Journal of the Endocrine Society, 2024, **8**, bvae060
https://doi.org/10.1210/jendso/bvae060
Advance access publication 27 March 2024
Clinical Research Article

Thyroid Cancer Prevalence, Risk Exposure, and Clinical Features Among Transgender Female Veterans

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Abstract

Purpose: Transgender women experience higher-than-average rates of multiple medical conditions. Thyroid cancer occurs more frequently in those assigned female at birth than in those assigned male at birth. We sought to characterize thyroid cancer among transgender female veterans.

Methods: We reviewed charts of veterans who were (1) seen in Veterans Affairs clinics across the United States from July 2017 to December 2022, (2) had an International Classification of Diseases, revision 10, diagnosis code for thyroid cancer, and (3) had an International Classification of Diseases, revision 10, diagnosis code for gender dysphoria or were assigned male at birth and ever had a prescription for estrogens. Charts of cisgender veterans were also reviewed for comparison.

Results: Compared with calculated estimates of 0.641% (95% CI, 0.572-0.724) among cisgender females and 0.187% (95% CI, 0.156-0.219) among cisgender males, the measured prevalence among transgender female veterans was 0.341% (34/9988). Average age at thyroid cancer diagnosis in this population was 53.8 (± SEM 2.61) years. A total of 32.3% (11/34) of these patients had extrathyroidal disease at diagnosis.

Discussion: To our knowledge, this study represents the first report of thyroid cancer prevalence among transgender women in the United States. Risk exposure among all transgender veterans including further assessment of the possible contributions of obesity, smoking, and gender-affirming hormone therapy are important future analyses.

Key Words: transgender medicine, thyroid cancer, health disparities, gender-affirming hormone therapy, veterans' health, epidemiology

Abbreviations: AMAB, assigned male at birth; BMI, body mass index; EBV, Epstein-Barr virus; FVPTC, follicular variant of papillary thyroid carcinoma; GAHT, gender-affirming hormone therapy; HCV, hepatitis C virus; ICD-10, International Classification of Diseases, 10th revision; VINCI, VA Informatics and Computing Infrastructure.

Thyroid cancer is the most common endocrine malignancy and the 13th most common malignancy in the United States [1]. Risk factors include radiation exposure [2], smoking status [3], personal or family history of thyroid disease or malignancy [4], infection with HIV [5] or hepatitis B or C [6, 7], and obesity [8]. Active cigarette smoking has been shown to confer a modest protective effect [9], although the mechanism is incompletely understood. There is evidence that human papillomavirus infection [10] and Epstein-Barr virus (EBV) infection [11] may also play a role, although the level of risk has not yet been definitively quantified.

The incidence of differentiated thyroid cancer is higher among those assigned female at birth than in those assigned male at birth (AMAB) [1, 12] to the extent that thyroid cancer ranks as the sixth most common malignancy in assigned female at birth patients in the United States. Although there is likely also some impact of overdetection bias [13] on the noted differences in incidence by sex, estrogens lead to the growth of both normal thyroid cells and tumor cells [14, 15], and it is suspected that differential exposures to circulating estrogens may also contribute to this higher incidence [16]. Emerging data demonstrate an increased risk of malignancies, including thyroid cancer, among cisgender women treated with exogenous estrogens [17-19] for various indications. The molecular mechanisms for a potential estrogen-induced increase in thyroid cancer incidence are incompletely understood [20]. Estrogens promote the growth of thyroid cells, but studies focused on the expression of estrogen receptor α and β in thyroid cancer specimens have been contradictory [14, 21]. A role for G protein-coupled estrogen receptor has been proposed [22]; exogenous estradiol may also increase the expression of telomerase reverse transcriptase [23], expression of which is associated with progression and more aggressive features of thyroid cancer [24, 25]. Additionally, very recent work has shown that estrogen-modulated genes appear to influence immunomodulation and tumor immune evasion in thyroid cancer cells [26].

