Thyroid Carcinoma: Do We Need to Treat Men and Women Differently?

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Keywords

Differentiated thyroid carcinoma · Gender disparity · Genetics · Hormonal status

Abstract

Background: For differentiated thyroid carcinoma, gender-specific differences exist in regard to incidence, age at onset, tumor stage, and recurrence, but causative factors remain to be elucidated. Possible and likely contributors are genetic and hormonal differences. While some of these factors are known to be differently distributed between the sexes, like, for example, BRAF-mutation and estrogen levels, their role in thyroid cancer initiation or promotion awaits further investigation. **Summary:** Apart from generally accepted risk factors for differentiated thyroid carcinoma, an apparent gender disparity of thyroid cancer with a general female predominance, an age-dependent difference in growth acceleration during the reproductive years, and a peak at the time of entering menopause have been demonstrated. Hormonal status and hormonal receptor mediation seem to be most likely to contribute to the differences in thyroid cancer phenotypes of males and females. However, specific cause-and-effect pathways have not yet been determined. **Key Messages:** Female gender is overrepresented in the incidence of differentiated thyroid carcinoma, as it is in the more favorable tumor stages. Besides the assumption of gender-specific differences in general health awareness and behavior, hormonal age-dependent and gender-specific factors appear to be contributory. In the advanced stage of thyroid cancer, males are overrepresented. Therefore, the real cause of gender dif-

ferences in thyroid cancer is likely due to a mixed effect. Present knowledge does not favor different treatment modalities of thyroid carcinoma according to gender.

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Introduction

A rapid increase in differentiated thyroid carcinoma (DTC) is observed globally, dominated by papillary microcarcinoma. At the same time, gender differences in incidence, aggressiveness, and prognosis of DTC are well confirmed and poorly understood. A predominance of females with 2.9 over men has been described [1, 2]. While female gender is predominantly associated with more favorable histological subtypes, more aggressive histology is observed with rather equal gender distribution [1–6].

Contrary to the overall tumor burden where male gender is predominant in all entities, the male to female ratio in DTC is 0.39 according to the SEER database and 0.33 according to the International Agency for Research on Cancer (IARC) [2, 7]. Siegel et al. [2] estimated 56,870 new DTC cancer cases for both sexes in 2017, with 14,400 in males versus 42,470 in females. For the same period, a total of 2,010 estimated deaths associated with DTC showed almost equal gender distribution with 920 males and 1,090 females [7].

Regarding cancer mortality, data for the USA demonstrate a significant increase of 0.9–1.0% (95% CI 0.7–1.5 total US thyroid cancer deaths; 95% CI 0.4–1.5 SEER total

thyroid cancer deaths) in the last 20 years. According to SEER data analysis, an increase of deaths in males was 1.0 versus 1.2 in females [3]. Afshar et al. [8] described a predominance of females in death from DTC compared to males. In the period 1994–2013, the gender incidence of DTC had a male to female ratio of 0.3 (20.8 female vs. 7.0 male; 95% CI 0.34–0.34). The mortality ratio, in contrast, was 1.0 (0.5 female vs. 0.5 male; 95% CI 0.99–1.08) [8].

These data correspond to the findings in Germany. According to a report from the Robert Koch Institute, the incidence of thyroid carcinoma clearly increased for both sexes and was markedly higher for females [9]. Regarding tumor stages, favorable stage T1 and T2 dominate in females with 62% and 14%, respectively, while T3 accounts for 19% and T4 for 4%. In males, T1 and T2 constitute 51% and 16%, respectively, while T3 accounts for 26% and T4 for 7% [9].

Potential Contributors

External radiation and ionizing radiation are established risk factors for thyroid carcinoma, especially when exposure occurs during childhood. Radiation-associated DTC is almost always papillary thyroid carcinoma (PTC). However, no clear gender differences can be observed [10–12].

Nutritional status and diet are assumed to influence the development of DTC. Contradictory data involve iodine status. Iodine deficiency is an established risk factor for DTC. At the same time, iodine excess is associated with a risk to develop PTC. Some reports state that chronic iodine deficiency as well as nutritional iodine and phytoestrogens have a protective effect against DTC in females, while no data are available for men. Thus, there is no clear evidence for dietary factors involved in the gender disparity of DTC [12–14].

