlated with the duration of use.[18] Similar findings were observed in a French study involving over 54 000 women and the Million Women observational study in the UK.[21 22] Following HRT cessation, the relative risk returned to that of non-users. The Women's Health Initiative Study, randomly assigning postmenopausal women to placebo or HRT (equine oestrogens with medroxyprogesterone acetate), was prematurely closed due to increased BC incidence.[23]

Table 2 GAHT regimens in transgender and gender-diverse adults (modified from WPATH Standards of Care 8.0)

Feminising GAHT		
Hormone	**Dose/frequency***	**Route**
Oestrogens		
► Estradiol		
	2–6 mg/day	Oral or sublingual
	0.025–0.2 mg/day	Transdermal patch
	Variable dosage/daily	Topic gel
► Estradiol valerate or cypionate		Intramuscular
	5–30 mg every 2 weeks	Intramuscular
	2–10 mg/week	
Antiandrogens		
► Spironolactone		Oral
	100–300 mg/day	
► Cyproterone acetate	10 mg/day	Oral
► Spironolactone		Subcutaneous/intramuscular
	3.75–7.50 mg/month	Subcutaneous/intramuscular
	11.25 mg every 3 months	Subcutaneous/intramuscular
	22.5 mg every 6 months	
Masculinising GAHT		
Hormone	**Dose/frequency***	**Route**
Androgens		
Testosterone enanthate		
	50–100 mg/week	Subcutaneous/intramuscular
	100–200 mg every 2 weeks	Intramuscular
Testosterone undecanoate		
	1000 mg every 10–14 weeks	Intramuscular
	750 mg every 10 weeks	Intramuscular
Testosterone	50–100 mg/daily	Topic gel
	2.5–7.5 mg/daily	Transdermal patch

*The adjustment of doses, either increased or decreased, is carried out until sex steroid hormone levels fall within the therapeutic range.
GAHT, gender-affirming hormone therapy; WPATH, World Professional Association for Transgender Health.

After 20 years, the study found increased BC incidence in women with intact uteri but no significant difference in cancer mortality.[24] The role of progestin component of HRT in BC risk is still a matter of debate due to the absence of unanimity regarding the inherent impact of oestrogen and its dosage, administration method and duration of treatment.

Regarding hormonal contraceptive therapy in premenopausal women, there is an increase of 20–30% with the use of old estradiol–progestin formulations.[25] With the use of contemporary hormonal contraceptive regimens, the relative risk of BC among current or recent users of any hormonal contraception was 1.20 (95% CI 1.14 to 1.26) in the Danish Sex Hormone Register Study.[26] Of interest, the risk appeared similar with the levonorgestrel-releasing intrauterine system and was time dependent: with the use of hormonal contraceptives for 10 or more years, the risk appeared higher, with a relative risk up to 1.38. The findings were confirmed in a recent UK nested case–control study, showing a similar risk of BC with progestogen-only hormonal contraceptives, and with progestogens delivered as oral pills, injections and uterine-releasing devices.[27] However, despite the utilisation of oral and injectable progestin-only formulations for contraception among premenopausal women, the clinical evidence regarding the exclusive impact of progestin remains sparse. Furthermore, introducing progestins could hinder ovulation, making it challenging to distinguish between the direct influence of the progestogen on the breast and the indirect repercussions linked to anovulation.[28]

Clinical data in transgender population. In transgender women, GAHT results in normal but not supraphysiological levels of oestradiol, promoting breast tissue development like in biologically female breasts.[29] The incidence of BC in cisgender men is around 1%, whereas the incidence in transgender women, including those undergoing GAHT, remains unknown. A 1997 retrospective study in the Netherlands found no increase in all-cause mortality related to GAHT in a cohort of over 2000 transgender

