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Title:
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Date:
2018-12-01

Citation:
McFarlane, T., Zajac, J. D. & Cheung, A. S. (2018). Gender-affirming hormone therapy and the risk of sex hormone-dependent tumours in transgender individuals—A systematic review. Clinical Endocrinology, 89 (6), pp.700-711. https://doi.org/10.1111/cen.13835.

Persistent Link:
https://hdl.handle.net/11343/284360

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Article type : 5 Unsolicited Review

Gender-affirming hormone therapy and the risk of sex hormone-dependent tumours in transgender individuals – a systematic review.

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Short running title: Transgender hormone therapy and tumours

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Keywords (MeSH): Transgender Persons; Neoplasms; Hormones; Gender Dysphoria; Testosterone; Estradiol; Review.

Acknowledgements: Ada S. Cheung is supported by a National Health and Medical Research Council of Australia (NHMRC) Early Career Fellowship (ID 1143333).

Conflicts of interest: The authors have nothing to declare.

Word Count: Abstract 245, Manuscript 3828, References 68, Tables 3, Figures 1

ABSTRACT/SUMMARY

Background: Cancers are a leading cause of death worldwide and transgender individuals are no exception. The effects of gender-affirming hormone therapy (GAHT) on sex hormone-

dependent tumours are unclear. Therefore, this review seeks to determine if tumour risk in transgender individuals differs from the general population, to guide clinical screening recommendations.

Methods: We performed a systematic review based on the PRISMA guidelines. MEDLINE, Embase and PsycINFO databases were searched for studies examining tumour incidence, prevalence or cancer-related mortality in transgender individuals. All English peer-reviewed publications were included if histological type and temporal relation to GAHT were reported. Case reports were included if there were ≥2 cases of the same histological type.

Results: The search strategy identified 307 studies. Excluding those that did not meet inclusion criteria, 43 studies (7 cohort studies, 2 cross-sectional studies and 34 case reports) were reviewed. Retrospective cohort studies suggest no increase in risk of tumour development in transgender individuals receiving GAHT compared to the general population. Notably, the mean ages of cohorts were young and were treated with GAHT for insufficient durations to assess tumour risk. Case reports raise potential associations between high dose estradiol and anti-androgen therapy with prolactinoma and meningioma respectively.

Conclusions: Further longitudinal studies are required to assess the risk of GAHT and hormone-dependent tumour development. Until further evidence is available, tumour screening should be based on guidelines for the general population and the presence of organs in transgender individuals rather than gender identity or hormonal therapy status.

1. INTRODUCTION

Cancers are a leading cause of death worldwide and screening is an important part of clinical practice to reduce morbidity and mortality through early detection. Many benign and malignant tumours are known to be sex hormone-dependent, however it is unclear whether the risk of these neoplasms is different amongst transgender individuals undergoing gender-affirming hormone therapy (GAHT)[1,2]. This is important to investigate, given that such hormone therapy is typically started at a young age and often continues lifelong[3]. Uptake of screening is also a major barrier and, given a limited evidence base in transgender individuals as well as frequent dysphoria to secondary sexual characteristics, complacency to undertake cancer screening may arise[2].

According to the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders, transgender individuals are those who persistently identify with a gender different from their

birth-assigned gender. This may be associated with gender dysphoria, which refers to the distress caused by the incongruence between one's experienced and one's assigned gender. Many individuals with gender dysphoria undergo treatment with GAHT (often termed cross-sex hormone therapy) to induce physical masculinising or feminising changes, to align their physical appearance with their inner gender identity. For transgender individuals transitioning from female-to-male, this typically consists of testosterone therapy and for individuals transitioning from male-to-female, estradiol with or without an anti-androgen agent are commonly prescribed[4,5]. Whilst there are no placebo-controlled randomised controlled trials for ethical reasons, observational studies suggest that GAHT is associated with significantly improved quality of life, reduced anxiety and depression and lower suicidality[6]. There is a lack of formal epidemiological data on the prevalence or incidence of transgenderism across any age group, however estimates are that between 0.5 – 1.3% of the population identify as transgender and the demand for transgender health services is rising[7].

Many cancers, such as breast or prostate, are sex hormone-dependent. Other typically benign, but potentially malignant tumours, in particular meningiomas and prolactinomas, display a significant difference in gender-specific prevalence, raising the question as to the role of sex hormones in their pathogenesis[8]. As many as 31 different organ-specific malignancies have been found to express sex hormone receptors[9]. However, there is little data available on the effect of GAHT on the development of hormone-dependent neoplasms amongst transgender individuals.

Whilst there is insufficient evidence, international guidelines published by the World Professional Association for Transgender Health in 2012 and the Endocrine Society in 2017 suggest estrogens pose a moderate risk of developing prolactinoma and breast cancer, with testosterone therapy associated with a moderate risk of breast and endometrial cancer[4,5]. Given the paucity of evidence, current cancer and tumour screening guidelines for transgender individuals on GAHT are based on the recommendations for individuals of the corresponding birth-assigned gender[4].