Frequently, genetic mutations, including genetic rearrangements, are observed in DTC. BRAF is specific to PTC and prevalent in 2/3 of these tumors. RET/PTC and NTRK1 are chromosomal rearrangements of a tyrosine kinase receptor. RET/PTC rearrangements were among the first frequently observed genetic alterations in PTC. Presently, 15 of these have been described. RET/PTC are identified in 20–40% of sporadic adult PTC, mainly RET/PTC3 and RET/PTC1, while NTRK1 is found in 13% of PTC [10, 11, 14].

RET/PTC rearrangements are associated with radiation. In a study of 39 children after low-dose radiation, a higher rate of RET/PTC rearrangements was reported; however, evidence with regard to phenotype of PTC and gender is poor. Only 1 study addressed NTRK rearrangement in PTC with an overall prevalence of 12% ($n = 33$). Of these, 12.5% (1/8) were found in men and 12% (3/25)

women. Thus, evidence is low for the association of a specific somatic mutation with gender in PTC [10–16].

The BRAF serine/threonine kinase mediates cellular response to growth factors and differentiation pathways. The most prevalent V600E BRAF mutation is found almost exclusively in PTC (97%) and is associated with a more aggressive phenotype, represented by larger tumor size, extrathyroidal tumor extension, poorer differentiation rate, lymph node and distant metastases, recurrence of tumor, older patient age, and gender disparity. With regard to BRAF mutations, 12 studies address gender differences. While 10 studies reported no difference in prevalence between the sexes, 2 studies described a higher BRAF mutation rate in males of 64% versus 27% in females, and 91% ($n = 35$) versus 70% ($n = 168$) were found in a study of 203 PTC patients. A small Japanese study found similar results with 91% BRAF mutations in males (10/11) and 55% (16/29) in females [10, 11, 14]. In a meta-analysis involving 1,168 patients (259 men and 909 women), however, the incidence of BRAF mutations was equally distributed between the sexes with 50% in males and 49% in females.

One study showed increased tumor growth in 46% of male patients compared to 36% of female patients. In summary, increased BRAF mutation in males is not commonly confirmed and the association appears weak, possibly influenced by advanced disease at the time of diagnosis [15].

There are numerous differences between males and females with regard to sex hormones and their influence on different body systems. In females, sex hormones fluctuate according to the menstruation cycle and with pregnancy. The peak incidence of PTC is seen at age 40–49 years with approaching menopause [17, 18]. Potential factors of influence, such as age at menarche and at menopause, as well as number of pregnancies, did not show uniform results. In a pooled analysis, Negri et al. [19] found that late menarche (OR 1.04), late primary delivery (OR 1.3), artificial menopause (OR 1.8), and miscarriage in primary pregnancy (OR 1.8) all represent significant but minor risk factors for the development of DTC. It may be hypothesized that effects of the menstruation cycle are expressed at a younger age and that this effect will be abolished when hormonal fluctuation ends at menopause. Rahbari et al. [10] in a comparative analysis of studies showed that, largely, none of the potential factors reached a level of significance, including age at menarche and at menopause, cycle irregularity, artificial menopause, parity, miscarriage, induced abortion, or oral contraceptives. Overall, the association of reproductive factors with DTC is weak.

Rahbari et al. [10] point out an age-dependent peak incidence of DTC that shows a gender disparity. The very steep increase of DTC in females occurs around the age

of 20 years, coincidental with the beginning of the reproductive phase. While females demonstrate a maximum turning point around 50 years, coincidental with menopause for most, in men the peak incidence of DTC lies 10 years later at 70 years, which remains unrelated to significant hormonal changes, and at 85 years the incidence of DTC levels for both sexes.

Epidemiologic studies also looked at gender differences of DTC. In a Japanese study of 37,986 persons aged 40–79 years, 68 developed DTC, and 70% of these were PTC. No difference was found in regard to risk of DTC associated with body mass index, smoking, diabetes, age of menarche and menopause, parity, or oral contraceptives [20]. The overall incidence of DTC was clearly lower in Japan (3.8/100,000) compared to the USA (14.2/100,000). It was hypothesized that the Japanese population may have been exposed to less hormonal changes, or population risk factors are different.

In an US matched-control study with 82% PTC, 12% follicular thyroid carcinoma, and 5% other type DTC, multivariate analysis showed no impact of reproductive factors, menarche, cycle regularity, parity, and number of pregnancies. However, an increase in DTC was seen with the rate of hysterectomy and ovariectomy [16]. Especially for PTC, no association was found for age of menopause and status of menopause. Menarche at <12 years was a weak but significant risk factor for PTC, as was parity at <15 years. Parity, however, demonstrated a disparate influence. While 2 live births were a risk factor for developing DTC, >3 live births were not significant. Oral contraceptives appeared protective against DTC with an OR of 0.73 [10, 11, 15].

