Risk factors of thyroid tumors: Role of environmental and occupational exposures to chemical pollutants

Facteurs de risque des cancers et nodules thyroïdiens: effet des polluants chimiques de l’environnement et risques professionnels

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Abstract

Background. – The rising incidence of thyroid cancer observed during the last few decades in most western countries is explained in large part by increasing numbers of diagnoses due to changes in medical screening practices. However, beside radiation exposure, exposure to environmental chemicals may also play a role in thyroid cancer etiology and in the increased incidence. This paper presents the main chemicals suspected to induce thyroid tumorigenesis, and epidemiological results on the association between chemical exposure and thyroid tumors.

Methods. – We reviewed experimental studies to identify the main chemicals possibly involved in thyroid tumorigenesis. We also reviewed the main epidemiological studies investigating the association between environmental chemical exposure and thyroid neoplasm in humans.

Results. – Environmentally abundant chemicals may disrupt thyroid function and/or play a role in tumorigenesis through a variety of mechanisms. Epidemiological results provide insufficient evidence of a causal link between exposure to environmental chemicals and thyroid tumors, but raise the hypothesis of an increased risk of thyroid neoplasm for workers in the leather, wood, and paper industries, and those exposed to certain solvents and pesticides.

Conclusion. – This paper highlights the need for large epidemiological studies evaluating the exposure to various groups of environmental chemicals and its impact on the thyroid gland.

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Keywords: Thyroid neoplasm; Occupation; Chemical exposure; Risk
1. Introduction

With 140,000 new cases diagnosed every year in the world, thyroid cancer accounts for 1% of all cancers and is the most frequent endocrine malignancy [1]. It is three to five times more frequent in women than in men, with important geographical disparities. High incidence rates of thyroid cancer have been described in certain regions of the world, particularly in Pacific populations [2–4]. An increase in the incidence of thyroid cancer has also been observed over the past few decades in industrialized countries, notably in France [5–11]. These increases mainly involve microcarcinomas that are detected more frequently as thyroid screening practices become more common. However, an increase in the incidence of larger cancers has also been observed suggesting a possible role of environmental factors [12].

In the absence of disease registries for benign thyroid tumors, the incidence of benign thyroid goiters and nodules cannot be estimated precisely. There are, however, close links between benign and malignant tumors. Most epidemiological studies have reported that the existence of a goiter or nodule of the thyroid is associated with excess risk of thyroid carcinoma [13]. Benign thyroid tumors may thus share common etiological factors with malignant tumors, and can be seen as precancerous lesions. The risk factors for thyroid diseases are, however, poorly known, and only ionizing irradiation exposure in childhood has clearly been associated with thyroid cancer [14,15]. The results of epidemiological studies suggest the influence of other factors, including menstrual, hormonal, anthropometric, dietary, and genetic factors [16–21]. Certain environmental pollutants are also suspected of playing a role in the occurrence of thyroid tumors. Experimental studies have demonstrated the ability of several chemical compounds of interfering with thyroid function. Even if these pollutants were found to induce benign or malignant thyroid tumors in experimental animals, their effects in humans at doses present in the environment remain very poorly known [22,23].

This article presents the main classes of chemical pollutants that may induce the development of thyroid tumors. We describe the physiopathological mechanisms possibly implicated in thyroid tumorigenesis as well as the results of the main epidemiological studies conducted to identify environmental risk factors of thyroid tumors. The role played by ionizing radiation in thyroid cancer has been the subject of an abundant literature, and will not be discussed in the present paper. Similarly, the role played by dietary iodine deficiency, a well-known cause of endemic goiters, is out of scope in the present paper.

2. Method

The main chemical pollutants that may promote thyroid tumorigenesis were identified based on a review of the experimental studies and the epidemiological studies indexed in PubMed with the keywords: “thyroid volume,” “thyroid disorder,” “thyroid neoplasm,” “endocrine disrupter,” “pesticides,” and “polychlorinated biphenyls.”