Evidence also suggests that a lack of knowledge, and potentially discrimination from the part of the medical profession, can result in suboptimal cancer screening for transgender individuals[2]. Further research into the risk of tumour development in transgender individuals is thus needed to provide better guidance regarding cancer prevention and screening in this

population. As such, we aimed to assess the risk of GAHT on tumour development in transgender individuals in order to guide clinical screening recommendations.

2. METHODS

Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) reporting guidelines were used in the development of this systematic review[10].

2.1. Eligibility criteria

All levels of evidence were included in this review, provided that the report was published in a peer-reviewed journal and in the English language.

No randomised controlled trials or prospective observational studies were identified. All included studies were observational retrospective cohort studies and one-time cross-sectional studies, as well as case reports and case series.

Observational studies (i.e. cohort and cross-sectional studies) were eligible for this review if enrolled participants were transgender and had commenced GAHT. Participants must have already been diagnosed with gender dysphoria according to the Diagnostic and Statistical Manual of Mental Disorders or an equivalent diagnosis according to the World Health Organisation International Classification of Diseases. Participants must have commenced GAHT, consisting of a minimum of exogenous estrogen (for male-to-female transgender individuals) or testosterone (for female-to-male transgender individuals) therapy. All forms of testosterone- or estrogen-containing GAHT were accepted, regardless of route of administration, dosage, dosing frequency or the presence of additional exogenous hormones (e.g. antiandrogens, progestins). Furthermore, only studies in which the diagnosis of a neoplasm was made subsequent to GAHT commencement were included. Both benign and malignant neoplasms were included.

Cases studies were eligible: if hormone therapy definitively preceded tumour diagnosis; if the duration and type of hormone therapy was stated; and if the age at the time of diagnosis was known. There were several isolated case reports describing tumour development in an individual receiving GAHT, however the significance of this was unclear. Therefore, we

required two or more case reports per histological tumour type for these to be included in the review.

2.2. Information sources and search strateg

The first author consulted an expert reference librarian to design and conduct the electronic database search with input from the last author. Eligible studies were identified by searching the following electronic databases from inception to 1st April 2018: Ovid MEDLINE®, Ovid PsycINFO® and Embase®. Controlled vocabulary supplemented with keywords were used to define the population (transgender individuals), intervention (GAHT) and outcome (neoplasm).

Our search of Ovid MEDLINE® database consisted of the following combination of keywords and Medical Subject Headings (MeSH) terms and keywords: (“transsexualism” (all terms) OR “transgender persons” (all terms) OR “gender dysphoria” (all terms) OR “gender identity” (all terms) OR “sexual and gender disorders” (all terms)) AND ("cross-sex hormone therapy" (keyword) OR “hormone replacement therapy” (all terms) OR “testosterone” (all terms) OR “estrogens” (all terms) OR “estradiol” (all terms) OR “cyproterone” (all terms) OR “spironolactone” (all terms)) AND “neoplasms” (all terms).

An PsycINFO® database search consisted of the following combination of keywords and Thesaurus of Psychological Index Terms: ((“transgender” (all terms) OR “transsexualism” (all terms) OR “sex change” (all terms) OR “gender identity” (all terms) OR “gender identity disorder” (all terms)) AND ((“sex hormones” (all terms) OR “estrogens” (all terms) OR “estradiol” (all terms) OR “cross-sex hormone therapy” (keyword) OR "hormone therapy" (all terms) OR “testosterone” (all terms) OR "estrogens" (all terms) OR "estradiol" (all terms) OR “antiandrogens” (all terms) OR "androgens" (all terms)) AND “neoplasms” (all terms).

Finally, our search of the Embase® database consisted of the following Emtree terms and keywords: (“transgender” (all terms) OR “transsexual” (keyword) OR “gender dysphoria” (all terms) OR “gender identity” (all terms) OR "sex transformation" (all terms)) AND (“cross-sex hormone therapy.m.p.” OR "hormonal therapy" (all terms) OR “testosterone” (all terms) OR “estrogen” (all terms) OR “estradiol” OR “antiandrogen” (all terms) OR

“cyproterone acetate” (all terms) OR "cyproterone" (all terms) OR "spironolactone"(all terms)) AND “neoplasms” (all terms).

Bibliographies of identified studies were also consulted to identify further articles.

2.3. Study selection

Our full search strategy is outlined in Figure 1.

2.4. Data collection

Data was collected via an electronic form to capture the data items listed below.

2.5. Data items

2.5.1. Participant characteristics

Age, birth-assigned sex, gender identity, GAHT duration.

2.5.2. Study characteristics

Study design, recruitment method, inclusion/exclusion criteria, location, sample size.

2.5.3. Control or comparison population

Recruitment method, setting, age, birth-assigned sex.

2.5.4. Outcomes

Description of context in which tumour was diagnosed, histological type, immunohistochemistry features of tumour such as sex hormone receptor staining, other pertinent neoplasm-specific serum investigations.

2.5.5. Statistical results

Adjusted and unadjusted prevalence or incidence estimates and measures of variability, number of patients.

2.6. Summary measures

For cohort studies, statistically significant ($p < 0.05$) differences in neoplasm incidence or mortality between transgender and comparison samples were analysed. The summary measures were incidence rate, standardised incidence ratio or standardised mortality ratio.

For cross-sectional studies, statistically significant ($p < 0.05$) differences in neoplasm prevalence between transgender and comparison samples were analysed.