Contributors to tumor development are sex hormones as known for breast and prostate cancer. Sex hormones mediate effects by specific nuclear receptors for gene expression and regulation of tumor cell biology. In PTC, α - and β -estrogen receptors mediate the estrogen effect. Therefore, polymorphism of the estrogen receptor may be a risk factor for DTC. While α -estrogen receptor density in PTC tumor cells is low, physiologic estrogen stimulation accounts for significant upregulation and increase of cell proliferation. Contrary, in anaplastic thyroid carcinoma (ATC) or follicular thyroid carcinoma, estrogen fails to change the estrogen receptor expression. In PTC, β -estrogen receptor expression is not changed by estrogen, whereas it is elevated in ATC, and while estrogen stimulates tumor growth in PTC cell lines, it inhibits tumor growth in ATC cells [11, 21].

Estrogen is associated with cell adhesion, invasion, and migration in thyroid carcinoma cell lines, effects that are reversible with use of estrogen antagonists, which may harbor therapeutic potential for treating advanced PTC. Likewise, during pregnancy, chorionic gonadotropin acts homologous to TSH and thus may trigger rapid

Table 1. Comparative trend scheme of gender disparity in DTC phenotype^a

DTC feature	Males	Females
Overall incidence of DTC	+	+++
Microcarcinoma DTC	+	++
Advanced-stage DTC	++	+
Onset age, years	>20	<20
Peak incidence age, years	>55	<50
Recurrence of DTC	++	+
Disease-specific mortality	+	–

+ Positive but weak expression. ++ Moderate positive expression. +++ Strong positive expression. ^a Trend summary comparing main DTC features for gender difference according to the literature review.

tumor growth. In a study with 123 DTCs during different phases of pregnancy, the rate of tumor persistence and recurrence was increased, and 87.5% of pregnant women showed α -estrogen receptor-positive tumors. Despite a potential bias due to a lack of studies in males, data strongly suggest a growth-stimulating role of estrogens [18].

Jonklaas et al. [22] showed in a study with 3,572 patients (2,619 females and 953 males) that outcome of DTC differs between genders in 2 age periods. While outcome for females aged <55 years was favorable when compared to males, outcome difference leveled off between sexes from the age of >55 years on. Zhang et al. [4] demonstrated in a multivariate analysis that female outcomes of all types of DTC differed according to pre- or postmenopausal state. Lee et al. [6] demonstrated that even for micro-PTC, males had a worse prognosis than females (recurrence 12.6 vs. 9.6%, $p = 0.03$; death 2.2 vs. 0.6%, $p < 0.001$). Jonklaas et al. [22] confirmed this gender-specific outcome disadvantage for males with DTC and demonstrated an increased mortality rate for men.

In a very recent study of 2,595 patients with DTC from the Canadian thyroid cancer network, Zahedi et al. [23] showed that cancer recurrence in males was higher than in females, even when adjusted for tumor stage at presentation. Overall, recurrence was significantly lower for females at 2.2% ($n = 46$) than for males at 8.5% ($n = 45$) ($p < 0.001$).

In summary, several studies show contradictory results with regard to reproductive and hormonal factors influencing DTC risk. No clear association can be found between menstruation, reproductive or hormonal history and DTC prevalence [23]. For the long-term outcome of patients with PTC and other DTC, however, female gender proved favorable for prognosis.

Conclusion

Several factors have been identified that cause or contribute to the observed gender disparities in incidence, tumor stage, and outcome of DTC. A schematic overview of the reported gender differences with regard to the trend estimation and clinical relevance is summarized in Table 1. Autoimmunity apparently is a positive factor. The reason for this, however, remains unclear. Estrogen receptor mediation is evident, but only a modifying effect is confirmed. General health behavior is different between males and females, but this remains an imperfect explanation for the differences in disease expression. Therefore, prevalent data underline gender differences in DTC. Analyses for root causes indicate contributors that need to be further investigated and it may well be that a cumulative effect of gender differences is responsible for the total effect. Intensified surveillance during pregnancy is warranted due to the pres-

ent findings; however, at present, the state of evidence does not allow for a generally different gender-specific surgical treatment.

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Author Contributions

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