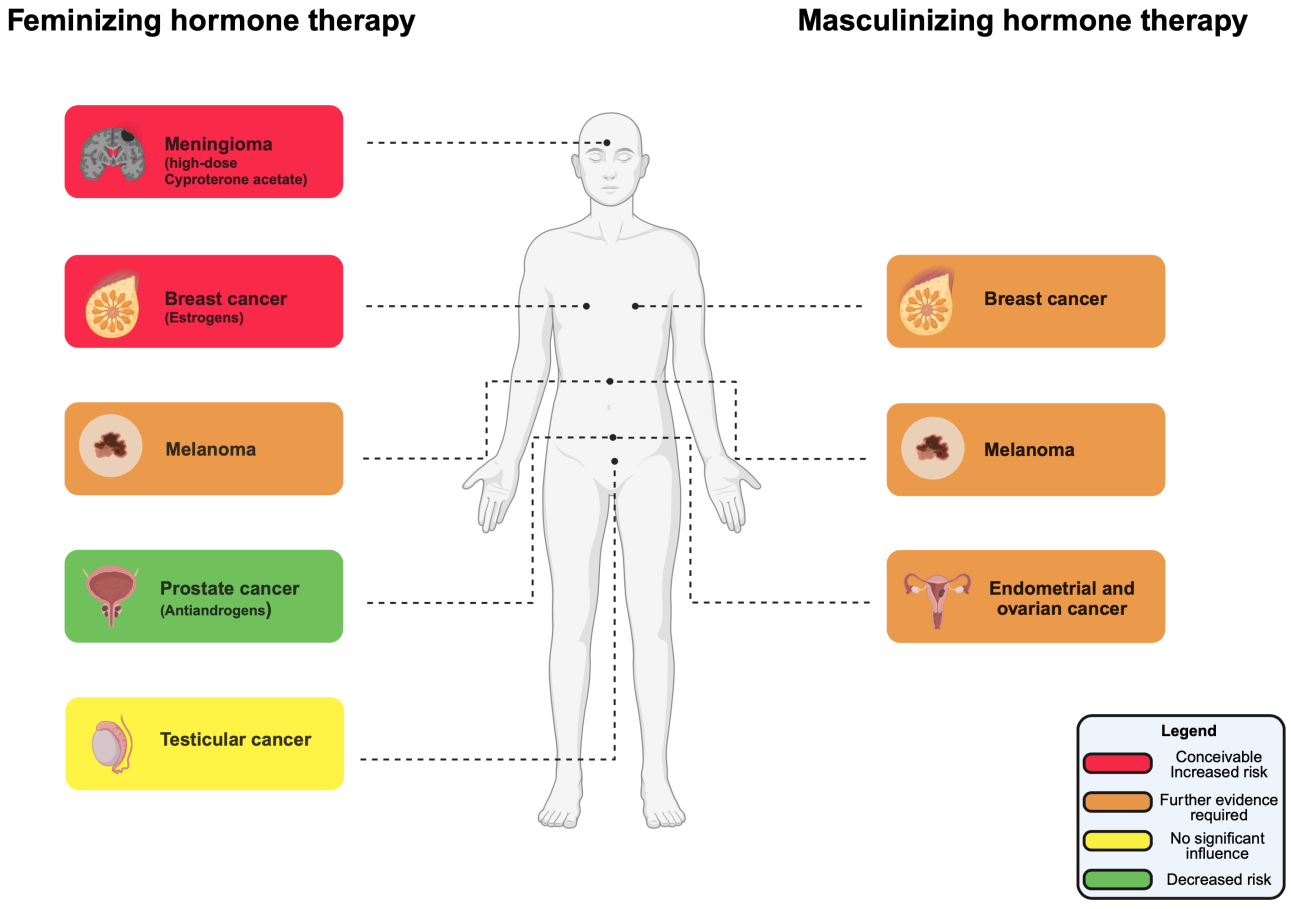

Figure 1 Summary of the evidence for effects of masculinising and feminising gender-affirming hormone therapy on breast cancer, meningioma, reproductive cancers and melanoma. These findings stem from a few, underpowered, retrospective studies and require confirmation from large prospective studies (figure 1 has been realised with BioRender).

women exposed to exogenous oestrogen for up to 41 years.[30] Subsequent studies, including a large series with long-term follow-up, reported minimal BC cases, leading to the conclusion that GAHT does not increase BC occurrence in transgender women.[31] Data from transgender veterans in the USA also showed a low incidence of BC, although limited by sample size and observation duration.[32] However, the most recent study, analysing a nationwide cohort study in the Netherlands, indicated a 46-fold increased BC risk in transgender women versus cisgender men, although still lower than cisgender women.[33]