2.7. Synthesis of results

Data was collated and outcome variables were grouped as follows: standardised incidence ratio, incidence, standardised mortality ratio, prevalence.

3. RESULTS

268 studies were identified using MEDLINE, Embase and PsycINFO and 39 additional studies were identified from bibliographic references. After screening title and abstracts, 76 duplicate results were removed, 161 were removed due to lack of relevance, 10 for being in a language other than English and 3 for not being published in a peer-reviewed journal. A further 2 cohort studies and 7 case studies were excluded as no data was available regarding the temporal duration of the hormone therapy, age at diagnosis and details regarding whether the cancer predated the commencement of hormone therapy. Of the 48 remaining studies, there were 7 retrospective cohort studies, 2 cross-sectional studies (Table 1) and 39 case reports (Table 2 and 3).

3.1. Retrospective Cohort Studies

All 7 of the cohort studies identified in this review were retrospective and are summarised in Table 1[11-16]. Other than one report utilising the US SEER database, all published studies derive from the VU Hospital in Amsterdam, Netherlands. Of these, 4 studies focused on the incidence of a specific organ-related cancer (breast and prostate cancer) in this population[11,13,14,17]. The remaining 3 articles focused on causes of mortality or morbidity in individuals receiving GAHT, of which cancer was a subcategory[12,15,16]. However, only two studies included individuals who had been on GAHT for over 10 years and both studies analysed the same database[11,13]. None found a significant association with hormone therapy.

The remaining 3 cohort studies examined the association between GAHT and cancer-related mortality12,15,16. In both their 1989 and 2011 studies, Asscheman and colleagues found no significant difference between cancer-related mortality in hormone-treated transgender individuals and the general Dutch population when stratified for age and birth-assigned

gender 15,16. Conversely, van Kesteren and colleagues found a lower cancer-related standardised mortality ratio for a population of 815 hormone-treated male-to-female participants.

3.2. Cross-sectional studies

Two cross-sectional studies have been published based on data from a well-established gender clinic in Belgium[18,19] (Table 1). The initial report of 100 transgender individuals found no cancer diagnoses after mean of 10 years of hormone therapy[19]. However, when additional individuals were assessed (138 female-to-male mean duration 6.0 years on hormone therapy and 214 male-to-female individuals mean duration 7.0 years on hormone therapy) several cancers were identified only in the male-to-female group which was not significantly different to the male general population. No cancers were identified in the female-to-male group[18].

3.2. Case reports

A large number of case reports were identified which reported tumour development following the commencement of GAHT. Case reports in female-to-male individuals are summarised in Table 2. The only histological type reported on greater than one occasion after commencement of testosterone therapy was breast cancer. Mean age of the individuals was 39 years and all cases were ductal carcinoma of the breast with variable hormone receptor status. Case reports of tumour development in male-to-female individuals on estradiol therapy are summarised in Table 3. Breast cancer was reported in 12 cases with mean age of 52 years on hormone therapy for mean of 16 years. Tumour histological type and hormone receptor status were variable. Prostate adenocarcinoma was also reported, with mean age of 66 years. Multiple case reports have been published describing meningioma and prolactinoma development following estradiol alone or estradiol and cyproterone acetate therapy, predominantly affecting individuals over the age of 40 years.

DISCUSSION

This is the first systematic review assessing the risk of sex hormone-dependent tumours in transgender individuals receiving gender-affirming hormone therapy and it demonstrates a lack of data. As high-level evidence is not feasible, most of the evidence arises from retrospective cohort studies which, whilst the best evidence-to-date, describe cohorts which

are relatively young and have received on average insufficient durations of hormone therapy to meaningfully interpret the risk of tumour development.

4.1. Retrospective Cohort Studies

Cohort studies summarised in Table 1 reveal that the most common cancer subtypes identified are not cancers commonly known to be hormone-dependent, unlike those featured in the case reports identified in this review. This likely reflects the fact that the absolute risk of common cancers still outweighs the smaller risk of cancers that may be more specific to those on exogenous hormone therapy. Indeed, the all-cause cancer mortality data seems to be relatively closely aligned with population statistics in terms of which malignancies are most likely to cause death[20].

Whilst undoubtedly the best evidence available to date, the ability to derive meaningful conclusions from the cohort studies is affected by a number of inherent factors. Firstly, a small number of cancer cases were identified per study (rarely numbering greater than 10), which inevitably leads to large confidence intervals and suggests insufficient person-years to analyse these outcomes.

Secondly, mean time on GAHT is typically relatively short. In the largest US cohort of 2645 transgender individuals assessing breast cancer standardised incidence, mean time on hormonal therapy was only 7.6 years[14]. Multiple large-scale epidemiological studies have found that breast cancer risk increases with increasing duration of hormone replacement therapy in postmenopausal women and is highest after 5 or more years of exposure[21]. Compounding the insufficient duration of hormone therapy exposure, the mean age of the cohorts is typically young. As breast cancer has a median age of diagnosis of 61, even in the study with the longest hormone exposure of mean 21 years, this is insufficient to evaluate breast cancer risk in individuals who commenced therapy at mean age of 29[13].

