Obesity and Thyroid Cancer: A Clinical Update

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Background: In the last decade, significant contributions have been made to our knowledge on the connection between the thyroid and adipose tissue. Modern society is faced with climbing rates of obesity and metabolic syndrome, and there is accumulating evidence of an association between obesity and increased cancer risk. The aim of this review is to summarize clinical data on the association between thyroid cancer (TC) and obesity and briefly to present plausible hypotheses explaining this interplay.

Summary: We performed a search on the PubMed database for studies published in English from 1980 to March 2013 using the terms “thyroid cancer,” “obesity,” and “body mass index.” Although there is inconsistency among the clinical studies, it seems that overweight and obesity are related to a modestly increased TC risk. Various factors, such as sex, ethnicity, and body changes during certain life periods, for example adolescence, may influence the association between obesity and TC risk. There are preliminary data linking obesity with a less favorable clinicopathologic profile of TC. However, validation with larger multicenter studies is needed. The precise underlying mechanisms have not yet been elucidated, but the insulin-IGF axis and adipokines, such as leptin and adiponectin, might be implicated in the link between excess weight and TC.

Conclusions: Given the rising prevalence of TC and the development of obesity as an epidemic, it is important to clarify its connection with TC as well as the mediating pathways. However, unless this association is confirmed and causation proven, screening for TC in overweight and obese subjects—a rapidly increasing body of the general population—does not seem justified.

Introduction

THYROID CANCER (TC) is the most common endocrine cancer, and its incidence has risen dramatically in recent decades (1–4). Despite improved screening strategies, it has been suggested that detection of the disease at an early stage cannot fully explain the significant increase of TC rates, and the alternative of a true rise in TC incidence should be considered. Interestingly, in the same time period, both developed and developing countries have been confronted with the escalating epidemic of overweight and obesity. There is epidemiological data to support that obesity is independently associated with an increased incidence of various solid tumors, including TC (5). Several hypotheses have been formulated to suggest potential mechanisms for this link, implicating factors such as inflammation, oxidative stress, hyperinsulinemia, and adipokines. The aim of this review is to provide a clinical update on the existing literature focusing on the relation of obesity with TC and briefly to present pathophysiologic pathways underlying this association. Accordingly, we performed a search of the PubMed database for studies published in English from 1980 to March

2013 using the terms “thyroid cancer,” “obesity,” and “body mass index.”

Review

Association of obesity with thyroid cancer risk

In recent decades, the incidence of TC has increased along with a marked rise in obesity rates (6). As shown in Figure 1, the increase in obesity rates preceded the rise of TC prevalence by some years, and although there is no sharp rise in the incidence of the latter, the two curves show a parallel steady increase after a certain point. Several studies have evaluated the effect of obesity on TC risk. In one of the first reports, Ron *et al.* identified a positive relation between obesity and TC risk in women (7). In a similar vein, Goodman *et al.* performed a population-based study and showed more than a fivefold increase in the risk for TC among males, and more than a twofold increase among females in the highest compared to the lowest quartiles of weight (8). In a large meta-analysis including 282,137 cancer patients, a 5 kg/m² increase in body mass index (BMI) was related to a slightly higher TC risk

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FIG. 1. Obesity prevalence and age-adjusted thyroid cancer incidence in the United States; trends from 1960 through 2010 using data from the National Health and Nutrition Examination Survey (for obesity rates) and the National Cancer Institute's Surveillance Epidemiology and End Results data set (for thyroid cancer).

(hazard ratio [HR] 1.14 [95% confidence interval (CI) 1.06–1.23] in females, and HR 1.33 [CI 1.04–1.7] in males) (5). Similarly, in a pooled analysis of five prospective studies examining a total of 434,953 males and 413,989 females, increasing BMI was associated with a higher risk for TC in both men and women after adjusting for potential confounding factors (9). In accordance were the results of a meta-analysis by Zhao *et al.* (10), the risk of TC was significantly increased in the presence of excess body weight, either overweight or obesity (odds ratio [OR] 1.18 [CI 1.11–1.25]). According to a recent systematic review, most studies agree that obesity is positively but modestly correlated with TC risk. However, the risk estimates range widely from 1.1 to 2.3 in men and 1.0 to 7.4 in women (11).

It is likely that sex influences the association of obesity status with TC, as several studies have found such associations only in women. In a population study performed in New Caledonia, BMI was found to be strongly related to TC risk in women but not in men (12), and a similar association was reported in a European prospective study by Rinaldi *et al.* (13), who found an association of TC risk with obesity only in women (HR highest vs. lowest BMI quintile 1.41 [CI 1.03–1.94]). Likewise, in an American cohort studied by Meinhold *et al.*, only women with a BMI $> 35 \text{ kg/m}^2$ (and not men) had a significantly higher risk of TC compared to normal-weight individuals (14). Higher BMI was also related to increased TC incidence in women in the prospective European cohort study by Almquist *et al.* (15). Similarly, in a recent large Korean study that used thyroid ultrasonography screening in 15,068 euthyroid subjects, obesity was found to be significantly related to TC risk in women. This finding was independent of age, smoking, and TSH levels. Again, this relation was not significant in males (16).

Hence, it may well be that the strength of the association of TC risk with obesity is heightened in the female population. Yet, there are also reports that elevated BMI is linked with TC risk in both sexes, or even only in males. In a large Norwegian study comprising two million participants, BMI was posi-

tively associated with TC in both sexes, but the degree of this relation was modest (17). It appears that there is considerable discrepancy between the various epidemiological reports. In a 10-year follow-up cohort of 781,283 Korean men, a significant relation of obesity with papillary thyroid cancer (PTC) was reported (18), in accordance with a study performed in American male veterans (19). Somewhat different results were reported from a prospective study of 484,326 American subjects followed up for eight years, where a higher TC incidence with increasing BMI was found in men but not in women (20). To summarize, although there is no uniform conclusion, most studies support a stronger association of obesity with TC risk in the female population. However, one should acknowledge that this could be partially attributed to the lower incidence of TC in men and, consequently, to the low statistical power of studies performed in male subjects.