Testosterone and BC

Biological background. Androgens exhibit antiproliferative effects in breast tissue; female athletes receiving high doses of anabolic androgenic steroids experience notable regression of breast tissue.[34] Furthermore, there seems to be an inverse relationship between breast cell proliferation and serum testosterone levels.[35] On the other hand, aromatase is abundantly present in various components of breast tissue, including parenchymal, adipose and stromal cells; considering that androgens undergo aromatisation to oestrogens, they may exert indirect proliferative effects.[36] However, studies exploring the effects of testosterone on the breast are limited by unreliable testosterone assays and challenges in measuring intracrine, autocrine and endocrine aromatisation of testosterone to oestrogen.[37]

Clinical data in general population. Arthur *et al* evaluated total testosterone and sex hormone-binding globulin (SHBG) with the risk of developing BC in postmenopausal women.[38] Total testosterone was associated with a higher BC risk (HR: 1.44; 95% CI 1.18 to 1.76); on the contrary, SHBG levels were inversely correlated with it (HR: 0.74, 95% CI: 0.59 to 0.92). In a Mendelian randomisation study, an increased BC risk with higher levels of total and bioavailable testosterone was observed.[39] Similarly, another Mendelian randomisation study assessed the role of different biomarkers in BC risk showing that testosterone levels correlated with an increased BC risk (OR 1.12; 95% CI 1.04 to 1.21).[40] Furthermore, Li *et al* demonstrated a positive relation between total testosterone and bioavailable testosterone with BC risk (OR 1.17; 95% CI 1.08 to 1.27 and 1.14; 95% CI 1.06 to 1.22, respectively).[41] Another Mendelian randomisation was conducted to investigate the impact of testosterone and SHBG over cancer risk: total testosterone concentration was associated with BC in women (OR 1.14;

Table 3 Discussion points on cancer risk and cancer screening advice for TGD people undergoing GAHT and/or gender-affirming surgery (GAS)

(A) Transgender women and transfeminine individuals		
Tumour	**What to discuss**	**Screening advice**
Breast cancer (BC)	Possible increased risk of BC due to feminising GAHT (but still lower than the risk of BC in cisgender women). Investigate other risk factors for BC, such as family history, known *BRCA1/BRCA2* and other mutation or obesity. Refer eligible patients to genetic counselling prior to start of GAHT and/or GAS.	BC screening recommendations according to local guidelines for cisgender women.
Prostate cancer	The risk of prostate cancer is reduced but not eliminated with feminising GAS as it typically does not involve prostatectomy.	Prostate cancer screening according to local guidelines for cisgender men with the exception that serum levels of PSA of 1 ng/mL should be considered the upper limit of normal in individuals under GAHT.
Meningioma	Possible increased risk of meningioma in individuals on CPA in high doses.	—
Anal cancer	Recommend HPV vaccination according to local guidelines. Anal HPV infection is correlated with engaging in anal intercourse (whether receptive or insertive) and number of sexual partners.	Transgender individuals who engage in anal intercourse and/or who live with HIV should be considered for annual anal Pap test.
Neovaginal cancer	Cancer may occur in neovagina (HPV related or not).	Annual gynaecological visit
Transgender men and transmasculine individuals		
Tumour	**What to discuss**	**Screening advice**
BC	BC risk is decreased after gender-affirming mastectomy but not eliminated, as breast tissue often remains. Investigate other risk factors for BC, such as family history, known *BRCA1/BRCA2* and other mutation or obesity. Refer eligible patients to genetic counselling prior to start of GAHT and/or GAS.	For transmasculine individuals who did not undergo mastectomy: BC screening according to local guidelines for cisgender women.
		For transmasculine individuals who undergo mastectomy: if breast tissue remains, consider the same BC screening as outlined in local guidelines for cisgender women. Otherwise, consider yearly chest and axillary examinations.
Endometrial cancer	No data about possible carcinogenic effects of masculinising GAHT on endometrium. Promptly consult the clinician if vaginal bleeding or discharge persists for 6 months after starting testosterone therapy.	Annual gynaecological visit according to local guidelines for cisgender women.