Approximately 0.5% of the US population older than age 13 years identifies as transgender [27]; this number is likely to increase with time because younger adults and adolescents are more likely to report they identify as transgender. The proportion of those who identify as transgender is similar between veterans and civilians [28]. Transgender people are disproportionately affected by many common medical conditions, primarily because of limited access to care driven by discrimination and marginalization and resultant mistrust of

Received: 22 January 2024. **Editorial Decision:** 21 March 2024. **Corrected and Typeset:** 17 April 2024

physicians and health care systems. Among these conditions are HIV [29], lung cancer [30], hepatitis B and C [31], and cardiovascular disease [30, 32].

Gender-affirming hormone therapy (GAHT) with estrogens is a cornerstone of treatment for transgender women, associated with improvements in mental health [33] because of the alignment of external sexual characteristics with internal gender identity. It is yet unknown whether any differences exist in thyroid cancer prevalence resulting from GAHT in this population because GAHT is in many ways distinct from endogenous estrogen secretion.

Because of the increased prevalence of multiple risk factors for thyroid cancer and the unknown impact of estrogens as GAHT in the transgender female population, thyroid cancer prevalence is important to assess. However, there are currently no available published data on rates of thyroid cancer specific to the transfeminine population. Using composite nationwide Veterans' Health Administration records, accessed via the VA Informatics and Computing Infrastructure (VINCI), we here sought to identify rates of thyroid cancer among transgender female veterans relative both to their cisgender female and male veteran peers and the general population as well as to characterize their clinical characteristics and exposures to risk factors known to be associated with thyroid carcinogenesis.

Materials and Methods

Patient Identification

Because of the retrospective nature of the analysis, institutional review board review and exemption were obtained.

Using the VINCI system to include all available VA patient information nationwide, we first estimated the number of veterans seen in outpatient sites within 5 years from July 2017 through December 2022. Because individual chart data on the assigned sex at birth were sometimes inaccurate, we then used previously published census reports to determine the proportion of veterans AMAB. Of these approximately 9 million veterans, we then identified all those who were age 18 years or older in July 2017, who had ever had an International Classification of Diseases, 10th revision (ICD-10), code of gender dysphoria, or who were AMAB and had ever had a prescription for estrogens: At the VA, estrogens are not approved for the treatment of prostate cancer, behavioral dyscontrol, or bone density in those AMAB.

Of these veterans, we then identified a subcohort who had ever had an ICD-10 code of thyroid cancer. Structured query language was used as the programming language both for the generation of the cohorts and for the extraction of patient information for subsequent chart review.

ICD-10 codes for gender dysphoria included the following: F64.0, F64.1, F64.2, F64.8, and F64.9. We also included the following ICD-9 codes later converted to ICD-10: 302.3, 302.85, and 305.2.

ICD-10 codes used for thyroid cancer included C73, D09.3, D44, and Z85.850. Again, for completeness, ICD-9 codes were included: 193, 237.4, and V10.87.

Chart Review and Parameters

For all veterans identified as transgender women with an ICD-10 code of thyroid cancer, we examined individual charts to verify these points. Two veterans were identified who were, in fact, transgender men but had had topical estrogen prescribed for vaginitis. A sizeable proportion of veterans were noted not to have had a true diagnosis of thyroid cancer but rather benign thyroid nodules; to avoid similar errors, thyroid cancer diagnostic verification was also performed for the cisgender subcohorts (see the following section).

Thyroid cancer pathologic characteristics were identified on pathology reports or as recorded in clinic notes. The age and body mass index (BMI) of the veteran at the time of thyroid cancer diagnosis (to the nearest month), time of military service, and, where possible, time of initiation of GAHT were also examined. In many cases, GAHT start dates or thyroid cancer diagnosis dates were vague (eg, "about 3 years ago" or "in 1981") or referenced only obliquely; actual dates were used wherever possible, and where impossible, the year of GAHT initiation was used with a concordant date of thyroid cancer diagnosis or, failing this, with the patient's birthday.

Risk factors for thyroid cancer were also reviewed among all those patients AMAB; qualitative radiation exposure history, smoking history, and family history of thyroid cancer were recorded in patients in whom these items were noted, although notation of absence of these risk factors was typically lacking. Similarly, although test results for HIV, hepatitis B virus, hepatitis C virus (HCV), herpes simplex virus, and EBV were examined, the majority of patients had had no such testing. Obesity was determined based on BMI at the time of diagnosis, using a threshold value of 30.0 to indicate obesity.