Thirdly, retrospective cohort studies lack a true control population. As a result, confounding variables known to be important for cancer incidence are either not addressed or only controlled via post-hoc statistical methods, rather than robust study design. In the largest cohort study assessing all-cause mortality in transgender individuals, lung cancer accounted for nearly 50% of the cancer-related deaths. While smoking status was taken into account as

a covariate in the calculation of statistical significance, it is unclear as to whether smoking pack-year history was considered and thus the extent to which this result is a product of longer smoking history in this population[15]. In studies evaluating breast cancer, important confounding factors relevant to female-to-male participants such as menarche, menopause status or parity are not addressed[13,14].

Overall, at present, there are insufficient data to support a significant difference in cancer risk between transgender individuals on GAHT and the general population.

4.2. Cross-sectional studies

Two cross-sectional surveys from the Ghent gender clinic have demonstrated mixed results[18,19]. An initial survey of 100 individuals did not identify any cancer diagnoses, however a later cross-sectional comparison of over 300 transgender individuals with an age- and gender-matched control population revealed rates of cancer similar to the general population. Rates of cancer diagnoses may appear reassuring, however, notably these were relatively young cohorts and longitudinal studies of greater duration are needed.

4.2. Case reports

The internal validity and generalisability of case reports are inherently limited (summarised in Table 2). Inevitably, publication bias exists, as the types of cancers that have been reported are those that either are known to be sex hormone-dependent, to express sex hormone receptors or to have different prevalence rates amongst males and females. Despite this, published cases highlight some important hypotheses regarding how hormone therapy may affect certain malignancies.

4.2.1. Case reports of tumours in male-to-female individuals

Breast cancer

Multiple studies have demonstrated that estrogen and progesterone can stimulate breast cancer growth in females mediated via estrogen receptors (ER) and progesterone receptors (PR)[22]. Less is known about the role of sex hormones in the pathogenesis of breast cancer in birth-assigned males, although it has been observed that conditions that can cause high estrogen levels (e.g. obesity) have been associated with increased breast cancer in this population[13]. Several cases of male-to-female individuals diagnosed with breast cancer have

been reported. As in the general female population, the overwhelming majority were invasive ductal carcinomas[23]. However, the cases are not homogenous in terms of their ER/PR expression, thus it is unclear as to the role of sex hormones in its pathogenesis.

Prostate cancer

Prostate cancer is exquisitely responsive to androgens and androgen deprivation has been used therapeutically for many decades[24]. Consistent with exogenous estrogen or progesterone therapy, all cases reported of male-to-female individuals with prostate cancer have serum testosterone in the castrate range. Whether exogenous estrogen therapy had any direct role in tumour growth is unclear. Estrogen does not seem to have a pro-carcinogenic effect on pre-existing prostate cancer, despite being associated with down-regulation of the antiproliferative β isoform of ER[25]. Furthermore, a review of 18 prospective studies found no association between the level of endogenous estradiol and prostate cancer risk[26].

In the general population, prostate cancer that progresses despite medical castration, termed castration-resistant prostate cancer, signifies advanced disease with worse prognosis[24]. Male-to-female individuals who present with clinical symptoms of prostate cancer represent a small subgroup of individuals with advanced prostate cancer who develop progression in an androgen-deprived environment. Notably, the mean age of male-to-female individuals with prostate cancer reported in the literature are relatively young and may represent individuals with risk factors for prostate cancer development, such as a genetic predisposition. Whilst data is lacking, there are likely many undiagnosed cases of low-grade prostate cancer that remain subclinical due to feminising hormone therapy and anti-androgen treatments in male-to-female individuals. Development of a male-to-female transgender specific prostate-specific antigen reference range (which is likely much lower than the general male population) may be a useful strategy to aid interpretation of screening results.

Meningioma

High-dose cyproterone acetate is also a feature of the majority of meningioma case reports in male-to-female individuals. An association between high-dose cyproterone (defined as >50mg/day) and meningioma risk in the general population has been observed[27]. In the published case reports ER and PR status varies and the mechanism by which cyproterone acetate may contribute to meningioma development is unclear. Notably, most meningiomas

in the general population express PR (with more variable expression of ER)[28] and the progestogenic effect of cyproterone may well play a role.

Prolactinoma

Both exogenous estrogen and cyproterone acetate have been separately associated with increased serum prolactin levels in prospective cohort studies of transgender populations and estradiol has been postulated to stimulate prolactin release[29,30]. In fact, it may be the progestogenic effect of cyproterone acetate, not estrogen, that is most important[31]. In a retrospective cohort study of 38 male-to-female individuals, Nota and colleagues note that prolactin levels rose with commencement of estradiol and cyproterone acetate, but normalised to baseline levels following gonadectomy and cessation of cyproterone acetate. This was despite an unchanged postoperative estradiol dose[29]. There are no large studies linking cyproterone acetate to frank prolactinoma development. Interestingly however, approximately half of the male-to-female individuals who developed prolactinomas in published case reports were on relatively high doses of cyproterone of at least 100mg/day[32-34]. There are no case reports identifying prolactinomas in individuals on an alternative form of anti-androgen such as spironolactone. However, the role of estrogen is still unknown given that multiple cases of prolactinomas have been identified in transgender individuals on exogenous estrogen without any form of antiandrogen therapy[35,36].