Besides the effect of current BMI status, there is also accumulating data on the role of anthropometric parameters during certain life periods or significant changes in body weight and their relation to TC risk. Weight gain during the transition from early to late adulthood was significantly associated with TC risk in postmenopausal women, but this relation was not significant in premenopausal individuals (8). Body weight in early adulthood was identified as a significant risk factor for TC in a case control study. In the same study, current BMI was identified as an independent risk factor for TC in the overall analysis after adjusting for age and other confounding variables, whereas high BMI during early adulthood was significantly related to TC risk only in males. Changes in weight and BMI did not have an effect on the risk for TC in either sex (21). Similarly, obesity in early adulthood was significantly associated with TC risk in a case control study in French Polynesia (22). Women who were overweight or obese at age 18 were at a significantly greater risk for TC compared to women with normal weight lifelong (OR 6.2 [CI 2.5–15.5]), and similar trends were observed for males. The longer the time period in the obese state, the higher the TC risk appeared to be. In this study, BMI changes from age 18 were

linked to a higher TC risk in women independently of their menopausal status (22). Likewise, in a French cohort of 91,909 middle-aged women, a 5 kg/m² increase in BMI was associated with a 21% increased risk of TC. The greatest risk was reported in women experiencing an increase in their body shape from lean to large during transition from menarche to adulthood with a HR of 2.17 [CI 1.04–4.53] compared to women who remained lean (23). In a pooled analysis of 12 TC studies, Dal Maso *et al.* found a direct association of BMI with TC risk in women but not in men. However, no consistent TC risk pattern could be associated with the BMI in early adulthood (24).

BMI status and weight gain in early adult life are likely to play a promoting role in TC and warrant further investigation. It could be hypothesized that there is sexual dimorphism on the effect of BMI and weight gain on TC risk and, if so, estrogens, also derived from peripheral aromatization in the adipose tissue, might be implicated in the underlying process. Despite the lack of data, one could speculate that the increase in circulating estrogens resulting from the peripheral aromatization in the adipose tissue might have a differential action in the two sexes. For example, in females, already producing significant amounts of estrogens, this might more easily exceed a “threshold” of estrogenic load, above which immune responses are possibly altered and mitogenic processes augmented. This effect could be more pronounced during transition to adulthood, a period of significant hormonal changes. Similarly, pre- and postmenopausal women also exhibit a different hormonal profile. Estrogenic deprivation after menopause might alter the response to an obesity-associated rise in circulating estrogens and its potential consequences on thyroid cell differentiation and proliferation.

The role of obesity among different TC subtypes has also been examined. Engeland *et al.* performed a histopathology-focused analysis showing that the relative risk for follicular and PTC increased with higher BMI values, and this was more prominent in women, whereas there was a trend toward decreased incidence of medullary cancer with higher BMI (17). Additionally, in a large U.S. prospective study, the relative risk for PTC increased with rising BMI values, whereas only a trend was noted for follicular and anaplastic TC and no relation could be demonstrated for medullary TC (20). Clearly, more studies are needed to elucidate the differential effect of obesity in the various TC types. According to the existing literature, obesity appears to be associated with follicular-cell derived well-differentiated thyroid tumors, whereas its effect on tumors of parafollicular and poorly differentiated cells, if any, is not clear. Of course, this may be due to the fact that these latter tumors are rare and any effect would require larger numbers in order to be shown.

Sedentary lifestyle is considered one of the major contributing factors to obesity. There are inconsistent data on the role of physical activity on TC risk. In the previously mentioned study, Leitzmann *et al.* found that the level of physical activity was unrelated to TC (20). Strangely, in a pooled analysis of five prospective studies, physical activity was associated with a higher risk for TC. This relation referred only to overweight and obese subjects and was not evident in normal-weight individuals (25). In the opposite direction, in a 15-year follow-up study, there was a trend toward lower risk for TC in women with long-term physical activity compared to their inactive peers (RR 0.77 [CI 0.57–1.04]) (26). Central adiposity was also identified as an independent determinant of higher

TC risk, which is more striking in men, whereas TC risk is further increased in the co-existence of central adiposity and obesity (27). It is also possible that not only excess weight but also the source of energy excess influences TC risk. Marcello *et al.* recently suggested that nutrient intake may play an important role in the link between obesity and TC (28). In their case control study, excess protein and carbohydrate consumption were significantly higher in TC patients compared to controls, whereas no difference was demonstrated in lipid and fiber intake and level of physical activity. When data from two case control studies with a predominantly female population from New Caledonia and French Polynesia were analyzed jointly, body surface area rather than BMI was identified as an independent determinant of TC risk (29). The association of obesity with thyroid carcinogenesis is apparently not straightforward but rather complicated, and there are several metabolic factors to be considered in the obesity–TC connection.

Despite the large body of literature linking overweight and obesity with elevated TC risk, there are some contradictory epidemiological studies showing no significant relation—or even an inverse one—between obesity and TC risk or the presence of thyroid nodules (30–32). In a recent case control study, Kitahara *et al.* evaluated 23 obesity-related gene regions in 341 TC cases and 444 control subjects (33). No association could be established between the obesity-related single-nucleotide polymorphisms and TC risk. There are also data even showing the opposite. In a case control study, Cappelli *et al.* found a lower prevalence of thyroid nodules in morbidly obese women compared to the normal-weight control group (34). In another study performed on 253 subjects with indeterminate thyroid nodule fine-needle aspiration biopsies, obesity was linked to lower malignancy rates in men. This was also shown in women under 45 years old, whereas in older women a positive relation of obesity with thyroid malignancy was present (35). Despite the few studies supporting the opposite, the majority of available literature and of large population studies favors the association of increasing BMI with higher risk of thyroid tumors. A summary of available studies evaluating the link of obesity with TC is presented in Table 1.