Cisgender Comparators

Separately, we identified simple random samples of 95 cisgender male veterans and 48 cisgender female veterans who were not included in the previous cohort for comparative purposes. These cohorts were selected from pools of 26 052 cisgender male and 7413 cisgender female veterans with ICD-10 codes of thyroid cancer: After noting the substantial difference between ICD-10 codes and true pathologic diagnosis which rendered individual chart review necessary, these cohort sizes were selected to yield a 10% margin of error on estimates of cancer prevalence. These cohorts were reviewed to establish the true prevalence among the larger pools of those with only an ICD-10 code diagnosis because it was not feasible to review all of the more than 10 000 available charts for cisgender patients. For estimates of thyroid cancer prevalence in the general population, we used the Surveillance, Epidemiology, and End Results database explorer tool [1].

Statistical Analyses

Prevalence was calculated in the standard manner alongside a 95% CI assessment according to the normal approximation method. In the case of the cisgender comparator subcohorts, the size of the simple random sample was determined to allow a 10% margin of error, which was then applied to the 95% CI. Because of the limited capacity for data extraction within VINCI using structured query language and the consequent need for individual chart review to determine specifics, it was not feasible to perform chart review for a larger portion of these groups because of the considerably greater number of cisgender patients with an ICD-10 code of thyroid cancer. Similarly, it was not feasible to perform matching.

Comparison between the transgender female and cisgender male veterans regarding risk factor exposures was carried out

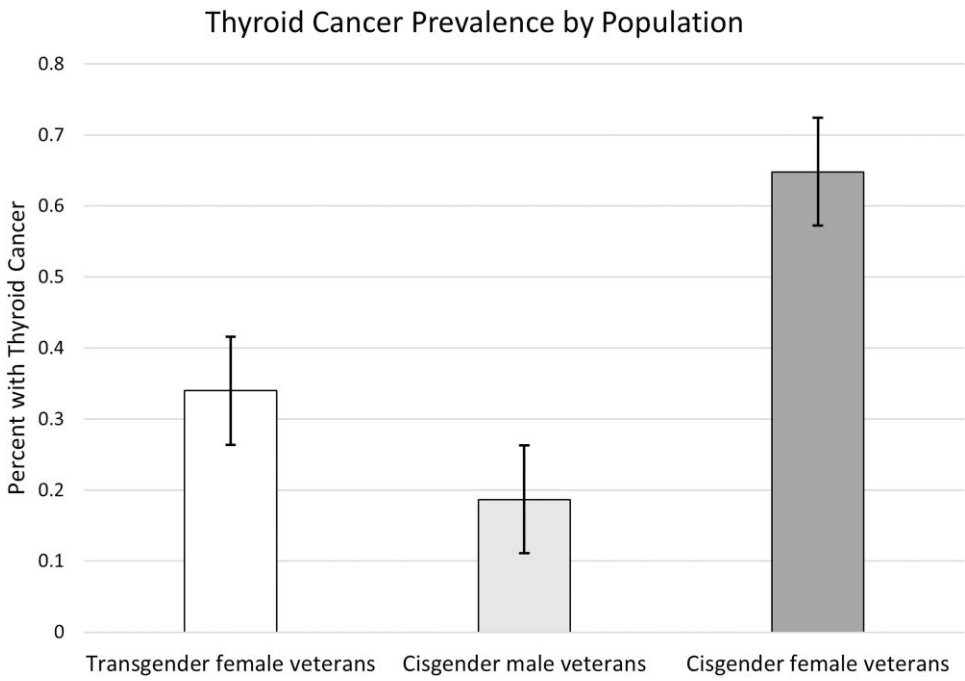

Figure 1. Complete prevalence of thyroid cancer expressed as a percentage, according to reported gender identity, among US Veterans seen at all outpatient VA clinics in the 5-year interval in question. All veterans demonstrate higher prevalence than previous estimates; among cisgender female veterans the rate is highest, followed by transgender female veterans, and then by cisgender male veterans. Error bars denote 95% CI.

using *z*-testing; differences in average BMI and age at diagnosis were assessed with *t* testing. All tests were 2-tailed, and α was defined as 0.05. Because the prevalence data we examined were complete prevalence (similar to what is available in previous estimates) rather than limited-duration prevalence, and all age-related analyses were performed with respect to age at diagnosis, age correction was not performed. Age-corrected prevalences for thyroid cancer in the general population are also unavailable [1].