4.2.2. Case reports of neoplasms in female-to-male participants

The number of case reports published about hormone-dependent neoplasm diagnoses in the female-to-male population is smaller than that of male-to-female and the majority focus on breast cancer[13,37-40].

Breast cancer

As in the general female population, the majority of breast cancers identified were ER-positive (Table 2). Seven out of these eight case reports describe individuals who are below the mean age for breast cancer diagnosis[20]. As in the case of prostate cancer in male-to-female individuals, it is unclear as to whether this reflects an inherent risk of testosterone therapy, whether testosterone has in some way selected for younger onset cases, or whether these individuals had a genetic predisposition to development of breast cancer unrelated to hormone therapy. There is conflicting data in the literature as to whether testosterone is

stimulatory towards breast cancer. Higher endogenous testosterone levels are associated with an increased risk of breast cancer in premenopausal women[41]. Moreover, despite 80% of breast cancers expressing AR, as the clinical significance is unclear this receptor is not part of standard breast cancer immunohistochemistry[42]. A prospective cohort study in the Nurses' Health Study of 1,359,323 person-years identified a significantly higher risk of breast cancer with combined estrogen and testosterone hormone replacement therapy compared to estrogen-only and untreated postmenopausal women[43]. Several studies have also examined breast histology in female-to-male breast tissue post-mastectomy. Uniformly, these have shown that testosterone induces breast changes similar to menopause, notably a marked reduction in glandular tissue and increase in fibrous tissue. However, no malignancies were found in 152 total specimens identified across three studies[44-46].

4.2.3. Summary

Many tumour subtypes express sex hormone receptors and the potential impact of long-term GAHT requires further study[9]. As basic prevalence data is already scant, there are no data to guide screening recommendations in transgender individuals. Recommendations can only be extrapolated from the general population, and as such, guidelines for tumour screening in transgender individuals receiving gender-affirming hormone therapy should be based on local screening recommendations and the presence of the organ (i.e. prostate, breast or cervix). Following genital reassignment surgery, prostate cancer can still occur in birth-assigned males who have fully transitioned to female and individual risk assessments for screening should be considered based on local guidelines. Breast cancer, potentially at a relatively young age, can also occur in birth-assigned females who have transitioned to male and clinical examination should be considered in individuals who have reached the age at which breast screening is recommended in the general population. Breast screening should also be considered in birth-assigned males on estradiol therapy as per local recommendations.

Estrogen with or without antiandrogen therapy may be associated with prolactinomas and high-dose cyproterone acetate may be associated with increased meningioma risk, but there is currently insufficient evidence to support screening. Using the lowest effective dose of estradiol and cyproterone acetate to achieve feminisation and suppress testosterone levels respectively, is a reasonable approach.

Further research is needed to clarify the effect of GAHT on tumour development, particularly consideration for longitudinal follow-up of cohorts over time. Incorporation of gender options other than male and female in existing health databases are needed to accurately identify transgender individuals and allow meaningful inferences from large epidemiological data sets[14].

Whilst considering potential long-term tumour risk, it should be noted that the benefits of gender-affirming hormonal therapy on mortality from suicide prevention and improved quality of life far outweigh any potential risk[12,15,16]. Thus, while more research in this area is needed to clarify the long-term risks of hormone therapy, clinical decisions are made on an informed, balanced risk-to-benefit consideration between treating clinicians and individuals.

5. CONCLUSIONS

Although theoretically plausible, there are no well-designed studies of sufficient duration to suggest GAHT increases the risk of hormone-dependent tumour development. Until more conclusive evidence is available, the minimum dose of hormone therapy to achieve masculinisation or feminisation is a sensible approach. Future well-designed prospective population-based studies of sufficient duration are needed to provide evidence-based guidelines for the transgender population. Until then, tumour-screening guidelines should be no different than the general population, based on the presence of organs in transgender individuals and not based on gender identity or hormonal therapy status.