The review of the epidemiological studies on humans on the association between environmental chemical exposure and thyroid tumors was done in the PubMed database using the keywords: “thyroid neoplasm,” “environment,” “occupation,” “chemical exposure,” and “risk.” We identified four studies based on job title (three case-control studies and one historical cohort study), three studies on occupational exposure (one population-based historical cohort study, one historical cohort study of occupational exposure, and one prospective cohort study of occupational exposure), two studies on environmental exposure (one ecological study and one historical cohort study on place of residence).

3. Results

3.1. Chemical compounds causing disorders of the thyroid gland

Many chemicals known for their mutagenic and genotoxic properties have been implicated in the occurrence of tumors, such as benzene or pesticides in blood malignancies [24–26] or formaldehyde in nasopharyngeal cancers [27]. These mutagenic or genotoxic compounds could also affect tumorigenesis of other organs, such as the thyroid. In the present paper, we focus on chemical compounds that may lead to thyroid tumorigenesis through disruption of normal functioning of thyroid hormones.

Experimental studies demonstrate that several natural or synthetic chemicals can disturb thyroid function at different levels: central, by interfering with the production or release of thyroid-stimulating hormone (TSH) by the pineal gland; thyroid, by acting on the synthesis or the secretion of thyroid hormones; peripheral, by competing with thyroid hormones during liaison with transport proteins, or by interfering with catabolism and excretion of thyroid hormones [28]. Because of the strong structural resemblance with thyroid hormones, certain polychlorinated aromatic hydrocarbons (dioxins, polychlorobiphenyls [PCBs], organochlorine pesticides) bind with their transport proteins and their receptors with high affinity and can disrupt the normal function of thyroid hormones. Certain anions, such as perchlorate, thiocyanate,
and nitrate, inhibit the synthesis of thyroid hormones by competing iodide (ion $I^-$) when entering thyroid cells [29–31]. Table 1 presents the main compounds known to disturb thyroid function.

When plasma levels of thyroid hormones are reduced, TSH is produced by the pituitary gland to stimulate thyroid activity [32]. Thyroid disrupters induce TSH hypersecretion, resulting in thyroid hyperplasia and development of thyroid tumors [33–35]. Evidence of thyroid tumorigenesis has been provided by experiments in laboratory animals exposed to high doses of thyroid disrupters. However extrapolation to humans exposed to low environmental doses cannot be made easily [36].

Several laboratory studies have reported changes in thyroid hormone levels among workers exposed to pesticides, in particular carbamate and organochlorine pesticides [37–42]. Organochlorinated hydrocarbons (particularly dioxins, PCBs, and organochlorine pesticides) are the thyroid disruptors that have been studied most frequently because of their structural resemblance to thyroid hormones and their ubiquitous presence in the environment. These studies were reviewed in 2003 by Hagmar et al. and in 2008 by Langer et al. [43,44]. Plasma contamination by organochlorinated compounds was associated with a modification in thyroid hormone levels and with thyroid hyperplasia. However, the results were inconsistent and require confirmation. It should also be pointed out that the estrogenomimetic properties of organochlorinated compounds may also stimulate the proliferation of thyroid gland cells [45,46].

A goitrogenic effect of anions such as perchlorates, thiocyanates, and nitrates has also been described in humans,
but this effect requires high exposure doses and concomitant iodide deficiency [42]. Thyroid function was studied by Gibbs et al. in 1998, Lamm et al. in 1999, and Braverman et al. in 2004 in employees of an ammonium perchlorate synthesis plant. None of these studies demonstrated hormone disturbance or clinical thyroid abnormalities related to perchlorate exposure [30,31,43]. According to several authors, the higher prevalence of goiters in smokers than in non-smokers may be explained by the high level of thiocyanate in tobacco smoke [44–47]. Several studies investigating the relation between smoking and thyroid function have also reported an increase in the plasma concentration of thyroid hormones and a reduction of TSH levels in smokers [46,48–52]. The relation between tobacco and thyroid is complex since tobacco is negatively associated with thyroid cancer in several epidemiological studies [53–55]. The mechanism explaining this association has not been elucidated, but it could imply a reduction in the TSH rate observed in smokers or an antiestrogenic effect of tobacco.