Results

Prevalence of Thyroid Cancer

A total of 9988 veterans were determined to be transgender female; of these, 76 had an ICD-10 diagnosis of thyroid cancer. After individual chart review, 34 transgender female veterans were determined to have had a true diagnosis of thyroid cancer.

Various rates of prevalence are shown in Fig. 1. All thyroid cancer prevalence rates among veterans were higher than in previously published estimates, and prevalence in transgender women was higher than in cisgender men but lower than in cisgender women. Thyroid cancer prevalence among transgender female veterans was 0.341% (95% CI, 0.223-0.459). In a secondary analysis, thyroid cancer prevalence among cisgender male veterans was found to be 0.187%, within a margin of error of 10% (95% CI, 0.156-0.219); among cisgender female veterans, the prevalence was found to be 0.648%, within a margin of error of 10% (95% CI, 0.572-0.724).

Previously published estimates broken down by sex reflected a prevalence of thyroid cancer in males of 0.133% (95% CI, 0.133-0.134) and in females of 0.441% (95% CI, 0.440-0.442) [1]; it is not known what proportion of these patients identified as transgender.

Risk Factor Assessments

A summary of risk factor exposures for all those veterans who were AMAB can be seen in Fig. 2. Risk factor assessments were not further conducted for cisgender women because, although transgender female veterans are women and identify more with cisgender women, the majority of our transgender female veterans started GAHT after diagnosis with thyroid cancer. Therefore, for this study, the exposure history and hormonal milieu were more consistent among all those AMAB at diagnosis than they would have been in a comparison of transgender and cisgender women.

A known history of radiation exposure was present for 5 patients. As a proxy for travel and hazardous material-related irradiation, durations of military service were also collected. Qualitative smoking history was noted in approximately 50% of patients. Thirteen veterans had a history of nonthyroid malignancy. All available data on infection status with EBV, hepatitis B virus, HCV, and HIV were reviewed; 5 patients had a known history of HCV infection, and 1 had had EBV infection, but there were otherwise no positive test results for any patient.

Obesity was the most common risk factor. As shown in Table 1, BMI at the time of diagnosis was documented for 26 transgender female veterans and 40 cisgender male veterans. The mean BMI for both groups was >30. Although there was a statistically significant difference in BMI, there was no difference in the proportion of patients with BMI >30 between the 2 groups.

There was a statistically significant difference in age at diagnosis with thyroid cancer, with transgender women diagnosed at a younger age.

Disease Characteristics

Data from the transgender female cohort regarding the age of the patient at time of pathologic diagnosis, subtype of thyroid

