[Frontiers in Bioscience S3, 555-564, January 1, 2011]

Obesity and thyroid cancer

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1. ABSTRACT

With the current trend of alarming rise in obesity rates, the health impacts of excess weight will become more apparent. While an increased incidence of cardiovascular disease and diabetes mellitus has been well documented, the association between obesity and carcinogenesis is just being appreciated and is receiving increasing attention. The current review focuses on the evidence linking thyroid cancer with obesity. We conclude that there is sufficient evidence that obesity can predispose to an increased risk of thyroid cancer in both men and women. This population-based association is mainly explained at a biological level through specific obesity-related endocrinopathies.

2. INTRODUCTION

The growing global epidemic of excess weight and obesity (1,2) has been shown to be associated with serious health impacts including hypertension, type 2 diabetes mellitus, dyslipidemia, cardiovascular disease, metabolic syndrome and musculoskeletal disorders (3). Accumulating epidemiologic evidence also shows that excess weight is linked with an increased risk of several common adult cancers (4). Breast, endometrial, prostate and colon cancer are the most cited malignancies where excess body fatness is recognized as an important risk factor (4-8). However, several other cancers have been linked with obesity, including thyroid cancer (5).

In the last decade, thyroid cancer incidence rose annually by 5.8% among men and 7.1% among women in the US, a more rapid increase than for any other cancer site, thus bringing thyroid malignancy as the seventh most common cancer in women in the US (9,10). Similar data has also been reported by several other industrialized nations, including Canada, Sweden, Norway and Great Britain (11,12). This pronounced upward trend can be explained by an improved detection of very small papillary tumours and revisions in diagnostic criteria, but it is likely that changes in environmental risk factors are also playing an important role (9). From radiation exposure from computed tomography imaging (13) to dietary changes, passing through female hormonal and reproductive factors, it is clear that etiologic heterogeneity is at play in the pathogenesis of thyroid cancer (11).

Interestingly, the rise in thyroid cancer incidence parallels the increasing trend of obesity, and one could wonder about a possible etiological relationship. Indeed, the most recent prospective studies seem to suggest that obesity might be one important underlying factor at least partially explaining the rising frequency of thyroid cancer (9). The present article is a review of the evidence linking thyroid malignancy with obesity with a special emphasis on the possible pathways of pathogenesis.

3. THE UNDERLYING EVIDENCE

3.1. Population-based studies

3.1.1. Case-control studies

Historically, thyroid cancer is relatively uncommon, accounting for less then 2% of all malignancies in Canada and worldwide (11). The search for its etiology was therefore started through a case-control approach, with eleven such published studies in 2000 looking at the effect of body mass index (BMI) on thyroid cancer risk (14-24). There was, however, considerable heterogeneity between studies as to the actual relationship between BMI and thyroid malignancy with only two studies documenting an increase in thyroid cancer among women with higher BMI, (17, 20) while no significant association was described in the other studies. In 2000, a pooled analysis of twelve case-control studies conducted around the world (the eleven previously mentioned studies and one personal unpublished communication) concluded that the BMI at the time of diagnosis was associated with a small increase in thyroid cancer risk in women only (odd ratio of 1.2 for the highest tertile of BMI with a 95%CI: 1.0-1.4), with a similar magnitude in older postmenopausal women as in the younger ones (25). The association was similar for both papillary and follicular phenotype of thyroid cancer (25).

Following the pooled analysis, a few additional well-controlled studies were published, but their results continue to feed the controversy on the relationship between thyroid cancer and obesity. Indeed, a case-control study of 292 premenopausal women with thyroid cancer from the Los Angeles county showed that BMI was not associated with thyroid cancer risk (26).

Conversely, in New Caledonia, a study with 332 cases of thyroid cancer found a strong positive association with weight and BMI in Melanesian women aged 50 years or more, with an odds ratio of 5.5 for BMI above 35 kg/m^2 compared with normal-weight women, with a clear dose-response trend. No association with BMI was found in men (27). Similarly, a case-control study of 219 patients with differentiated thyroid cancer among native-residents of French Polynesia found that women who were overweight or obese at age 18 and before diagnosis had an increased risk compared with those with a normal lifelong weight (Odds ratio of 6.2; 95% CI 2.5-15.5; p less than 0.01) (28).