Continued

Table 3 Continued

Transgender men and transmasculine individuals		
Tumour	**What to discuss**	**Screening advice**
Cervical cancer	Recommend HPV vaccination according to local guidelines. Lack of adherence to cervical screening programmes is correlated with an increased risk of cervical cancer.	All transgender individuals with a cervix in situ should be screened for cervical cancer, according to the local guidelines for cisgender women. Testosterone therapy may cause vaginal atrophy and shrinkage, leading to challenges in speculum insertion and cervical sampling collection. Consider screening with self-collected HPV-DNA testing when possible.
Ovarian cancer	Decisions regarding preventative ovariectomies at the time of GAS should be individualised, considering the potential long-term effects of surgical menopause. In high-risk populations, such as individuals with pathogenic variants of *BRCA1* or *BRCA2* gene mutations, risk-reducing salpingo-oophorectomy is recommended.	Annual gynaecological visit according to local guidelines for cisgender women.
Anal cancer	Recommend HPV vaccination according to local guidelines. Anal HPV infection is correlated with engaging in anal intercourse (whether receptive or insertive) and number of sexual partners.	Transgender individuals who engage in anal intercourse and/or who live with HIV should be considered for annual anal Pap test.

CPA, cyproterone acetate; GAHT, gender-affirming hormone therapy; GAS, Gender Affirming Surgery; HPV, human papillomavirus; PSA, prostate-specific antigen; TGD, transgender and gender-diverse.

95% CI 1.06 to 1.23), while a high concentration of SHBG in men was correlated with lower BC risk (OR 0.94; 95% CI 0.89 to 1.00).[42]

Clinical data in transgender population. Regarding transgender people, a retrospective cohort study conducted by de Blok *et al* showed that 17 out of 2260 transgender women had a diagnosis of at least one BC (15 invasive BC), recording a lower overall risk compared with cisgender women (0.3; 95% CI 0.2 to 0.4).[33] On the other hand, 4 out of 1229 transgender men developed invasive BC, with a substantially higher risk of incidence (58.9; 95% CI 18.7 to 142.2) compared with cisgender men. However, no data on GAHT were available. A recent systematic review about the impact of exogenous testosterone on BC risk in transmasculine people showed that, overall, transmasculine people had a lower incidence of BC compared with cisgender women, but they had a younger median age of presentation (47–50 vs 65–74 years).[43] Of note, these studies did not consistently specify whether cancer diagnosis occurred before or after gender-affirming mastectomy procedures.

Oestrogens and prostate cancer

Biological background. During embryogenesis, the activity of ER-β influences the prostate gland development, promoting organ growth in the early phase of life. Conversely, ER-α acts mainly in the postnatal period.[44] Moreover, ER-α may stimulate proliferation and epithelial–mesenchymal transition, while ER-β may inhibit proliferation and foster cell differentiation.[45] The expression of ER in prostate cancer increases from low-grade to high-grade carcinomas and is the highest in castration-resistant tumours and metastatic lesions.[46] In vitro, agonists of ERs activate a molecular response mediated by PI3K/AKT that confers a proliferative and invasive phenotype.[47] Additional preclinical findings showed that oestrogens could induce cancer transformation in human prostatic stem cells if supported by an androgen-rich environment.[48] Moreover, other animal models support the hypothesis that prostate carcinogenesis requires the aromatisation of androgens to oestrogens.[49]