Obesity and thyroid cancer profile

Three recent studies have focused on the role of obesity in the clinical and pathological features of PTC. In a retrospective study of 2057 PTC patients, Kim *et al.* found that higher BMI was related to a more aggressive PTC phenotype, that is, increased tumor size, extrathyroidal invasion, and advanced disease stage, independently of age, sex, and other confounding factors. No relation was found between obesity and recurrence rates (36). Similarly, greater BMI values were linked to a more advanced stage and aggressive histopathologic subtype of PTC in the study of Harari *et al.* assessing 443 PTC patients (37). These studies are discordant from the findings of Paes *et al.* (38) who found no association of BMI with stage, vascular invasion, and recurrence of differentiated TC. In fact, the authors reported an inverse relation of BMI with nodal metastasis and tumor invasion that remained statistically significant in the multivariate analyses. One has to consider the retrospective nature of these studies as a limiting factor. Clearly, more studies are needed to clarify the link of

TABLE 1. SUMMARY OF LITERATURE DATA ON THE ROLE OF OBESITY IN THYROID CANCER RISK

<i>Author year (Ref.)</i>	<i>Study type</i>	<i>Study population</i>	<i>Results</i>
Renahan <i>et al.</i> , 2008 (5)	Meta-analysis	282,137 incident cases of various cancer types	5 kg/m ² increase in BMI associated with modestly increased TC risk <ul style="list-style-type: none"> • HR 1.14 [CI 1.06–1.23] in females • HR 1.33 [CI 1.04–1.70] in males
Goodman <i>et al.</i> , 1992 (8)	Population-based case control	151 TC cases and 431 controls TC cases: 51 men and 140 women	Higher TC risk in subjects with highest compared to lowest BMI <ul style="list-style-type: none"> • HR 6.0 in males • HR 2.3 in females
Kitahara <i>et al.</i> , 2011 (9)	Pooled analysis of five prospective U.S. studies	434,953 men and 413,979 women Thyroid cancer cases: 388 men and 768 women	Higher TC risk in postmenopausal women with highest compared to lowest degree of weight gain (OR 3.1, $p=0.04$) No significant association in premenopausal women Positive association of increasing BMI with TC risk (per 5 kg/m ² increase) <ul style="list-style-type: none"> • HR 1.16 [CI 1.08–1.24] in women • HR 1.21 [CI 0.97–1.49] in men
Zhao <i>et al.</i> , 2012 (10)	Meta-analysis	8,099,411 total sample size 5154 TC cases	Positive link between BMI in young adulthood and TC risk per 5 kg/m ² increase: HR 1.18 [CI 1.03–1.35] Excess body weight associated with increased TC risk <ul style="list-style-type: none"> • OR: 1.18 [CI 1.11–1.25] • OR: 1.13 [CI 1.04–1.22] for overweight • OR: 1.29 [CI 1.18–1.41] for obesity
Guignard <i>et al.</i> , 2007 (12)	Countrywide case control	332 TC cases and 412 population controls	Positive association of obesity with TC risk in women <ul style="list-style-type: none"> • HR 1.92 [CI 1.14–3.22] compared to normal weight
Meinhold <i>et al.</i> , 2010 (14)	Cohort	90,713 radiologic technologists 282 incident TC cases (242 women, 40 men)	Insignificant relation in men Positive relation of BMI >35 kg/m ² with TC risk in women <ul style="list-style-type: none"> • HR 1.74 [CI 1.03–2.94] compared to normal weight
Rinaldi <i>et al.</i> , 2012 (13)	Cohort	343,765 female and 146,824 male participants 566 incident TC cases (508 women, 58 men)	No significant association in men Significant association of obesity with TC risk in women <ul style="list-style-type: none"> • HR highest vs. lowest quintile: 1.41 [CI 1.03–1.94]
Almqvist <i>et al.</i> , 2011 (15)	Cohort	578,700 participants 388 incident TC cases (255 women, 133 men)	Insignificant relation in men Positive association of BMI with TC risk in women <ul style="list-style-type: none"> • Adjusted calibrated relative risk 1.24 [CI 1.03–1.48] for standardized BMI
Han <i>et al.</i> , 2013 (16)	Cross-sectional	8491 men and 6577 women screened with thyroid ultrasonography 267 TC cases	No significant relation in men Higher TC risk with higher BMI values in women Per 5 kg/m ² of BMI increase <ul style="list-style-type: none"> • OR 1.63 [CI 1.24–2.10]
Engeland <i>et al.</i> , 2006 (17)	Cohort	2,001,727 participants	Insignificant association in men <ul style="list-style-type: none"> • OR 1.16 [CI 0.85–1.57] Increased TC risk in obese vs. normal weight <ul style="list-style-type: none"> • HR 1.14 [CI 0.82–1.56] in men • HR 1.29 [CI 1.13–1.46] in women <ul style="list-style-type: none"> ◦ HR 1.19 [CI 1.01–1.41] for papillary carcinoma ◦ HR 1.63 [CI 1.24–2.15] for follicular carcinoma ◦ HR 0.35 [CI 0.16–0.79] for medullary carcinoma

(continued)

TABLE 1. (CONTINUED)