At the same time, a Japanese case-control study of 173 cases of thyroid cancer showed that body size at the age of 20 as well as at the time of diagnosis was associated with an increased risk of thyroid cancer in both men and women, with the current BMI adjusted odds ratio for thyroid cancer being 1.71 (95%CI 1.06-2.78; trend p equal to 0.034). There was no association between thyroid cancer risk and change in anthropometric factors since age 20 years (29).

Overall, the case-control studies conducted up to now seem to suggest that obesity is linked with thyroid cancer in women and such a relationship is likely stronger in postmenopausal women. There is, however, a debatable level of evidence for the existence of such a relationship in men, but it is possible that the lower incidence of thyroid malignancy in males and the small number of cases makes it harder to draw any significant conclusions.

3.1.2. Prospective cohort studies

The relationship between thyroid cancer and obesity has been investigated in eight cohort studies (9,30-36) out of which five were included in a meta-analysis (5). Despite the prospective nature of these studies and the large population sizes, controversial results still persist.

Indeed, two large population-based studies (the first undertaken in 204,964 subjects from the San Francisco Bay area followed for a median of 20 years (30) and the second involving 145,000 Austrian adults followed over an average of 9.9 years (31)) showed no correlation between an increased BMI and increased risk of thyroid malignancy for both sexes.

In studies conducted exclusively in men, variable results were also obtained. In one large cohort of male US veterans (3,668,486 whites; 832,214 blacks) the diagnosis of obesity was associated with an increased risk of thyroid cancer for both white and black men to a similar extent (respectively, RR:1.4; 95%CI 1.09-1.18 and RR:1.92; 95%CI 1.09-3.4) (32). Similarly, in a 10-year follow-up cohort of 781,283 Korean men there was a significant positive dose-dependent relationships between BMI and thyroid cancer. In this population, it was estimated that the population-attributable fraction of obesity-related thyroid cancer was 18.4% (95%CI: 9.0-26.8) (34). However, no clear association was observed in a study of 362,552 Swedish construction workers where obesity was associated with a relative risk for thyroid cancer of 0.98 (95%CI 0.49-1.96, p-trend equal to 0.48) (33).

Several prospective studies have documented the significant impact of obesity on thyroid cancer risk in women. In a cohort study of 22 964 Icelanders, weight, BMI, body surface area and body fat were significant positive risk factors for thyroid cancer in females (35). Remaining in the Scandinavian region, a study of 2 million Norwegians showed a moderately increased relative risk of thyroid cancer for a BMI of 30 kg/m^2 or more for all women, but no difference in magnitude with respect to age was noted (RR:1.25; 95% CI 1.04-1.51; p equal to 0.04 for women under the age of 50, and RR:1.31; 95%CI 1.09-1.57; p equal to 0.001 for women of 50 years and older) (36). The anthropomorphic measures were, however, taken on average 15 years before the diagnosis of cancer, and the weight gain occurring at the time of menopause might have not been taken into account. Histology specific analyses revealed that the relative risk of follicular carcinoma increased more than the risk of papillary carcinoma with increased BMI, in both men and women (36). In the most recent prospective study of 90 713 US radiologic technologists, a BMI over 35 was associated with a moderately elevated risk in women only (hazard ratio 1.74 CI:1.03-2.94, p equal to 0.04) (9). This study estimated that 6% of thyroid cancer is attributable to obesity in this cohort where obesity prevalence was 11%. In the US adult population, where the prevalence of obesity is 33%, this translates to a population attributable risk of 17% (9).

Finally, a meta-analysis of prospective observational studies on the link between obesity and 20 cancer types has found that a 5 kg/m^2 increase in BMI was strongly associated with thyroid cancer in men with a relative risk of 1.33 (95% CI: 1.04-1.70; p equal to 0.02), and a weaker, but positive, association was noted in women with a relative risk of 1.14 (95% CI: 1.06-1.23; p equal to 0.001) (5).