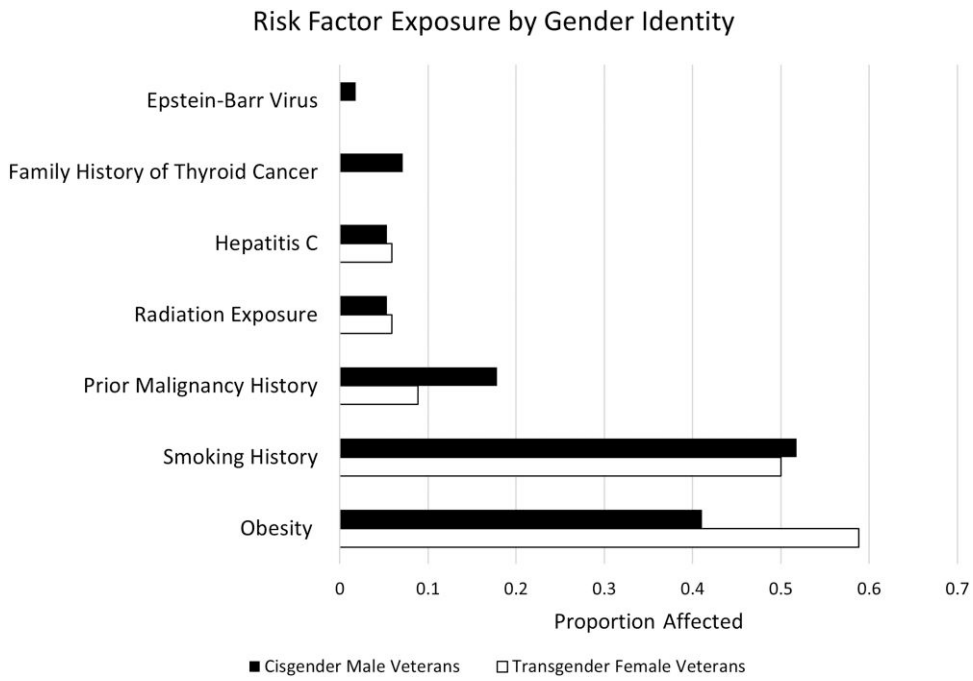

Figure 2. Proportions of veterans exposed to certain risk factors for the development of thyroid cancer. *P* values are shown for 2-tailed *z*-tests with $\alpha = 0.05$. Among transgender female veterans, obesity and smoking history were the most common risk factors, but they did not differ significantly in this exposure from a comparator cohort of cisgender male veterans.

Table 1. Patient characteristics at diagnosis of thyroid cancer

Transgender female veterans	Median	Mean	SEM	Cisgender male veterans	Median	Mean	SEM	*P*
Age (n = 34)	56.5	53.8	2.61	Age (n = 56)	64.0	61.8	1.72	.00880*
BMI (n = 26)	32.0	33.8	1.33	BMI (n = 40)	31.0	30.4	0.799	.0229*
Military service, wk (n = 34)	168	339	67.5	Military service, wk (n = 56)	154	222	35.6	.0963
Time on GAHT, wk (n = 11)	156	176	45.6					

Asterisk (*) denotes statistical significance.
Abbreviations: BMI, body mass index; GAHT, gender-affirming hormone therapy.

cancer, size of primary tumor, and presence of extrathyroidal disease at time of diagnosis can be found in Table 2. Average age at diagnosis was 53.8 years (SEM, 2.61 years; median, 56.5 years). The most common subtype was papillary carcinoma (79.4%, n = 27), of which 5 cases (18.5%) were the follicular variant. Follicular carcinoma was seen in 9 patients (33%), of which 4 cases (44.4%) were noted to be Hürthle cell carcinoma. Four patients (11.8%) were noted to have at least 1 focus of both papillary and follicular carcinoma. One patient's pathology records were not available.

Eleven cases presented with known extrathyroidal extension of tumor at diagnosis, including lymphovascular invasion and nodal and distal metastasis. The primary tumor was known to be larger than 1 cm in the greatest dimension in all but 2 of these cases; in these latter, the initial dimensions were not known.

Use of GAHT

Of those 11 veterans who had started GAHT before thyroid cancer diagnosis, the average duration of GAHT treatment at the time of diagnosis was 176 weeks (SEM, 45.6 weeks; median, 156 weeks). Data on the specific regimen of each veteran were available for 8 veterans. At the time of cancer diagnosis, oral estradiol doses ranged from 1 to 5 mg daily; 2 veterans were on 3 mg intramuscular doses weekly; and 3 veterans were using concomitant transdermal patches.

Only 7 veterans had any serum estradiol levels tested. Because of the infrequent reassessment of serum estradiol, it was not possible to determine a clinically meaningful area under the curve for estradiol exposure, or indeed to compare estradiol exposures between veterans.

Discussion

For the first time to our knowledge, we here demonstrate an increased prevalence of thyroid cancer among veterans compared with previous estimates. Among all those AMAB, transgender female veterans have the greatest increase in thyroid cancer prevalence. Interestingly, transgender female veterans were diagnosed with thyroid cancer at a significantly younger age. Perhaps not surprisingly, given the historical marginalization of this population, approximately 33% of these veterans presented with at least minimal extrathyroidal extension, which is an increased proportion from previous estimates of approximately 9% [34]. We also demonstrate a higher proportion of the follicular variant of papillary