<i>Author year (Ref.)</i>	<i>Study type</i>	<i>Study population</i>	<i>Results</i>
Oh <i>et al.</i> , 2005 (18)	10-year follow-up cohort	781,283 men	Higher TC risk in men with BMI 27–29.9 kg/m ² compared to BMI 18.5–22.9 kg/m ² • HR 2.23 [CI 1.40–3.55]
Samanic <i>et al.</i> , 2004 (19)	Cohort	4,500,700 veterans	Increased TC risk in obese compared to nonobese U.S. veterans • HR 1.40 [CI 1.09–1.81] in white men • HR 1.92 [CI 1.09–3.40] in black men
Leitzmann <i>et al.</i> , 2010 (20)	Cohort	484,326 participants 352 incident TC cases (171 men, 181 women)	Higher TC risk in obese compared to normal-weight men • HR 1.89 [CI 1.21–2.96] No significant relation in women Obesity associated with papillary TC; no relation with follicular, anaplastic, and medullary TC • OR 1.47 [CI 1.03–2.10] for papillary TC • OR 1.49 [CI 0.79–2.82] for follicular TC • OR 0.97 [CI 0.27–3.43] for medullary TC • OR 5.80 [CI 0.99–34.19] for anaplastic TC No relation of physical activity with TC risk • OR 1.01 [CI 0.76–1.34]
Suzuki <i>et al.</i> , 2008 (21)	Case-control	173 TC patients and 865 age- and sex-matched controls	Positive association of current BMI and weight at 20 years with TC risk OR in the top compared to lowest tertile • 1.71 [CI 1.06–2.78] and • 2.69 [CI 1.71–4.25] respectively
Brindel <i>et al.</i> , 2009 (22)	Case-control	219 cases of TC with 359 population controls	Higher TC risk in overweight/obese women compared to women with normal weight lifelong • OR 6.2 [CI 2.5–15.5]
Clavel-Chapelon <i>et al.</i> , 2010 (23)	Cohort	91,909 women 317 incident thyroid cancer cases	Higher TC risk in women with an increase of body weight between menarche and adulthood compared to women who remained lean • HR 2.17 [CI 1.04–4.53]
Dal Maso <i>et al.</i> , 2000 (24)	Pooled analysis of 12 case control studies	2056 female and 417 male cases, 3358 female and 965 male controls	Positive association of BMI with thyroid cancer risk in females • OR 1.2 [CI 1.0–1.4] for the highest compared to the lowest tertile No significant relation of BMI with TC risk in males
Kitahara <i>et al.</i> , 2012 (25)	Pooled analysis of five U.S.-based prospective cohorts	Total population of 362,342 men and 312,149 women 308 men and 510 women with TC	Increased TC risk in higher vs. lower level of physical activity • HR 1.18 [CI 1.00–1.39] Significant association in overweight and obese subjects • HR 1.34 [CI 1.09–1.64] Insignificant relation in normal weight subjects • HR 0.92 [CI 0.69–1.22]
Cash <i>et al.</i> , 2013 (26)	Prospective cohort	116,939 women 275 TC cases	Trend toward lower TC in women with long-term physical activity compared to inactive ones • RR: 0.77 [CI 0.57–1.04]
Kitahara <i>et al.</i> , 2012 (27)	Cohort	Study population 125,347 men and 72,363 women 106 men and 105 women with TC	Central adiposity linked with higher TC risk • HR 1.79 [CI 1.21–2.63] in men • HR 1.54 [CI 1.05–2.26] in women

(continued)

TABLE 1. (CONTINUED)

Author year (Ref.)	Study type	Study population	Results
Marcello <i>et al.</i> , 2012 (28)	Case control	115 TC cases 103 healthy individuals	The combination of central adiposity with obesity further increased TC risk <ul style="list-style-type: none"> • HR 2.13 [CI 1.18–3.85] in men • HR 1.91 [CI 1.31–3.25] in women Excess weight (BMI > 25 kg/m ²) associated with increased TC risk <ul style="list-style-type: none"> • OR 3.787 [CI 1.12–6.81] OR 5.89 [CI 3.12–11.10] for excess calories OR 4.60 [CI 1.63–12.95] for excess protein OR 4.90 [CI 2.59–9.28] for excess carbohydrate No relation of TC risk with lipid/ fiber intake ($p=0.894$) No relation with physical activity ($p=0.593$) Higher TC risk with highest vs. lowest BMI values <ul style="list-style-type: none"> • OR 3.01 [CI 2.02–14.48] for women • OR 1.69 [CI 0.65–4.42] for men BSA identified as an independent risk factor for TC in women OR 3.21 [CI 1.25–8.30] per m ² increase of BSA No significant relation of overweight/obesity with TC risk
Cléro <i>et al.</i> , 2010 (29)	Pooled analysis of two case control studies	554 TC cases (65 men and 489 women) 776 age- and sex-matched control subjects	
Iribarren <i>et al.</i> , 2001 (30)	Cohort, 20-year follow-up	204,964 subjects 196 incident thyroid cancers: 73 men and 123 women	
Rapp <i>et al.</i> , 2005 (31)	Population-based cohort	167,371 adults (49,336 females) 61 incident TC cases in women	No significant association of BMI status with TC risk <ul style="list-style-type: none"> • HR 1.45 [CI 0.82–2.58] for overweight • HR 1.18 [CI 0.53–2.65] for obesity No difference in BMI between malignant and benign thyroid nodules
Kim <i>et al.</i> , 2012 (32)	Cross-sectional	7763 subjects (4681 men and 3082 women)	No significant association of 23 obesity-related single-nucleotide polymorphisms with TC risk
Kitahara <i>et al.</i> , 2012 (33)	Case control	341 PTC cases and 444 controls	Lower prevalence of thyroid nodules in obese compared to nonobese women
Cappelli <i>et al.</i> , 2012 (34)	Case control	108 female euthyroid obese patients and 97 nonobese controls	• OR 0.29 [CI 0.21–0.38]
Mijovic <i>et al.</i> , 2009 (35)	Cross-sectional	253 patients with indeterminate thyroid nodule FNABs	Lower TC rate in obese compared to normal weight and overweight men and in women < 45 years (36% vs. 72%, $p=0.003$ and 36% vs. 68%, $p=0.043$ respectively)
Kim <i>et al.</i> , 2013 (36)	Retrospective	2057 patients with PTC	Independent association of BMI status with larger tumor size, microscopic extrathyroidal invasion and advanced disease stage
Harari <i>et al.</i> , 2012 (37)	Retrospective	443 patients with PTC	Significant relation of obesity with more advanced disease stage at presentation and more aggressive histopathologic subtype
Paes <i>et al.</i> , 2010 (38)	Retrospective	259 differentiated TC patients	Inverse association of BMI with nodal metastasis and tumor invasion in uni- and multivariate analyses

TC, thyroid cancer; BMI, body mass index; HR, hazard ratio; CI, 95% confidence interval; OR, odds ratio; FNAB, fine needle aspiration biopsy; PTC, papillary thyroid carcinoma; BSA, body surface area.