Overall, most prospective studies seem to suggest the existence of a positive relationship between obesity and thyroid cancer for both men and women.

3.2. Sub-population-based studies

3.2.1.The obese population

A team in Rome (Italy) studied a large population of obese individuals and found a 31% prevalence of single cold nodule (37) with an 8% occurrence of carcinoma (38) which was considered higher than the one reported in their normal-weight subjects (5-6%). They therefore concluded that obese individuals appear more likely than non-obese ones to have thyroid nodules harboring malignancy. The level of statistical significance was, however, not reported.

3.2.2. The population with thyroid nodules

One study investigated the significance of obesity in a population of patients with thyroid nodule and an indeterminate pre-operative fine-needle aspiration biopsy (39). For the first time, a significant dose-dependant protective effect of obesity was documented in women under the age of 45 years and men of all ages. In addition to sound biological bases, the diametric discrepancy between these results and those reported in the literature was explained by the uniqueness of the population studied where obesity might be playing a different role, modulating rather than etiologic, since lesions already exist in all patients. Nevertheless, further research in this population of patients appears necessary to fully validate the subtle relationship at play between excess weight and thyroid malignancy.

From case-control studies to large prospective cohort studies and their respective meta-analyses, there is a moderate level of evidence suggesting that obesity is likely to be a risk factor for the development of thyroid malignancy in both men and women. The different putative pathways and biologic bases to such relationships are discussed in the following section. The impact of obesity in patients with thyroid nodules still remains controversial and would benefit from future larger controlled studies.

4. PATHOGENESIS – THE HYPOTHESES

With the rise of obesity in most industrialized nations and its significance at a public health level, scientific literature on the carcinogenic pathways of obesity is growing at an exponential rate. In this section, we will explore the various factors and proposed mechanisms linking obesity and an increased risk for thyroid cancer.

4.1. Endocrinology

Numerous studies have emphasized that the regulation of thyroid cell growth and function involves a complex interactive network of trophic endocrine, paracrine and autocrine factors. With respect to obesity and thyroid malignancy, it is likely that insulin/insulin-like growth factor 1 (IGF-1), adipose tissue-generated cytokines (adipokines), alterations in sex hormones, thyroid stimulating hormone (TSH) and vitamin D are all important endocrine factors at play providing biological grounds to the positive relationship encountered.

4.1.1.Insulin and IGF-1

Obesity is associated with insulin resistance, compensatory hyperinsulinemia and increased growth-factor production, which in turn may stimulate mitogenesis and carcinogenesis, thus linking obesity and malignancies throughout the body.

Chronic elevation of insulin is associated with increased availability of IGF-14 through insulin-mediated upregulation of growth hormone (GH) receptors in the liver.

Both insulin and IGF-1 have been shown to act as cancer promoting agents (40). In thyroid, TSH receptor gene expression and thyroglobulin gene expression are influenced by insulin/IGF-1 at a transcriptional level. Both hormones are considered necessary co-factors for the action of TSH on thyroid follicular cells, synergizing with TSH to induce thyrocyte proliferation while maintaining differentiated function (41). Traditionally, they are not considered mitogenic agents and their role is described as rather permissive for TSH-mediated thyroid cell stimulation (40). There is, however, increasing evidence showing over-expression of IGF-1 and IGF-1 receptors in

thyroid cancer with positive correlation with tumour diameter and intrathyroidal extension (42). In addition, in humans, it has been recorded that thyroid tumours produce increased levels of IGF-1 (41). It is thus possible that in a pathological state, the proliferative effect of insulin and IGF-1 might be greater than traditionally demonstrated.

Moreover, IGF-1 inhibits apoptosis through the PI3K/AKT cell survival pathway4 and stimulates vascular endothelial growth factor (VEGF) synthesis in thyroid carcinomas (40). It also inhibits the synthesis of the sex-hormone-binding globulin (SHBG), thus increasing the levels of free sex hormones and promoting sex hormone-dependent tumorigenesis which is discussed more in detail in the following section (4).