3.2. Does environmental exposure cause an increased risk of thyroid tumor in humans?

Besides experimental studies, epidemiological studies have examined the association between chemical exposure and the occurrence of thyroid tumors in humans. Very few epidemiological studies have investigated the role of environmental exposure in thyroid diseases, because assessing low- or very-low-dose exposure to chemical compounds is very difficult. Most studies conducted so far, were occupational studies. Studies describing the risk of thyroid cancer in specific occupations have been conducted. Further studies were designed to investigate the role played by specific occupational exposures. Recent studies also investigated the risks of benign thyroid tumors in relation to specific occupational or environmental exposures. These studies are summarized in Table 2.

3.2.1. Studies describing thyroid tumor risk in relation to the job title

In this paper, we present studies pertaining to thyroid cancer only, excluding occupational cohort studies in which very small numbers of thyroid cancer cases were included among many other cancer sites.

In 1995, Wingren et al. studied the risk for papillary cancer of the thyroid in relation to occupation in 185 female cases and 426 controls living in the northern and southern regions of Sweden. The results demonstrated a significantly increased risk for papillary thyroid cancer in women working as dentists or dental assistants and a non-significant increased risk in women working in the shoe industry. Exposure to ionizing radiation, to unspecified chemical products, and to computer screens, all assessed from a self-administered questionnaire, were associated with an increased risk of papillary cancer [56].

Another Swedish case-control study conducted by Wingren et al. investigated 31 follicular cancers, 44 cases of benign nodules, and 387 controls. The results showed an increase in the risk of thyroid cancer in women working in a laboratory and in men working as painters or who declared being exposed to solvents. Follicular thyroid cancer was increased in women who declared being exposed to unspecified chemical products and in men working as farmers and masons [57]. These results are difficult to interpret because of the very small size of the study and of possible selection bias.

In Canada, Fincham et al. studied the risk of thyroid cancer according to occupation in a study of 1272 cases of thyroid cancer and 2666 population controls. The results demonstrated an increase in the risk of thyroid cancer in people working in the pulp and papermaking industry and in wood processing [58]. A slight increase in risk was also observed in the sale and service industry.

More recently, in 2005, Lope et al. published a historical cohort study for the 1971–1989 period conducted on the entire Swedish population of salaried workers. During the follow-up period, 1103 cases of thyroid cancer diagnosed in men and 1496 cases diagnosed in women were identified in the Swedish national cancer registry. The subjects’ occupations were obtained from population census data. In men, the risk for thyroid cancer increased in teachers, construction carpenters, police officers, and prison/reformatory officials, as well as in the pulp and papermaking industry, manufacture of agricultural machinery, and manufacture of computing/accessories. In women, the risk was higher for medical technicians, tailors, and shoe cutters, in manufacture of prefabricated wooden buildings, electric installation work, and wholesale of agricultural products [59].

The results of these studies are globally inconsistent but certain points deserve mention. The increased risks of thyroid cancer in medical technicians [59] and dentists and dental assistants [56] could be related to repeated exposure to ionizing radiation. The elevated risk of thyroid cancer in dentists and dental assistants has been observed repeatedly in other cohort studies on the relation between occupational exposure to ionizing radiation and thyroid cancer [60,61]. Similarly, the increased risk of thyroid cancer in women in pulp and papermaking in Canada [58] is consistent with a similar increase in Swedish women [59] as well as in male woodcutters and construction carpenters in the same study [59]. Workers in the wood industry may have been exposed to solvents, formaldehyde, wood preservatives, and pesticides. Interestingly, the Canadian [58] and the Swedish study [59] independently reported an increased risk for thyroid cancer in pulp and papermaking workers. These workers are potentially exposed to chlorinated compounds such as dioxins and other chemical compounds. The excess risk in leather workers, in particular shoe cutters [56,59], should also be pointed out given the high number of chemical exposures that can occur in this industrial sector. Finally, exposure to industrial polyhalogenated pollutants, such as PCBs or polychlorobiphenyls (PCBs), can occur in workers in agricultural machinery manufacture workers, and workers in computer and accessory manufacture, or in the electric installation sector, in which increases in the incidence of thyroid cancer have been described [59].
Table 2
Epidemiological studies of the association between environmental pollution exposure and thyroid cancer.