FIG. 2. Proposed mechanisms underlying the obesity–thyroid cancer relation. IR, insulin receptor; IRS-1, insulin receptor substrate 1; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; mTOR, mammalian target of rapamycin; AMPK, AMP-activated protein kinase; IGF-1, insulin-like growth factor 1; IGF-1R, IGF-1 receptor; IGFBPs, IGF-1 binding proteins; MAPK, mitogen-activated protein kinase; RAF-1/MEK/ERK, proto-oncogene serine/threonine-protein kinase/MAPK kinase/extracellular-signal-regulated kinase; PAI-1, plasminogen activator inhibitor-1; VEGF, vascular endothelial growth factor; SHBG, sex hormone binding globulin; IL-6, interleukin 6; TNF- α , tumor necrosis factor alpha; NF- κ B, nuclear factor kappa-beta; FFA, free fatty acids; ROS, reactive oxygen species.

adiposity with clinicopathological features of TC and evaluate its possible role as a prognostic factor.

Possible underlying mechanisms

Various hypotheses have been offered to interpret the connection of obesity with TC, including the upregulation of mitogenic pathways in the presence of hyperinsulinemia, low-grade inflammation, and oxidative stress, common denominators of obesity, especially with central fat distribution. A plausible scenario could involve proliferative pathways activated by insulin and IGF-1. TC patients were found to have insulin resistance at a significantly higher rate compared to the control group in the study of Rezzonico *et al.* (50% vs. 10%, $p < 0.001$). However, the number of cases was very small (39). There is discordance in the current literature on the association of insulin resistance with TC risk (16,40), and there are also epidemiological studies, in which this factor has not been controlled for (17,20,22,23).

Additionally, there are accumulating epidemiological data showing an independent association of TSH levels with obesity even in the absence of hypothyroidism (41), while at the same time TC patients have, as a group, higher TSH levels (42). There is also evidence of a positive association between TSH levels and advanced disease stage (43). One cannot exclude the possibility that the higher TSH levels observed in overweight and obese subjects might have a direct effect in thyroid tumorigenesis. This is supported by *in vitro* and animal models demonstrating a mitogenic effect of TSH on thy-

roid follicular cells (44). The TSH receptor mediated increase in intracellular cAMP levels is considered the major stimulus for thyroid cell proliferation. It appears that TSH interacts with other growth factors, such as insulin and IGF-1 (45), and other pathways, including the RAS-BRAF and the PI3 kinase-AKT pathways, are also implicated (46).

Furthermore, there are recent data supporting the notion that adipokines, such as leptin and adiponectin, may be directly implicated. Leptin levels were higher in TC patients compared to healthy subjects in the case control study of Hedayati *et al.* (47). In the studies of Cheng *et al.*, leptin and its receptor were found to be overexpressed in PTC cells and associated with an aggressive phenotype, that is, larger tumor size and nodal metastasis (48). The same authors also provided evidence that epigenetic effects and stimulation by insulin regulate leptin and leptin receptor expression in PTC (49). In the same line, Uddin *et al.* demonstrated that leptin acts via its receptor to induce PTC cell proliferation and inhibit apoptosis (50). Leptin was also shown to enhance migration of PTC cells, whereas it inhibited migration of anaplastic and follicular cancer cells (51,52). Concerning adiponectin, an opposite pattern was identified. Although Cheng *et al.* showed overexpression of its receptors in certain thyroid tumor types, this was linked to a better clinicopathological profile and improved outcomes (53). In a study in humans, Mitsiadis *et al.* reported an inverse relation of circulating adiponectin levels with TC risk (54). The role of adipokines in the interplay between obesity and TC is an interesting subject of research and should be further explored.

Lastly, the stronger association of obesity with TC in females observed in many studies could point to a direct effect of sex steroids in thyroid carcinogenesis. There are experimental data supporting a mitogenic effect of estrogen in thyroid tumors (55), whereas a pooled analysis of clinical studies suggested a modestly increased risk in women receiving oral contraceptives, gradually decreasing after discontinuation (56). Still, both *in vitro* and clinical findings concern the effect of exogenous hormones, whereas the role—if any—of endogenous sex steroids has not been well determined. A significant alteration in the balance between estrogens and androgens occurs in women in the menopausal transition, a time period usually accompanied by weight gain and increase of central fat, whereas also in obese men, aromatase activity in the adipose tissue contributes to endogenous estrogen production. Should a causative link between obesity and TC exist, it is most likely multifactorial with a cross-talk between the various pathways. A summary of potential pathophysiologic pathways linking obesity with thyroid tumorigenesis is illustrated in Figure 2.

Caveats

Clearly, there are certain factors that should be considered when trying to interpret studies of TC risk in overweight and obese individuals. It is possible that confounders, such as age, sex, ethnicity, smoking habits, as well as heterogeneity in study size, may explain the lack of uniformity in the reported findings. The different methodology of the studies and the varying BMI should also be taken into account. Obesity is the result of various genetic, metabolic, and environmental factors, and it is therefore very difficult to control independently for each one of these and clarify its possible contribution to the obesity–TC relation. The importance of a statistically significant finding depends on the level of its clinical relevance and the impact it could have on everyday practice. Unless larger prospective studies validate the positive association between obesity and TC and the underlying pathways are untangled, screening for TC in overweight and obese subjects, a rapidly increasing body of the general population, does not seem justified.