Insulin resistance has recently been studied in patients with thyroid pathologies. Patients with insulin resistance were shown to have larger thyroid volumes and a higher prevalence of thyroid nodules (43). In addition, a case-control study of 20 women with differentiated thyroid cancer and their age, gender and BMI-matched euthyroid controls, showed an insulin resistance incidence of 50% in patients with thyroid cancer compared to 10% in their cancer-free controls (p less than 0.001) (43). These results provide further evidence, at the clinical level, that a high circulating insulin level might be an important risk factor for developing differentiated thyroid carcinoma.

4.1.2. Cytokines

Adipose tissue is the largest endocrine organ in the body (7) that secretes a variety of factors including cytokines and hormone-like substances such as leptin and adiponectin.

4.1.2.1. Chronic inflammation

As the expanding adipose tissue outgrows its blood supply, a low-grade of hypoxia induces cytokine release to stimulate angiogenesis. The vast majority of these are pro-inflammatory substances such as tumour necrosis factor alpha (TNF-alpha), interleukin (IL) 6, 8, 10, thus linking obesity to a chronic state of low-grade inflammation. These inflammatory mediators are known for their ability to alter tumorigenesis in several cancer types through increased cell cycling, loss of tumour suppressor function, stimulation of oncogene expression and formation of reactive oxygen species (4). One well demonstrated mechanism is the cytokine induced increase in NF-kappa-B, a nuclear factor that is a very strong inducer of antiapoptotic activity, thus linking inflammation and cancer at a molecular level (43).

In thyroid cancer, studies have demonstrated that growth of thyroid cells can be stimulated by some of the cytokines, namely IL-1-alpha, IL-6, IL-4 and IL-10 and that those are closely linked with the RET/PTC3 oncogenic mutation (44). In addition, TNF-alpha and IL-6 can act in either autocrine or paracrine manners to increase the production of aromatase that is directly related to increased synthesis of peripheral estrogen which correlates with higher rates of thyroid cancer, as explained in the following section (45).

4.1.2.2. COX-2

Cyclooxygenase-2 (COX-2) is an inducible enzyme upregulated during cell proliferation and inflammation in response to multiple stimuli. More recently, COX-2 has been implicated in the development of numerous types of epithelial cancers (4). The contribution of COX-2 carcinogenesis is related to its abilities to increase production of prostaglandins, convert procarcinogens into carcinogens, inhibit apoptosis, promote angiogenesis, modulate inflammation and immune function and increase tumour cell invasiveness (4). It is known that COX-2 is expressed in thyroid epithelial neoplasms, including papillary and follicular carcinomas, but not in normal thyroid tissue (46). Although data is lacking for the thyroid, it has been demonstrated in other epithelial tumors that COX-2 deregulation in normal mucosa might be driven by excess weight (47). It is therefore possible that obesity driven induction of COX-2 is involved in thyroid cancer.

4.1.2.3. Leptin

Leptin, the product of obesity gene (Ob), is a 16 kDa protein hormone produced predominantly by adipocytes in direct proportion to the amount of body fat, that acts through the leptin receptor (Ob-R), a member of class I cytokine receptor family (48-50). It relays information regarding the level of energy stored, thereby directing the regulation of energy homeostasis, neuroendocrine function and metabolism (51). In addition to its role in energy balance, leptin is a crucial hormonal factor for regulating several other physiologic processes, including inflammation, angiogenesis, hematopoiesis, immune function and reproduction (52).

Because leptin is elevated in the serum of obese individuals in direct correlation to the fat mass, it has been investigated as a possible biological link between obesity and various types of cancers (48). Aberrant expression of leptin and Ob-R has been observed in several types of cancers, including endometrial cancer, colorectal cancer, breast cancer, gastric cancer, hepatoma and most recently papillary thyroid cancer (50) where the expression of either proteins was associated with larger tumor size, (50) higher incidence of nodal metastases (50) and poor disease-free survival (53). This relationship is unlikely to be simple and linear, as no study up to date demonstrated that patients with greater body weight have larger thyroid tumors or a greater likelihood of nodal metastases.