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FIGURES AND TABLES

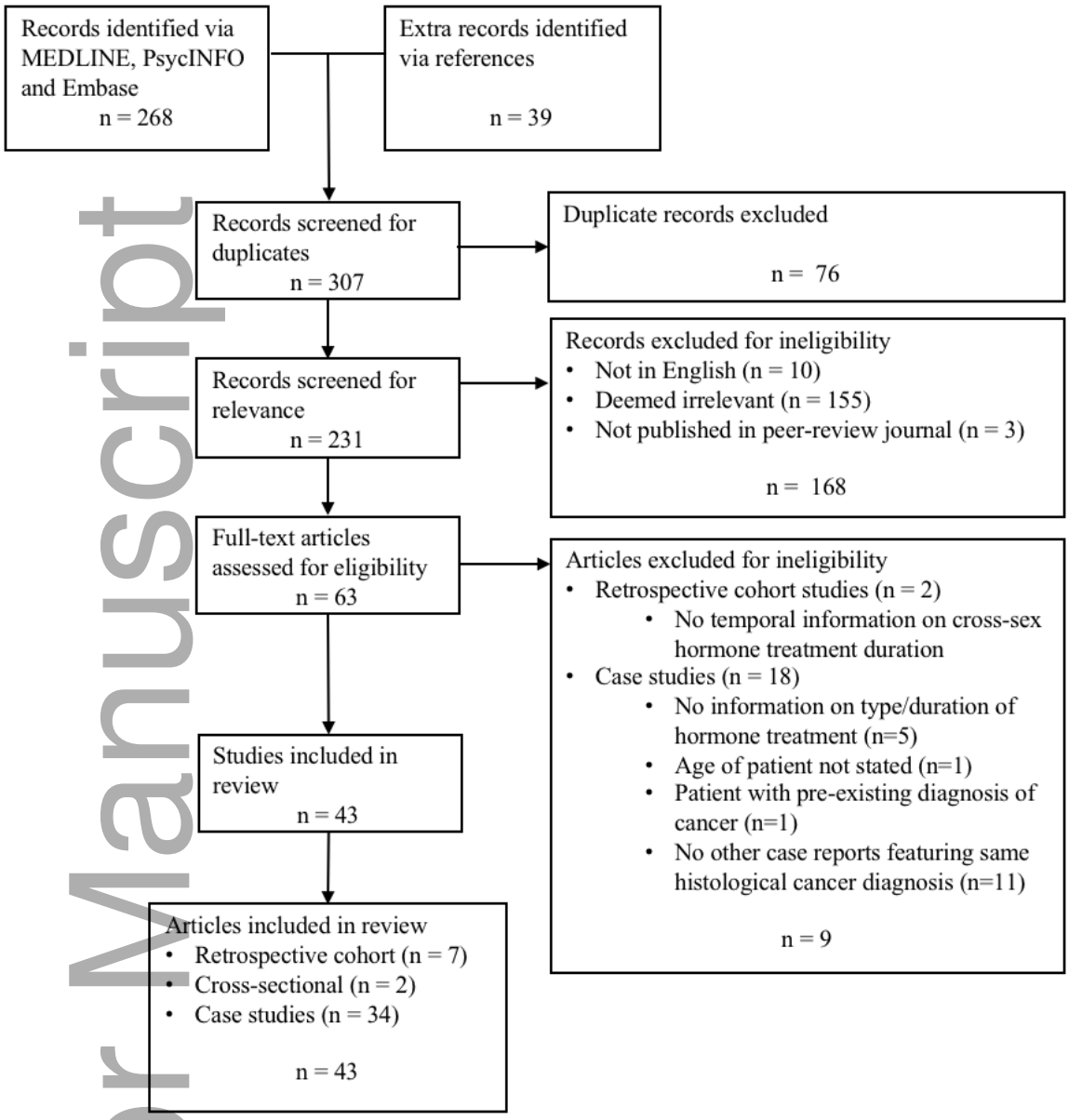

Figure 1 – Search strategy used in MEDLINE.

Table 1 – Epidemiological studies examining association between gender-affirming hormone therapy and tumours in transgender individuals

First Author, Year	Study Type	Transgender database	Comparison population	Sample Sizes	Age at Commencement of GAHT (mean years +/- SD)	Time on GAHT (mean years +/- SD)	Tumour Type	Outcome Measure	Gender	Outcome (+/- 95% CI or p-value)	Tumour Site
Brown, 2015 [14]	Retrospective cohort	Veteran's Health Affairs	SEER database (USA)	1386 MTF 1259 FTM	48.69 +/- 12.31 49.17 +/- 11.04	5.54 +/- 4.60[E] 7.60 +/- 4.86[E]	Breast	Standardised Incidence Ratio	FTM MTF	0.26 (0 – 3.69) 0	Breast (n=1) Breast (n=0)
Gooren, 2013 [13]	Retrospective cohort	VU Hospital, Amsterdam	Dutch population statistics	2,307 MTF 795 FTM	29.3 +/- 12.7 23.2 +/- 6.5	21.4 +/- 8.7 20.1 +/- 7.3	Breast	Incidence Rate	MTF FTM	4.1[A] (0.8 - 13.0) 5.9[A] (0.5 – 27.4)	Breast (n=2) Breast (n=1)
Gooren, 2014 [11]	Retrospective cohort	VU Hospital, Amsterdam	-	2,306 MTF	29.3 +/-12.7	21.4 +/- 8.7	Prostate	Incidence Rate	MTF	1.95[A]	Prostate (n=1)
Van Kesteren, 1996[17]	Retrospective cohort	VU Hospital, Amsterdam	-	9 MTF	46.8 (30-64)[C]	15.8 (13-19)[C]	Prostate	Incidence	MTF	0	Prostate (n=0)
van Kesteren, 1997 [12]	Retrospective cohort	VU Hospital, Amsterdam	Netherlands Central Bureau of Statistics	815 MTF 293 FTM	41[H] (18-86)[G] 24[H] (17-70)[G]	2 months – 41 years[F]	Any	Standardised Mortality Ratio	MTF FTM	0.46 (0.20 – 0.91) 11.49 (0.29 – 64.05)	Lung (n=3) Gastric (n=1) Leukaemia (n=1) Glioblastoma (n=1) Meningioma (n=1) Colon (n=1)
Asscheman, 1989 [16]	Retrospective cohort	VU Hospital, Amsterdam	Netherlands Central Bureau of Statistics	303 MTF 122 FTM	32 (16-67)[C] 25.4 (16-54)[C]	4.4[D] 3.6[D]	Any	Standardised Mortality Ratio	MTF FTM	0 0	Total (n=0) Total (n=0)
Asscheman, 2011 [15]	Retrospective cohort	VU Hospital, Amsterdam	Netherlands Central Bureau of Statistics	966 MTF 365 FTM	31.4 +/- 11.4 26.1 +/- 7.6	19.4 +/- 7.7 18.8 +/- 6.3	Any	Standardised Mortality Ratio	MTF FTM	0.98 (0.88 – 1.08) 0.99 (0.65 – 1.44)	Lung (n=13) Haematological (n=6) GI tract (n=3) Brain (n=2) Other (n=4) Lung (n=1) GI tract (n=2) Haematological (n=1) Other (n=1)