Clinical data in transgender population. The study by Silverberg *et al* found that transgender women had a reduced incidence of prostate tumours compared with a cohort of patients extracted from the Surveillance, Epidemiology and End Results registry (HR 0.4; 95% CI: 0.2 to 0.9).[50] The study did not report data on the use of GAHT, but the authors claimed a probable protective role of oestrogens. In a study conducted in the Netherlands on 2306

transgender women undergoing GAHT and who underwent bilateral orchiectomy, an incidence rate of prostate cancer of 0.04% was found.[51] It was lower than in the general population of the USA. The age of onset was in the sixth decade and the tumour was in a high-risk and advanced stage at diagnosis. Another Dutch cohort study on 2281 transgender women on GAHT showed a lower risk of prostate adenocarcinoma than cisgender men, suggesting a protective role of androgen deprivation.[52] In a further study conducted in the USA on 805 TGD individuals, a lower incidence of prostate cancer compared with the general population was reported (proportional incidence ratio (PIR) 0.2; 95% CI 0.2 to 0.4), without any reference to the sex assigned at birth and to GAHT.[53] Another cohort study conducted on 155 transgender women with a diagnosis of prostate adenocarcinoma showed that among the 39 patients with active or previous use of oestrogens, there was a higher percentage of high-grade histologies compared with the general population (35% vs 16%).[54]

Oestrogens and testicular cancer

Biological background. The peak of ER activity in the testicles seems localised in the rete testis and the efferent ductules, with induction of tissue hyperplasia.[55] ER expression (mainly ER-β) is suppressed in determined testicular germ cell tumours, such as seminomas and embryonal cell carcinomas, while rarer tumours retain high expression levels, such as endodermal sinus tumours and teratomas.[56] An excessive oestrogen exposition by testicular tissues, from prenatal to later life phases, is one of the putative carcinogenetic mechanisms of testicular cancer.[57] Evidence suggests that oestrogens, agents with oestrogen-like activities or polymorphisms in ER, can cause the proliferation of testicular cancer in vitro and during prenatal life.[58–61] Additional studies have also highlighted the possible role of other oestrogen-responsive genes and non-genetic oestrogen-dependent cellular pathways in testicular carcinogenesis.[62 63]

Clinical data in transgender population. A study conducted in the USA on 805 TGD people reported a lower incidence of testicular cancer compared with cisgender men (PIR: 0.2, 95% CI 0.1 to 0.6), without any reference to the sex assigned at birth and to GAHT.[53] A study conducted on 3026 transgender women who did not undergo orchiectomy and on therapy with antiandrogens (cyproterone acetate (CPA)), growth hormone-releasing hormone agonists (triptorelin) and oestrogens (estradiol) showed only three cases of testicular carcinoma.[64] The authors suggested that testicular cancer risk in transgender women is comparable with the risk in cisgender men. Furthermore, a subgroup analysis with a longer follow-up period (5 years) suggested that longer exogenous oestrogen exposure does not increase testicular cancer risk. Finally, a retrospective study conducted on 2555 transgender women reported six cases of incidental findings of testicular cancer in patients who underwent bilateral orchiectomy as part of gender-affirming surgery after an average of 3.5 years of GAHT.[65]

Progestins and meningiomas

Biological background. Meningioma is the most common primary intracranial tumour, with a female-to-male ratio ranging from 2 to 3.5:1.[66] In over 90% of cases, it expresses progesterone receptors.[67]

Clinical data in general population. Several retrospective and prospective cohort studies demonstrated a strong correlation between CPA and meningioma.[68–72] This relation has been shown to be dependent by the dose and by the cumulative use.[73 74]

Clinical data in transgender population. Feminising GAHT regimens, in some cases and mostly in the past, might include a significantly higher dosage of CPA compared with the contraceptive dosage used among cisgender women. A systematic review focused specifically on CPA and transgender women.[75] The authors included 12 case reports in their analysis. The most prescribed CPA dosages were either 50 or 100 mg/day, with only two patients receiving 200 mg/day or 10 mg/day, and a median treatment duration of 9.5 years (IQR 6.5–17.5 years). Seven transgender women were diagnosed with multiple meningiomas. In 2018, Nota *et al* focused on benign brain tumour incidence in a cohort of 2555 transgender women undergoing GAHT, showing a higher incidence rate compared with cisgender men (standardised incidence ratio (SIR) 11.9, 95% CI 5.5 to 22.7) and cisgender women (SIR 4.1, 95% CI 1.9 to 7.7).[76]