The carcinogenic effect of leptin appears to be mediated through its ability to act as a mitogen and an angiogenic factor. Indeed, it has been shown that leptin can regulate neoangiogenesis by itself and in concert with vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) 2. This adipokine can also enhance endothelial cell growth and suppression of apoptosis through a Bcl-2 dependent mechanism. The role of leptin in neovascularisation is supported additionally by the observation that the hormone can increase the levels and activity of enzymes involved in angiogenesis (48).

At the level of the thyroid, in vitro studies show that leptin stimulates proliferation of thyroid papillary cancer and inhibits apoptosis through activation of phosphatidylinositol 3' kinase (PI3K)/protein kinase B (AKT) signaling pathway via the Ob-R (53). In addition, leptin has been shown to stimulate thyrotropin-releasing hormone (TRH) expression in the hypothalamus, and subsequently production of TSH, (54) which in rats correlated to higher thyroid gland weight with exogenous leptin administration (55). It therefore appears that increased levels of leptin in obesity can stimulate thyroid malignancy directly through Ob-R but also indirectly through increased levels of TSH. Clinically, a case-control study of 43 euthyroid women with papillary thyroid carcinoma showed that serum leptin levels were significantly higher in the patients with papillary thyroid cancer compared to the healthy controls (49). There was however no difference in BMI between the two groups, and leptin levels significantly decreased following total thyroidectomy in patients with papillary thyroid carcinoma, perhaps hinting that the relationship between leptin and thyroid carcinoma might be more complex that initially envisioned.

4.1.2.4. Adiponectin

Adiponectin is the most abundant peptide secreted by adipose cells, and is inversely related to body fat (56). Indeed, circulating concentrations of adiponectin are reduced in obesity, type 2 diabetes and congenital lipodystrophic syndromes and have a strong inverse association with parameters of central and overall obesity, independently of age, menopausal status and estradiol concentrations (7).

Adiponectin is considered to have beneficial antineoplasic actions through well demonstrated antiproliferative, anti-inflammatory and antiangiogenic effects along with its ability to antagonize insulin resistance (7). Several tumour cell lines express adiponectin receptors, and these beneficial effects have been documented in breast, endometrial, prostate, colon, gastric, renal and hematologic cancers (7). However, there are no studies conducted up to now that document the effects or presence of adiponectin receptor on benign or malignant thyrocytes.

4.1.3. Sex hormones

The incidence of thyroid cancer is known to be three to five times higher in women than in men, and this female excess is greatest from ages 14-54, with a decrease noted after the menopause (24,57). The difference in incidence between the genders suggests that growth and progression of thyroid tumours is influenced by sex hormones, particularly estrogens (5). Excess body fatness-mediated changes in circulating concentrations of endogenous hormones provide additional biological grounds to explain the relationship between obesity and thyroid cancer.

Indeed, as previously mentioned, adipose tissue is an active endocrine and metabolic organ that has an important impact on the synthesis and bioavailability of endogenous sex steroids.

In obese premenopausal women, an increased frequency of anovulation is noted, which has been shown to decrease serum estradiol and progesterone levels (6,58). In addition, the increased leptin levels from fat stores of obese young women inhibit ovarian estrogen production (58).

In postmenopausal women, the conversion of androstenedione into estrone by aromatase in adipose tissue provides an important and continuous source of estrogen whose production is related to the size of adipose tissue (56). In premenopausal women where cyclic hormone levels predominate, the peripheral conversion of adrostenedione is believed to be insignificant (58). Thus, excess fatness might decrease estrogen levels in obese premenopausal women while contributing to higher levels in obese postmenopausal women. In man, obesity has also been associated with lower levels of total testosterone as a result of decreased sex-hormone binding proteins (3,59).