Conclusions

In this review, an attempt has been made to summarize clinical data on the relation of obesity with TC. The prevalence of TC is rising, and evidence is beginning to accumulate that obesity is independently related to an increased TC risk. Although there is some discordance in the existing literature, this association might be stronger in the female population. It is also possible that weight changes during early adulthood might play a role in thyroid tumorigenesis. More studies are required to elucidate the role of obesity in the progression and outcome of TC. Increased vigilance for TC among overweight and obese individuals is not justified at the moment. However, the possibility of a causative relation between obesity and TC could increase public awareness. It could potentially function as an additional motive in obesity prevention campaigns in order to pursue a healthier lifestyle and avoid weight gain. Furthermore, if the link between obesity and TC is proven to be causative and strong, a successful public health program decreasing the prevalence of obesity is anticipated to be accompanied by a decrease in TC rates in the long term. Given the development of obesity as an epidemic, it is im-

portant to clarify its connection with TC, as well as the contribution of several obesity-related signaling pathways in the pathogenesis of TC.

Author Disclosure Statement

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References

- Morris LG, Myssiorek D 2010 Improved detection does not fully explain the rising incidence of well-differentiated thyroid cancer: a population-based analysis. *Am J Surg* **200**:454–461.
- Davies L, Welch H 2006 Increasing incidence of thyroid cancer in the United States, 1973–2002. *JAMA* **295**:2164–2167.
- Chen AY, Jemal A, Ward EM 2009 Increasing incidence of differentiated thyroid cancer in the United States, 1988–2005. *Cancer* **115**:3801–3807.
- Enewold L, Zhu K, Ron E, Marrogi AJ, Stojadinovic A, Peoples GE, Devesa SS 2009 Rising thyroid cancer incidence in the United States by demographic and tumor characteristics, 1980–2005. *Cancer Epidemiol Biomarkers Prev* **18**:784–791.
- Renahan AG, Tyson M, Egger M, Heller RF, Zwahlen M 2008 Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet* **371**:569–578.
- Simard EP, Ward EM, Siegel R, Jemal A 2012 Cancers with increasing incidence trends in the United States: 1999 through 2008. *CA Cancer J Clin* **122**:Jan 4 [Epub ahead of print]; DOI: 10.3322/caac.20141.
- Ron E, Kleinerman RA, Boice JD Jr, LiVolsi VA, Flannery JT, Fraumeni JF Jr 1987 A population-based case-control study of thyroid cancer. *J Natl Cancer Inst* **79**:1–12.
- Goodman MT, Kolonel LN, Wilkens LR 1992 The association of body size, reproductive factors and thyroid cancer. *Br J Cancer* **66**:1180–1194.
- Kitahara CM, Platz EA, Freeman LE, Hsing AW, Linet MS, Park Y, Schairer C, Schatzkin A, Shikany JM, Berrington de González A 2011 Obesity and thyroid cancer risk among U.S. men and women: a pooled analysis of five prospective studies. *Cancer Epidemiol Biomarkers Prev* **20**:464–472.
- Zhao ZG, Guo XG, Ba CX, Wang W, Yang YY, Wang J, Cao HY 2012 Overweight, obesity and thyroid cancer risk: a meta-analysis of cohort studies. *J Int Med Res* **40**:2041–2050.
- Peterson E, De P, Nuttall R 2012 BMI, diet and female reproductive factors as risks for thyroid cancer: a systematic review. *PLoS One* **7**:e29177.
- Guignard R, Truong T, Rougier Y, Baron-Dubourdieu D, Guénel P 2007 Alcohol drinking, tobacco smoking, and anthropometric characteristics as risk factors for thyroid cancer: a countrywide case-control study in New Caledonia. *Am J Epidemiol* **166**:1140–1149.
- Rinaldi S, Lise M, Clavel-Chapelon F, Boutron-Ruault MC, Guillas G, Overvad K, Tjønneland A, Halkjær J, Lukanova A, Kaaks R, Bergmann MM, Boeing H, Trichopoulos A, Zylis D, Valanou E, Palli D, Agnoli C, Tumino R, Polidoro S, Mattiello A, Bueno-de-Mesquita HB, Peeters PH, Weiderpass E, Lund E, Skeie G, Rodríguez L, Travier N, Sánchez MJ, Amiano P, Huerta JM, Ardanaz E, Rasmuson T, Hallmans G, Almquist M, Manjer J, Tsilidis KK, Allen NE, Khaw KT, Wareham N, Byrnes G, Romieu I, Riboli E, Franceschi S 2012 Body size and risk of differentiated thyroid carcinomas: findings from the EPIC study. *Int J Cancer* **131**:E1004–E1014.
- Meinhold CL, Ron E, Schonfeld SJ, Alexander BH, Freedman DM, Linet MS, Berrington de González A 2010 Nonradiation