Wierckx, 2013 [18]	Cross-sectional	University Hospital of Ghent	Recruited from population study in Flanders	214 MTF 138 FTM	MTF: 43.7 +/- 12.6 FTM: 37.5 +/- 11.0	6.0 (3-11) 7.0 (4-13)	Any	Prevalence	MTF FTM	28.0[B] (p>0.05 for both birth-assigned men and women) 0.0[B] (p=0.05 for men, p<0.05 for women)	Colon (n=3) Melanoma (n=2) Lymphoma (n=1) Total (n=0)
Wierckx, 2012 [19]	Cross-sectional	University Hospital of Ghent	-	50 MTF 50 FTM	MTF: 30 +/- 8.2 FTM: 36.7 +/- 9.8	9.2 10	Any	Prevalence	MTF FTM	0 0	Total (n=0) Total (n=0)

GAHT = gender-affirming hormone therapy; SD = standard deviation; MTF = male-to-female transgender individual; FTM = female-to-male transgender individual; SD = standard deviation; CI = confidence interval

[A]Incidence per 100,000 person-years; [B]Prevalence per 1000 persons; [C]Total range as opposed to confidence interval; [D]Median years; [E]Patient-years; [F]Total age range of participants at time of study; [G]Age of participants at time of study as opposed to HT commencement; [H]Median age (as opposed to mean age)

Table 2 – Case reports in which a female-to-male transgender individual was diagnosed with a primary tumour following commencement of GAHT

Study (first author, year)	Age at diagnosis	GAHT used	Years on GAHT	Histological type	Hormone assays
			Breast cancer		
Burcombe, 2003 [37]	33	Testosterone	13	Invasive ductal carcinoma	ER+ PR+
Shao, 2011 [38]	53	Testosterone	5	Invasive ductal carcinoma	ER+ PR- HER2+ Ki-67 30% BRCA-
	27	Testosterone	6	Invasive ductal carcinoma	ER+ PR- HER2+ Ki-67 90% BRCA-
Gooren, 2015 [39]	48	Testosterone 250mg fortnightly	9	Invasive ductal carcinoma	ER- PR- HER2-
	41	Testosterone gel (50mg daily)	1	Tubular ductal carcinoma	ER+ PR+ HER2-
Gooren, 2013 [13]	27	Testosterone	3	Tubular ductal carcinoma	ER+ PR+
Nikolic, 2012 [40]	42	Testosterone	2.5	Invasive ductal carcinoma	ER- PR- HER2- Ki-67+ AR 2%
Katayama, 2016 [47]	41	Testosterone	15	Invasive ductal carcinoma	ER+ PR+ HER2- Ki-67 11.4%
Mean ± SD	**39 ± 9.4**		**6.8 ± 5.1**		

GAHT = gender-affirming hormone therapy, ER = estrogen receptor; PR = progesterone receptor; HER2 = Human epidermal growth factor receptor 2; AR = androgen receptor

Table 3 – Case reports in which a male-to-female transgender individual was diagnosed with a primary tumour following commencement of GAHT

Study (first author, year)	Age at	GAHT used	Years on GAHT	Histological type	Hormone assays