At the level of the thyroid, the presence of estrogen (60) and testosterone (59) receptors has been well established, and both hormones modify the proliferation of thyroid cancer cells, independently of TSH (3). The human thyroid follicular cells are known to express estrogen receptors alpha (ER-alpha) and beta (ER-beta), whose effects on the thyrocytes are antagonistic, with ER-alpha inducing proliferation and ER-beta promoting apoptosis and decreased proliferation (57). Studies have shown that estradiol administration increases the level of ER-alpha in follicular cells while the level of ER-beta remains unchanged (57). In parallel, analyses of malignant thyrocytes demonstrate an increased expression of ER-alpha in thyroid cancer cells, and low or absent expression of ER-beta (57). In addition, a significantly higher increase in ER-alpha receptors has been noted in females in response to 17-beta-estradiol, the natural form of estrogen (61). Therefore, with higher estrogen levels, the balance of ER-alpha versus ER-beta is affected favoring proliferation and cancer promotion, with such a response being even more pronounced in females.

Besides the receptor-mediated hormonal activity, an array of mechanisms to explain the estrogen carcinogenic effect has emerged. It has been hypothesized that the natural estrogen or its metabolites may directly induce neoplastic transformation of the normal cell (57). At the level of the thyroid, a case-control study has found an imbalance between the proliferative (16-alpha-hydroxyestrone) and anti-proliferative (2-hydroxyestrone) estrogen metabolites to be associated to proliferative thyroid disease with the least favorable ratios measured in malignant cases (60). It is also thought that estrogens may generate a direct genotoxic effect to increase mutation rates through a cytochrome-mediated metabolic activation (57). Finally, estrogen may impair the formation of mitotic spindles and thus contribute to chromosomal nondisjunction and aneuploidy induction (57).

At a population level, different female reproductive factors have been investigated for their relationship to thyroid cancer. A pooled analysis of 13 case-control studies concluded that the use of oral contraceptives is associated

with a moderate increased risk of developing thyroid cancer (62). Some studies have also found that a longer reproductive period correlated with papillary thyroid cancer (63-65) while higher parity was also shown by some, (65,66) but not others, (63,64) to be associated with increased risk of thyroid malignancy. In the presence of such a relationship, it was hypothesized that elevated estrogens associated with pregnancy could induce proliferation of malignant thyroid cells (65). All these associations further strengthen the existence of a possible role of female hormones in thyroid cancer promotion.

Although it appears clear that higher estrogen levels are linked to thyroid carcinogenesis both at a molecular and a population level, its role as a causative factor explaining the association between excess weight and risk of thyroid cancer appears applicable for postmenopausal women only, as they are the only subgroup where obesity has been linked with overall increase in female hormones.

4.1.4. TSH

Thyroid function with its effects on metabolism and body weight is always a possible factor in any relationship between obesity and thyroid cancer. Goiter and benign thyroid disease are the strongest risk factors for thyroid cancer (apart from radiation exposure) (67) and reduced thyroid activity can lead to depressed tissue oxidation and increased weight. However, virtually all patients with thyroid carcinoma are euthyroid (68) and prior history of hypothyroidism was not associated with increased cancer risk (67). Nevertheless, TSH is known to have a trophic effect on thyroid cancer growth, and it has been demonstrated that the risk of malignancy rises in parallel with the serum TSH concentration at presentation, allowing for subclinical hypothyroidism and even TSH concentrations in the upper half of the normal range to increase the risk of malignancy in the euthyroid patients (68). Since then, it has been reconfirmed on multiple occasions that the likelihood of thyroid cancer increases with higher serum TSH concentration, even in euthyroid subjects (68-70).

At the same time, some, but not all, (71) studies have demonstrated that a higher level of serum TSH, even within the normal range, is positively correlated to obesity (72-74). Borderline elevated TSH levels are reversible in case of body weight reduction in obese individuals (75). It remains, however, unclear whether high TSH levels are responsible for obesity or represent a secondary phenomenon.