Table 2. Thyroid tumor characteristics among transgender female veterans

Patient number	Age at diagnosis, y	Primary tumor type	Secondary tumor type	Size of largest focus	Extrathyroidal extension
1	61	Papillary	—	0.7 cm	None
2	57	Follicular variant of papillary	—	2.2 cm	None
3	56	Follicular variant of papillary	—	5 cm	None
4	59	Papillary	—	2.2 cm	Lymphadenopathy, extracapsular extension
5	55	Papillary	Follicular	0.9 cm	None
6	67	Follicular	—	7 cm	None
7	49	Papillary	—	Multiple microfoci	None
8	37	Papillary	—	2.8 cm	Lymphadenopathy, lymphovascular invasion
9	54	Papillary	—	1.1 cm	Lymphadenopathy
10	54	Hürthle cell	—	<1 cm	None
11	64	Papillary	—	2.1 cm	Unknown
12	37	Papillary	Follicular	6 cm	Unknown
13	73	Papillary	—	1.8 cm	Unknown
14	60	Papillary	—	0.2 cm	None
15	61	Papillary	—	1.3 cm	Lymphadenopathy
16	53	follicular variant of papillary	—	1.5 cm	None
17	32	Papillary	—	Unknown	Unknown
18	69	Papillary	—	2 cm	Unknown
19	29	Follicular variant of papillary	—	4 cm	None
20	37	Hürthle cell	—	6.1 cm	Angioinvasion
21	25	Papillary	—	2 cm	None
22	25	Papillary	—	1.5 cm	Extensive lymphadenopathy
23	38	Papillary	—	Unknown	Unknown
24	55	Papillary	—	Unknown	None
25	62	Hürthle cell	—	Unknown	Extracapsular extension
26	67	Hürthle cell	Papillary	4.8 cm	Extracapsular extension
27	71	Follicular variant of papillary	Papillary	1.4 cm	None
28	70	Papillary	—	1.1 cm	None
29	63	Papillary	—	0.7 cm	None
30	22	Unknown	—	Unknown	Lymphadenopathy
31	64	Follicular	—	4 cm	Lymphadenopathy
32	72	Papillary	—	2.3 cm	None
33	59	Papillary	—	1.5 cm	None
34	73	Follicular	—	7.5 cm	Distant metastases

thyroid carcinoma—18.5% of papillary thyroid carcinomas in our population, compared with 10% to 15% in previous estimates [35]—and of Hürthle cell carcinoma—11.8% of our population, compared with 3% to 4% of cancers in previous estimates [36, 37]. It remains unknown whether these rates will hold on a larger scale if examined among all veterans.

Although it would be correct to say that transgender female veterans display an increased prevalence of thyroid cancer when compared with cisgender male veterans, this comparison is not as appropriate as noting, equally correctly, that transgender female veterans appear to have a lower prevalence of thyroid cancer than their cisgender female peers. All veterans who are women demonstrated an increased thyroid cancer prevalence compared with civilian women, and it may be that transgender women are protected in some fashion from the degree of risk exposure of their cisgender peers.

Because of the small size of this retrospective analysis, we are unable to assess completely the causal roles of the risk factors examined for thyroid cancer. Few veterans had any known family history of thyroid cancer, and a very small number had known radiation exposure. Chronic infections known to increase the risk of malignancy were also largely not identified, although this may have been due to lack of testing. Although the transgender female veterans did demonstrate a

statistically significantly higher BMI at thyroid cancer diagnosis than cisgender males did, the proportion of patients with a BMI >30 was not different, suggesting the presence of obesity alone is not sufficient to explain the discrepancy. However, increased BMI is associated with increased visceral adiposity, increased de novo lipogenesis, and increased inflammation and aromatase expression [38, 39]. The absolute difference in BMI was about 2 kgm^2; prior studies have estimated a 19% to 42% increased risk of thyroid cancer with each 5-point increase in BMI [40], although there are not enough data to suppose a linear relationship. Finally, although active smoking has been shown in some studies to be protective against thyroid cancer development and prior smoking has not been shown to confer any increased risk [9], approximately half of our cohort had a qualitative smoking history, which merits reporting whether protective or deleterious.