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<tr>
<th>Reference</th>
<th>Country</th>
<th>Type of study</th>
<th>Population studied</th>
<th>Exposure measurement method</th>
<th>Occupation or exposure</th>
<th>RR (95 % CI)</th>
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<td>426 controls</td>
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<td>Shoe manufacture</td>
<td>5.3 [0.8–46]</td>
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<td>Wingren and Axelson (1997) [57]</td>
<td>Sweden</td>
<td>Case–control</td>
<td>Men</td>
<td>Job title and brief evaluation of exposure</td>
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<td>Fincham et al. (2000) [58]</td>
<td>Canada</td>
<td>Case–control</td>
<td>1272 thyroid cancers</td>
<td>Job title</td>
<td>Wood/pulp and papermaking industries</td>
<td>2.83 [1.27–6.29]</td>
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<td>2666 controls (1986–1988)</td>
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<td>Historical cohort in population</td>
<td>Men</td>
<td>Job title or branch of activity</td>
<td>Construction carpenter/furniture making</td>
<td>1.41 [1.06–1.89]</td>
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<td>Sweden</td>
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<td>Job title or branch of activity</td>
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<td>Lope et al. (2009) [62]</td>
<td>Sweden</td>
<td>Historical cohort in population</td>
<td>Men 1,780,000 salaries workers 1103 thyroid cancers between 1971 and 1989 Women 1,066,000 salaried workers 1496 thyroid cancers between 1971 and 1989</td>
<td>Job-exposure matrix (13 occupational exposures)</td>
<td>Wholesale of agricultural products</td>
<td>2.83 [1.27–6.31]</td>
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<tr>
<td>Wong et al. (2006) [63]</td>
<td>China, Shanghai</td>
<td>Historical cohort study of occupational exposure</td>
<td>267,400 women employed in textile industry 130 thyroid cancers between 1989 and 1998</td>
<td>Job-exposure matrix specific to textile industry</td>
<td>Solvents: probable exposure</td>
<td>0.93 [0.65–1.33]</td>
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<tr>
<td>Lee et al. (2004) [66]</td>
<td>USA</td>
<td>Cohort study of occupational exposure</td>
<td>50,000 farmers (Agricultural Health Study [AHS]) 16 thyroid cancers between 1993 and 2000</td>
<td>Specific questionnaire on farm work</td>
<td>Benzene, Formaldehyde, Organic or inorganic gases</td>
<td>1.91 [1.05–3.45]</td>
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<td><strong>Studies on environmental exposures</strong></td>
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<td>Pavuk et al. (2004) [67]</td>
<td>Slovakia</td>
<td>Cohort study on place of residence</td>
<td>Men 115 residents near factor producing PCBs 7 thyroid cancers Women 110 residents near factor producing PCBs 22 thyroid cancers</td>
<td>Place of residence</td>
<td>Exposed to PCBs compared to overall population</td>
<td>1.26 [0.50–2.59]</td>
<td>Low number of cases Non-measured exposure Possible confounding bias</td>
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3.2.2. Studies on specific occupational exposures

The data from the above-described Swedish cohort was used in a second publication where the exposure to 13 different chemical compounds was assessed for each job title using a job-exposure matrix. An exposure score (none, possible, or probable exposure) was assigned to each occupation [62]. In men, a non-significant increased risk of thyroid cancer was observed with possible exposure to textile dust. In women, the risk for thyroid cancer increased significantly by a factor of 2 with probable exposure to solvents, occurring mainly in the shoe industry [62]. No association with other exposures was observed (arsenic, asbestos, chrome/nickel, metals, oils, HPA, pesticides, or petroleum products).