- risk factors for thyroid cancer in the US Radiologic Technologists Study. *Am J Epidemiol* **171**:242–252.
15. Almquist M, Johansen D, Bjørge T, Ulmer H, Lindkvist B, Stocks T, Hallmans G, Engeland A, Rapp K, Jonsson H, Selmer R, Diem G, Häggström C, Tretli S, Stattin P, Manjer J 2011 Metabolic factors and risk of thyroid cancer in the Metabolic Syndrome and Cancer Project (Me-Can). *Cancer Causes Control* **22**:743–751.
 16. Han JM, Kim TY, Jeon MJ, Yim JH, Kim WG, Song DE, Hong SJ, Bae SJ, Kim HK, Shin MH, Shong YK, Kim WB 2013 Obesity is a risk factor for thyroid cancer in a large, ultrasonographically screened population. *Eur J Endocrinol* **168**:879–886.
 17. Engeland A, Tretli S, Akslen LA, Bjørge T 2006 Body size and thyroid cancer in two million Norwegian men and women. *Br J Cancer* **95**:366–370.
 18. Oh SW, Yoon YS, Shin SA 2005 Effects of excess weight on cancer incidences depending on cancer sites and histologic findings among men: Korea National Health Insurance Corporation Study. *J Clin Oncol* **23**:4742–4754.
 19. Samanic C, Gridley G, Chow WH, Lubin J, Hoover RN, Fraumeni JF Jr 2004 Obesity and cancer risk among white and black United States veterans. *Cancer Causes Control* **15**:35–43.
 20. Leitzmann MF, Brenner A, Moore SC, Koebnick C, Park Y, Hollenbeck A, Schatzkin A, Ron E 2010 Prospective study of body mass index, physical activity and thyroid cancer. *Int J Cancer* **126**:2947–2956.
 21. Suzuki T, Matsuo K, Hasegawa Y, Hiraki A, Kawase T, Tanaka H, Tajima K 2008 Anthropometric factors at age 20 years and risk of thyroid cancer. *Cancer Causes Control* **19**:1233–1242.
 22. Brindel P, Doyon F, Rachédi F, Boissin JL, Sebbag J, Shan L, Chungue V, Bost-Bezeaud F, Petitdidier P, Paoaafaite J, Teuri J, de Vathaire F 2009 Anthropometric factors in differentiated thyroid cancer in French Polynesia: a case-control study. *Cancer Causes Control* **20**:581–590.
 23. Clavel-Chapelon F, Guillas G, Tondeur L, Kernaléguen C, Boutron-Ruault MC 2010 Risk of differentiated thyroid cancer in relation to adult weight, height and body shape over life: the French E3N cohort. *Int J Cancer* **126**:2984–2990.
 24. Dal Maso L, La Vecchia C, Franceschi S, Preston-Martin S, Ron E, Levi F, Mack W, Mark SD, McTiernan A, Kolonel L, Mabuchi K, Jin F, Wingren G, Galanti MR, Hallquist A, Glatte E, Lund E, Linos D, Negri E 2000 A pooled analysis of thyroid cancer studies. V. Anthropometric factors. *Cancer Causes Control* **11**:137–144.
 25. Kitahara CM, Platz EA, Beane Freeman LE, Black A, Hsing AW, Linet MS, Park Y, Schairer C, Berrington de González A 2012 Physical activity, diabetes, and thyroid cancer risk: a pooled analysis of five prospective studies. *Cancer Causes Control* 2012 Feb 1 [Epub ahead of print]; DOI: 10.1007/s10552-012-9896-y.
 26. Cash SW, Ma H, Horn-Ross PL, Reynolds P, Canchola AJ, Sullivan-Halley J, Beresford SA, Neuhauser ML, Vaughan TL, Heagerty PJ, Bernstein L 2013 Recreational physical activity and risk of papillary thyroid cancer among women in the California Teachers Study. *Cancer Epidemiol* **37**:46–53.
 27. Kitahara CM, Platz EA, Park Y, Hollenbeck AR, Schatzkin A, Berrington de González A 2012 Body fat distribution, weight change during adulthood, and thyroid cancer risk in the NIH-AARP Diet and Health Study. *Int J Cancer* **130**:1411–1419.
 28. Marcello MA, Sampaio AC, Geloneze B, Vasques AC, Assumpção LV, Ward LS 2012 Obesity and excess protein and carbohydrate consumption are risk factors for thyroid cancer. *Nutr Cancer* **64**:1190–1195.
 29. Cléro E, Leux C, Brindel P, Truong T, Anger A, Teinturier C, Diallo I, Doyon F, Guénel P, de Vathaire F 2010 Pooled analysis of two case-control studies in New Caledonia and French Polynesia of body mass index and differentiated thyroid cancer: the importance of body surface area. *Thyroid* **20**:1285–1293.
 30. Iribarren C, Haselkorn T, Tekawa IS, Friedman GD 2001 Cohort study of thyroid cancer in a San Francisco Bay area population. *Int J Cancer* **93**:745–750.
 31. Rapp K, Schroeder J, Klenk J, Stoehr S, Ulmer H, Concin H, Diem G, Oberaigner W, Weiland SK 2005 Obesity and incidence of cancer: a large cohort study of over 145,000 adults in Austria. *Br J Cancer* **93**:1062–1067.
 32. Kim JY, Jung EJ, Park ST, Jeong SH, Jeong CY, Ju YT, Lee YJ, Hong SC, Choi SK, Ha WS 2012 Body size and thyroid nodules in healthy Korean population. *J Korean Surg Soc* **82**:13–17.
 33. Kitahara CM, Neta G, Pfeiffer RM, Kwon D, Xu L, Freedman ND, Hutchinson AA, Chanock SJ, Sturgis EM, Sigurdson AJ, Brenner AV 2012 Common obesity-related genetic variants and papillary thyroid cancer risk. *Cancer Epidemiol Biomarkers Prev* **21**:2268–2271.
 34. Cappelli C, Pirola I, Mittempergher F, De Martino E, Casella C, Agosti B, Nascimbeni R, Formenti A, Rosei EA, Castellano M 2012 Morbid obesity in women is associated to a lower prevalence of thyroid nodules. *Obes Surg* **22**:460–464.
 35. Mijović T, How J, Pakdaman M, Rochon L, Gologan O, Hier MP, Black MJ, Young J, Tamilia M, Payne RJ 2009 Body mass index in the evaluation of thyroid cancer risk. *Thyroid* **19**:467–472.
 36. Kim HJ, Kim NK, Choi JH, Sohn SY, Kim SW, Jin SM, Jang HW, Suh S, Min YK, Chung JH, Kim SW 2013 Associations between body mass index and clinico-pathological characteristics of papillary thyroid cancer. *Clin Endocrinol (Oxf)* **78**:134–140.
 37. Harari A, Endo B, Nishimoto S, Ituarte PH, Yeh MW 2012 Risk of advanced papillary thyroid cancer in obese patients. *Arch Surg* **147**:805–811.
 38. Paes JE, Hua K, Nagy R, Kloos RT, Jarjoura D, Ringel MD 2010 The relationship between body mass index and thyroid cancer pathology features and outcomes: a clinicopathological cohort study. *J Clin Endocrinol Metab* **95**:4244–4250.
 39. Rezzónico JN, Rezzónico M, Pusiol E, Pitoia F, Niemniesz H 2009 Increased prevalence of insulin resistance in patients with differentiated thyroid carcinoma. *Metab Syndr Relat Disord* **7**:375–380.
 40. Randi G, Ferraroni M, Talamini R, Garavento W, Deandrea S, Decarli A, Franceschi S, La Vecchia C 2008 Glycemic index, glycemic load and thyroid cancer risk. *Ann Oncol* **19**:380–383.
 41. Fox CS, Pencina MJ, D'Agostino RB, Murabito JM, Seely EW, Pearce EN, Vasan RS 2008 Relations of thyroid function to body weight: cross-sectional and longitudinal observations in a community-based sample. *Arch Intern Med* **168**:587–592.
 42. Fiore E, Vitti P 2012 Serum TSH and risk of papillary thyroid cancer in nodular thyroid disease. *J Clin Endocrinol Metab* **97**:1134–1145.
 43. McLeod DS, Cooper DS, Ladenson PW, Ain KB, Brierley J, Fein HG, Haugen BR Md, Jonklaas J, Magner J, Ross DD, Young MS Md, Steward D, Maxon H, Sherman SI 2013 Prognosis of differentiated thyroid cancer in relation to se-