Testosterone and endometrial cancer

Biological background. Traditionally, exogenous androgens were believed to elevate the risk of endometrial hyperplasia and cancer due to the aromatisation of testosterone into oestrogen, especially in postmenopausal women. Furthermore, the presence of androgen receptors (ARs) in the endometrial epithelium and stroma suggests a possible direct proliferative influence of androgens on endometrial glands or through upregulation of growth factor receptors in the stromal compartment.[77]

Clinical data in general population. In cisgender women, a hyperandrogenic state, such as polycystic ovarian syndrome, and elevated blood concentrations of free testosterone have been linked to an increased risk of endometrial cancer.[41 78] However, transdermal testosterone administered in clinical trials for the treatment of sexual dysfunction in postmenopausal women did not show an increased risk of endometrial cancer.[79 80]

Clinical data in transgender population. Despite the high prevalence of amenorrhoea in transgender men undergoing GAHT, endometrial atrophy was observed in less than half of premenopausal patients at the time of hysterectomy.[81–83] Retrospective studies have shown that proliferative endometrium was present in 15–64.9% of cases, suggesting that testosterone may fail to induce endometrial atrophy in a significant portion of patients. The relative hyperoestrogenism, resulting from androgen

conversion, unopposed by progesterone, theoretically increases the risk of endometrial hyperplasia and cancer.

Testosterone and ovarian cancer

Biological background. ARs are typically expressed in the epithelial cells of the ovarian surface and in the fallopian tubes.[84] Preclinical studies have compellingly demonstrated that androgens play a crucial role in the genesis and progression of ovarian cancer, both directly through the activation of receptor signalling and indirectly as oestrogen precursors.[85 86] Elevated androgen concentrations induce ovarian tumorigenesis and progression by mediating the transcriptional regulation of various target genes, including interleukins and growth factors.

Clinical data in general population. The most recent analysis of the EPIC trial revealed a positive correlation between androgen concentrations, specifically dehydroepiandrosterone and androstenedione, and the risk of low-grade and type I ovarian cancer.[87] Conversely, a potential protective effect of free testosterone concentrations against high-grade ovarian cancer was observed in a recent Mendelian randomisation study.[88] Nevertheless, conflicting results have emerged from studies involving typical hyperandrogenic states such as polycystic ovarian syndrome or the use of exogenous testosterone in cisgender female populations.[89 90] These inconsistencies may be attributed to small sample sizes, the heterogeneity of exposures and outcomes, and the presence of uncontrolled confounding factors. Additionally, concerns have been raised regarding the potential link between testosterone use and an increased risk of endometrioid and mucinous tumours, particularly in endometriosis-associated cancers.[91]

Clinical data in transgender population. There are limited data available on the potential association between GAHT using testosterone and an elevated risk of ovarian cancer, as no retrospective studies have been conducted to the best of our knowledge.

Sex hormones and melanoma

Biological background and clinical data in both the general population and transgender population regarding the possible correlations between sex hormones and melanoma are described in online supplemental appendix 1.

DISCUSSION

GAHT frequently serves as an essential, life-saving treatment for TGD individuals.[92] Therefore, in the event of a demonstrated direct correlation between GAHT and increased cancer risk or an interaction between GAHT and cancer care, essential shared decision-making discussions must take place between oncology practitioners and patients, even though such instances are rare in clinical practice.[93] On the other hand, dismissing any clinically relevant association between GAHT and cancer risk would put an end to the phenomenon, rooted in a transphobic society, where TGD individuals frequently perceive their cancer diagnoses as a consequence of their gender identity and hormonal therapy.

The correlation between exogenous oestrogens and BC risk in transgender women is reasonably acceptable. Such a risk has been demonstrated for the use of exogenous oestrogens for contraception and control of menopausal symptoms in cisgender women. An important aspect to highlight is that most retrospective cohort studies included transgender women undergoing old regimens of GAHT with synthetic oestrogens such as ethinylestradiol or conjugated oestrogens. However, whereas available data impose clinicians to warn transfeminine individuals interested in starting GAHT about the possible increased BC risk, it is paramount to underline how the risk remains significantly lower than that of cisgender women. BC screening must be offered to all TGD individuals undergoing GAHT with oestrogens. Additionally, considering other risk factors for BC in transgender women, such as family history, *BRCA1/BRCA2* and other mutations, obesity, or androgen insufficiency, is essential for comprehensive oncological care and counselling.[94] With regard to the risk of androgens on BC development in transgender men, more data are needed.[95] By now, it is suggested that transgender men undergo screening programmes as per cisgender women since BC can occur after GAHT and gender-affirming mastectomy.[96]