Overall, higher levels of TSH appear to be linked to both obesity and thyroid cancer, but the exact nature of the role of TSH in this relationship as a common underlying cause or a step in the pathogenesis still remains to be clarified.

4.1.5. Vitamin D

In addition to metabolic alterations, obese individuals are known to have reduced serum levels of 25-hydroxyvitamin D, (76-81) and the most recent studies have also documented a significantly lower serum concentrations of 1,25-dihydroxyvitamin D with increased BMI (80-82). This hormone, in addition to its role in calcium homeostasis, has been recognized to play a role in the modulation of the proliferation and differentiation of several cell types (83). In vitro studies have demonstrated that vitamin D inhibits the proliferation of well-differentiated thyroid cancer cells through G1-phase arrest in a dose-dependent manner (83,84). Therefore, as vitamin D is suggested to be to be protective in terms of thyroid cancer, insufficient levels of this hormone might be contributing to an increased cancer risk in individuals with excess weight. In this respect, two studies have reported lower circulating levels of 1,25-dihydroxyvitamin D in patients with differentiated thyroid carcinoma compared with healthy controls, although no differences of serum 25-hydroxyvitamin D level were found (85,86).

4.2. Toxins

4.2.1. Diet and food

Body weight and height being the result of energy balance and nutrition, diet could be involved in the observed links between BMI and thyroid cancer. Previous studies have mainly looked into the effects of consumption of cruciferous vegetables, known to contain goitrogenic substances (22,26,87-89) and iodine deficiency or excess (22,26,88,89) on the incidence of thyroid cancer. A pooled analysis has shown that cruciferous vegetables are not positively related to increased risk of thyroid cancer, but appear rather protective, and no difference between iodine-rich or iodine-deficient areas was detectable (88). This could be explained by the presence of a variety of other constituents in cruciferous vegetables, such as flavones, phenols, isothiocyantes and beta-carotene that are known to inhibit carcinogenesis. Similarly, obese patients are likely consuming diets rich not only with calories, but also with proteins and other essential nutrients that might be protective. In marked contrast, however, Truong and her colleagues recently reported that high consumption of cruciferous vegetables was associated with thyroid cancer but this was significant only in women with low iodine intake (90). It is thus possible that iodine intake in a given individual may modulate any potential link between consumption of cruciferous vegetables and thyroid cancer risk.

One study has also documented an increased risk of thyroid cancer with high consumption of butter and starchy food such as pasta, rice and bread which would have a direct effect on body weight (89). These foods and their constituents most likely have no direct effect on the thyroid, and the risk of cancer is suspected mediated through hyperglycemia (40).

Overall, it appears unlikely that increased consumption of carcinogenic substances is underlying the relationship between obesity and thyroid cancer.

4.2.2. The storage hypothesis

A number of goitrogenic and carcinogenic chemicals and pollutants have been identified as initiators and promoters of thyroid carcinogenesis (89). It has been hypothesized that excess adipose tissue can act as a

reservoir for lipophilic, liposoluble environmental carcinogens and release them at convenient dose in the blood circulation thus targeting peripheral tissue and inducing carcinogensis (3). This hypothesis has not yet been demonstrated in the case of thyroid cancer.

5. CONCLUSION

With the current trends of alarming rise in obesity rates, the health impacts of excess weight will become more apparent. The current review focused on the evidence linking thyroid cancer with obesity. We conclude that there is sufficient evidence that obesity can predispose to an increased risk of thyroid cancer in both men and women. This population-based association is mainly explained at a biological level through specific obesity-related endocrinopathies. The detailed pathways are however complex, several aspects are still very poorly understood and numerous questions remain: What is the role of COX-2 in thyroid carcinogenesis and what is its relation to excess weight? Are there adiponectin receptors on thyroid cells? In the association between TSH and obesity, which one is causing the other?

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Key Words: Obesity, BMI, Thyroid Neoplasm, Pathogenesis, Etiology, Endocrinology, Insulin, Igf-1, Cytokines, COX-2, Leptin, Adiponectin, Sex Hormones, TSH, Vitamin D, Toxins, Review

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