- rum TSH and thyroglobulin antibody status at time of diagnosis. *Thyroid* **24**:35–42.
44. Rivas M, Santisteban P 2003 TSH-activated signaling pathways in thyroid tumorigenesis. *Mol Cell Endocrinol* **213**: 31–45.
45. Takada K, Amino N, Tada H, Miyai K 1990 Relationship between proliferation and cell cycle-dependent Ca²⁺ influx induced by a combination of thyrotropin and insulin-like growth factor-I in rat thyroid cells. *J Clin Invest* **86**:1548–1555.
46. Xing M 2013 Molecular pathogenesis and mechanisms of thyroid cancer. *Nat Rev Cancer* **13**:184–199.
47. Hedayati M, Yaghmaei P, Pooyamanesh Z, Zarif Yeganeh M, Hoghooghi Rad L 2011 Leptin: a correlated peptide to papillary thyroid carcinoma? *J Thyroid Res* **2011**:832163.
48. Cheng SP, Chi CW, Tzen CY, Yang TL, Lee JJ, Liu TP, Liu CL 2010 Clinicopathologic significance of leptin and leptin receptor expressions in papillary thyroid carcinoma. *Surgery* **147**:847–853.
49. Cheng SP, Liu CL, Hsu YC, Chang YC, Huang SY, Lee JJ 2012 Regulation of leptin receptor expression in human papillary thyroid cancer cells. *Biomed Pharmacother* **66**:469–473.
50. Uddin S, Bavi P, Siraj AK, Ahmed M, Al-Rasheed M, Hussain AR, Ahmed M, Amin T, Alzahrani A, Al-Dayel F, Abubaker J, Bu R, Al-Kuraya KS 2010 Leptin-R and its association with PI3K/AKT signaling pathway in papillary thyroid carcinoma. *Endocr Relat Cancer* **17**:191–202.
51. Cheng SP, Yin PH, Hsu YC, Chang YC, Huang SY, Lee JJ, Chi CW 2011 Leptin enhances migration of human papillary thyroid cancer cells through the PI3K/AKT and MEK/ERK signaling pathways. *Oncol Rep* **26**:1265–1271.
52. Cheng SP, Yin PH, Chang YC, Lee CH, Huang SY, Chi CW 2010 Differential roles of leptin in regulating cell migration in thyroid cancer cells. *Oncol Rep* **23**:1721–1727.
53. Cheng SP, Liu CL, Hsu YC, Chang YC, Huang SY, Lee JJ 2013 Expression and biologic significance of adiponectin receptors in papillary thyroid carcinoma. *Cell Biochem Biophys* **65**:203–210.
54. Mitsiades N, Pazaitou-Panayiotou K, Aronis KN, Moon HS, Chamberland JP, Liu X, Diakopoulos KN, Kyttaris V, Panagiotou V, Mylvaganam G, Tseleni-Balafouta S, Mantzoros CS 2011 Circulating adiponectin is inversely associated with risk of thyroid cancer: in vivo and in vitro studies. *J Clin Endocrinol Metab* **96**:E2023–E2028.
55. Manole D, Schildknecht B, Gosnell B, Adams E, Derwahl M 2001 Estrogen promotes growth of human thyroid tumor cells by different molecular mechanisms. *J Clin Endocrinol Metab* **86**:1072–1077.
56. La Vecchia C, Ron E, Franceschi S, Dal Maso L, Mark SD, Chatenoud L, Braga C, Preston-Martin S, McTiernan A, Kolonel L, Mabuchi K, Jin F, Wingren G, Galanti MR, Hallquist A, Lund E, Levi F, Linos D, Negri E 1999 A pooled analysis of case-control studies of thyroid cancer. III. Oral contraceptives, menopausal replacement therapy and other female hormones. *Cancer Causes Control* **10**:157–166.

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