	diagnosis				
			Breast cancer		
Ganly, 1995 [48]	50	Conjugated estrogen (0.625mg daily)	14	Invasive ductal carcinoma	ER-
Pritchard, 1988 [49]	45	Conjugated estrogen (1.25mg daily)	11	Invasive ductal carcinoma	ER- PR+
Gooren, 2015 [39]	52	Ethinyl estradiol (35mcg daily); cyproterone acetate (2mg daily)	30	Adenocarcinoma	ER+ PR- BRCA-
	46	Transdermal estrogen (1mg weekly)	5	Invasive ductal carcinoma	ER+ PR+ HER2+
Teoh, 2015 [50]	41	Estrogen and antiandrogen	14	Invasive ductal carcinoma	ER- PR- HER2-
Maglione, 2014 [51]	65	Conjugated estrogen (2.5mg daily); conjugated estrogen (medically unsupervised)	13	Invasive ductal carcinoma	ER+ PR+ BRCA-
	55	Estradiol valerate (20ug monthly)	30	Invasive ductal carcinoma	ER- PR-
Gooren, 2013 [13]	56	Estrogen	17	Poorly differentiated carcinoma	
	57	Estrogen	36	Invasive ductal carcinoma	ER+ PR- HER2-
Pattison, 2013 [52]	43	Estrogen; cyproterone followed by spironolactone	15	Invasive ductal carcinoma	ER- PR- HER2- Raised serum prolactin
Sattari, 2015 [53]	60	Estrogen	8	Invasive ductal carcinoma	ER+ PR+ HER2- BRCA-
Dhand, 2010 [54]	58	Estrogen	13	Adenocarcinoma	ER+ PR+
Corman, 2016 [55]	46	Estradiol gel, 2 pumps daily; cyproterone acetate 50mg twice daily	7	Invasive ductal carcinoma	ER+ PR+ HER2- AR+ Ki-67 50% BRCA2 heterozygous mutation c.9117G>A
Mean ± SD	**51.8 ± 7.3**		**16.4 ± 9.6**		
			Prostate cancer		
Miksad, 2006 [56]	60	Conjugated estrogen 1.25mg daily	41	Gleason 8 prostate adenocarcinoma	AR+ ER_{α}- PR- PSA 240ng/ml Testosterone 44ng/dL DHEA 188 μg/dL Nil family history of prostate cancer
Turo, 2013 [57]	75	Conjugated estrogen 1.25mg daily	30	Gleason 7 prostate adenocarcinoma	PSA 13.5 ng/mL Testosterone in castrate range Nil family history
Dorff, 2007 [58]	78	Estrogen	23	Prostate adenocarcinoma	PSA 20.6 ng/mL Testosterone in castrate range
Van Haarst, 1998 [59]	63	Ethinyl estradiol; cyproterone acetate	10	Prostate adenocarcinoma	PSA > 100 ng/mL
Thurston, 1994 [60]	64	Conjugated estrogen 7.5mg/day	12	Poorly differentiated prostate adenocarcinoma	PSA 27.3 ng/mL Free testosterone 1.2 pmol/L
Sharif, 2017 [61]	56	Depot estrogen injections	20	Prostate adenocarcinoma	PSA 5 ng/mL Serum testosterone 10 ng/dL ERα+ ERβ- PR+ AR+
Mean ± SD	**66 ± 8.6**		**22.7 ± 11.6**		
			Meningioma		
Cebula, 2010 [62]	48	Estradiol; cyproterone acetate (100mg/day)	10	-	-
Deipolyi, 2010 [63]	36	Estradiol (100mcg fortnightly)	10	-	PR+ ER-
Gazzeri, 2007 [64]	28	Ethinyl estradiol (100ug/day); cyproterone 100mg/day	5	WHO grade I mesothelial meningioma	ER- Ki-67 5% MIB-1 index 3.4%
Wengel, 2016 [65]	46	Estradiol 100ug/day; cyproterone 100mg/day	5	WHO grade II meningioma	PR+ ER-
	51	Ethinyl estradiol 100ug/day; cyproterone 100mg/day	25	WHO grade I meningioma	ER+ PR-
	65	Conjugated estrogen 1.25mg/day; cyproterone 100mg/day	19	WHO grade I meningioma	ER+ PR-
Bergoglio, 2013 [66]	35	Estradiol 100ug/day; cyproterone 100mg/day	4	WHO grade I meningioma	ER- PR+ Ki-67 3%

Knight, 2013 [67]	60	Estradiol 16mg daily; cyproterone 50mg daily	10	WHO grade I transitional meningioma	ER+, PR+
Mean ± SD	**46.1 ± 12.7**		**11.0 ± 7.4**		
			Prolactinoma		
García-Malpartida, 2010 [32]	33	Conjugated estrogens 2.5mg/day; cyproterone acetate 200mg/day	0.5	Prolactinoma	PRL 8.09 ng/mL[A] (6 months after)
Cunha, 2015 [35]	41	Ethinyl estradiol 35mcg/day; cyproterone 2mg/day; estradiol 17β-enanthate 10mg/fortnight	18	Prolactinoma	PRL 7.50 ng/mL[A]
	42	Estradiol 17β-enanthate 10mg/fortnight	25	Prolactinoma	PRL 7.37 ng/mL[A]
Bunck, 2009 [33]	52	Ethinyl estradiol 100ug/day; cyproterone 100mg/day	15	Prolactinoma	PRL 2.3 IU/L
	69	Ethinyl estradiol 50ug/day	30	Prolactinoma	PRL 40 IU/L
Serri, 1996 [34]	32	Ethinyl estradiol 1.5mg daily; cyproterone acetate 150mg/day	4	Prolactinoma	History of Klinefelter's syndrome, PRL 7.77 IU/L[A]
Kovacs, 1994 [36]	33	Estrogen	17	Prolactinoma	PRL 2.43 IU/L[A] ER+
Gooren, 1988 [68]	26	Ethinyl estradiol 100ug daily; cyproterone 100mg daily, estradiol-17-undecanoate 100mg twice-weekly	0.8	Prolactinoma	PRL 5.2 IU/L
Mean ± SD	**41.0 ± 13.8**		**13.8 ± 11.1**		

GAHT = gender-affirming hormone therapy; [A] = converted to IU/L from ng/mL; ER = estrogen receptor; AR = androgen receptor; PR = progesterone receptor; PSA = prostate-specific antigen; PRL = prolactin