Perhaps the most important limitations of our study are the retrospective nature of the analysis, the relatively small overall number of transgender female veterans with thyroid cancer, and inaccuracies and gaps in the electronic medical record. This latter limitation was very challenging to work around for the transgender veteran population because many aspects of a veteran's gender identity are not easily extrapolated as quantifiable data. As the collection of the veteran's gender identity information varies from 1 VA clinic to the next and relies on patient reports and the interaction between the patient and their care providers, inaccurate assumptions may be carried forward in the chart.

Standards of care for transgender people have also evolved significantly because many of these veterans were first diagnosed with thyroid cancer, such that many of those on GAHT did not have follow-up laboratory tests drawn at the currently recommended frequency [41], if at all. Additionally, many veterans' charts carried inaccurate ICD-10 code diagnoses for gender dysphoria. As many VA systems updated diagnosis codes from ICD-9 to ICD-10, it seems certain mental health diagnoses were incorrectly cross-identified, such that individual chart review was required to verify whether a patient did identify as transgender. Nevertheless, our analyses were carried out in such a way to include as many veterans as possible in our cohorts of interest, and any such inaccuracies would therefore tend to skew toward underrepresentation of the true thyroid cancer prevalence among transgender female veterans. Although it is important to consider selection bias as potentially influencing the prevalence of thyroid cancer in a patient population requiring specialist referral to receive GAHT, the majority of our veterans had already been diagnosed with thyroid cancer before discussion of their transitions.

In our analyses, some veterans were diagnosed with the follicular variant of papillary thyroid carcinoma (FVPTC), an entity not without controversy. Since the time that the veterans were diagnosed with this disease, a great deal of research has been performed indicating that many people previously diagnosed with so-called FVPTC may instead now be reclassified as having noninvasive follicular thyroid neoplasia with papillary-like nuclear features, which among some authorities is no longer considered a thyroid cancer [42]. We elected to include all patients diagnosed with FVPTC for several reasons: Diagnostic techniques evolved after these diagnoses were rendered, and we did not have access to pathology slides to reclassify veterans; previous work demonstrated a relatively low rate of approximately 33% definitive reclassification of previously identified FVPTC as noninvasive follicular thyroid neoplasia with papillary-like nuclear features [43]; and the prevalence rates in the Surveillance, Epidemiology, and End Results database have not been reclassified but have only adjusted as diagnostic techniques have been updated [44]. All the same, it is conceivable that some of these veterans would not have been included in our cohort if they had undergone thyroidectomy at a subsequent date.

There are several important next steps that these findings prompt. First, confirmation of a similar thyroid cancer prevalence among transgender women in the civilian population will be very important because this population is considerably larger than the veteran population and may be exposed to less risk.

Next, the underlying reason for this discrepancy is still unclear; several possible explanations were explored without definitive conclusions. In particular, given the sizable proportion of transgender female veterans with a qualitative smoking history and who were obese at the time of diagnosis, a larger case-control study could be carried out to determine the extent to which these factors enhance the risk of thyroid cancer development among these veterans. Obesity appears to be common in general among the veterans we analyzed and could be evaluated for its quantitative impact on the risk of thyroid cancer in a future study. Additionally, transgender male veterans were not included in the present analysis because it was beyond our intended scope and the vast majority of veterans are AMAB; this will be a very important analysis to perform in the future. Last, the possible role of GAHT in the development of thyroid cancer must be further clarified. Although our incomplete data and relatively small study size mean we cannot determine the relative risk of thyroid cancer in those treated with GAHT or the correlation of thyroid cancer risk with estradiol dose or serum concentration, these questions bear further investigation in prospective analyses.

Conclusions

All groups of veterans we analyzed demonstrated an increased prevalence of thyroid cancer compared with the general population; even so, the prevalence of thyroid cancer is considerably higher among transgender female veterans than cisgender male veterans and than the general population of all those AMAB. Although the reasons for this remain unclear as of yet, increased rates of social determinants of health associated with malignancy such as smoking and obesity likely play a role. Given mounting evidence that estrogens are associated with an increased risk of thyroid cancer, the role of GAHT in explaining this phenomenon should also be addressed in further studies.

Acknowledgments

None.

Funding

None.

Disclosures

J.D.C., H.T.B., and J.J.L.A. all report that they have no significant financial or conflict of interest disclosures to make.

Data Availability

Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality. The corresponding author will, on request, detail the restrictions and any conditions under which access to some data may be provided.

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