The lower risk of prostate adenocarcinoma in transgender women compared with cisgender men seems to be related mostly to androgen deprivation, as suggested by the 'saturation model' of Morgentaler and Traish.[97] According to this hypothesis, prostate tissue growth is limited by androgen serum concentrations below a specific saturation threshold. Beyond this critical point, concentrations above it do not contribute to any additional biological effects. In adult transgender women who have not undergone orchidectomy, androgen deprivation is typically achieved using CPA or spironolactone. However, in some cases, gonadotropin-releasing hormone analogues or bicalutamide are employed.[98] More research is needed to explore the possible selection of aggressive histotypes as a consequence of antiandrogen use. Regarding the use of oestrogens, its impact on prostate cancer remains uncertain due to conflicting preclinical data. Additionally, the low incidence of prostate cancer in this population might also be linked to potential underdiagnosis because of reduced screening practices.

CPA is not approved for use in the USA, but it is used in several countries worldwide for different indications, including feminising GAHT. Notably, the correlation between CPA and meningiomas has been observed in cohorts of patients taking high doses of CPA. Recently, the European Medicines Agency imposed restrictions on the use of CPA in doses exceeding 10 mg/day. Further research is necessary to determine whether this dosage limit is safe for transgender women over an extended period.

Testosterone is a preferred androgen used in the masculinisation of GAHT, with reported effects on sex-dependent

tissues and organs. Notably, only 25% of TGD individuals in Europe, and 27% in the USA, reported having undergone any kind of gender-affirming surgery.[99 100] In the USA, only 8% of individuals designated female on their original birth certificate have undergone hysterectomy, and only half of the respondents expressed a desire for it in the future. This is noteworthy considering the significantly higher percentage of TGD individuals undergoing testosterone therapy as part of GAHT. Consequently, the uteruses of these individuals will be exposed to the long-term effects of testosterone. To date, there is no defined evidence demonstrating an increased risk of endometrial or ovarian cancer in transmasculine individuals because of the paucity of clinical data. However, TGD individuals with an intact uterus should be advised to promptly consult their clinician if vaginal bleeding or discharge persists for 6 months after starting testosterone therapy to rule out malignancy.

Current guidelines do not advocate for ovarian cancer screening procedures in average-risk transgender men, mirroring recommendations for cisgender women, including in the setting of high risk, due to the absence of an effective surveillance strategy for early detection. Decisions regarding preventative ovariectomies at the time of gender-affirming surgery should be individualised, considering the potential long-term effects of surgical menopause and the overall well-being of the patient. In high-risk populations, such as individuals with pathogenic variants of *BRCA1* or *BRCA2* gene mutations, risk-reducing salpingo-oophorectomy is recommended. It should be similarly discussed in TGD men.

In a landscape such as this, deficient in data and substantial prospective studies, clinicians must be prepared to propose personalised screening or treatment strategies. In this respect, effective communication and the avoidance of paternalistic and stigmatising attitudes are crucial. According to demographic data, it is likely that in the future, healthcare providers involved in cancer care will encounter an increasing number of TGD patients. There is an urgent and essential need for training campaigns on these issues at every level, starting from medical schools up to specialised continuing education courses.

CONCLUSIONS

The positive or negative correlations between GAHT and cancer risk remain poorly defined. It is imperative to conduct long-term prospective, observational studies to provide conclusive answers. The collection of data encompassing gender identity, sexual anatomy, hormonal profiles and GAHT status within cancer registries and clinical records is of paramount importance. An effective strategy to enrich databases and deepen our comprehension of this subject entails actively involving representatives from organisations and the TGD community in research initiatives. Additionally, fostering collaborations between cancer care providers and specialists in TGD medicine, such as endocrinologists, is crucial. Urgent efforts are required to overcome barriers and enhance cancer prevention and care within this population.

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