In China, Wong et al. studied the associations between occupational exposures and thyroid cancer in an occupational cohort of 267,400 women employed in the textile industry in Shanghai in 1989. The incident cases of thyroid cancers in this cohort were identified until 1998. Occupational exposures were evaluated based on the job history of each woman through a job-exposure matrix specifically designed for this study. The authors reported an increased risk of thyroid cancer in women exposed for at least 10 years to benzene and formaldehyde [63].

Agricultural workers are more particularly exposed to pesticides. In a study from the Swiss cancer registries on cancer cases recorded between 1980 and 1993, an excess risk of thyroid cancer was observed in agricultural workers. However, according to the authors, this excess risk could stem from a deficit in iodine in the agricultural regions studied [64]. In the American prospective cohort on 90,000 pesticide applicators and their wives (Agricultural Health Study, AHS), the incidence of thyroid cancers was increased compared to the general population in the follow-up conducted up to 2001 [65]. In a publication on the subgroup of pesticide applicators, a moderate non-significant increase in the risk for thyroid cancer in agricultural workers exposed to Alachlor, an herbicide, was reported, but the authors underscored the lack of power resulting from the low number of cases [66].

These studies illustrate the difficulty of exposure assessment. Only broad classes of chemical substances can be taken into account, making unlikely the possibility of detecting the effect of a specific chemical. In addition, it is difficult to detect an association of rare or low dose exposures with thyroid diseases. These studies, however, may provide interesting clues for further research. The existence of an association between exposure to solvents in the Swedish study [62] and an association with benzene or formaldehyde in the study on textile workers [63] suggests that these exposures could play a role in thyroid carcinogenesis.

3.2.3. Studies on environmental exposure

In Slovakia, Pavuk et al. studied the incidence of cancers in 225 subjects living near a chemical factory producing PCBs and in 207 people living in a zone not exposed to PCBs. They reported higher standardized incidence ratios of thyroid cancer in women geographically not exposed to PCBs. According to the authors, this result was explained by confounders such as lifestyle, and other environmental factors [67].

In other studies, environmental exposure to naturally occurring chemicals was found to be the cause of endemic goiters in areas without iodine deficiency. In a region located in western Colombia, the prevalence of goiter remained high despite adequate iodine intake by the population. It was found that the geological composition of sedimentary rock rich in organic matter (coal and shales) led to drinking water contamination by resorcinol, phthalate esters, and sulfur-containing organic compounds [68] with thyroid disrupting properties. Other examples of endemic goiter areas without iodine deficiency were identified in other regions of the world [22].

4. Discussion

The only risk factor of thyroid cancer currently established is exposure to ionizing radiation in childhood [14,15]. The existence of other risk factors is, however, suggested by recent studies. These are hormonal and reproductive factors as well as anthropometric, dietary, and genetic factors [16–21]. Very few epidemiological studies have investigated chemical environmental exposures as risk factors for thyroid cancer.

A large number of environmental chemicals interfere with thyroid hormone function and could cause goiters, benign nodules, or cancers. These pollutants, of industrial or natural origin, can alter regulation mechanisms, metabolism or excretion of thyroid hormones. These compounds, present in water, air, or food, could account for a large part of thyroid diseases. Synergistic effects of multiple exposures to thyroid disruptors could also occur. Knowledge of the role played by environmental exposure in human thyroid diseases is of primary importance. However, epidemiological studies are scarce, illustrating the complexity of evaluating human exposure to environmental chemicals at low levels. A second problem specific to thyroid diseases stems from the screening of thyroid nodules within large cohorts. The results of epidemiological studies are insufficient to draw conclusions on the causal link between exposure to a pollutant and occurrence of thyroid nodules in humans. However, they raised the hypothesis of a relation with certain occupations (wood, leather, and pulp and papermaking industries that are the source of many chemical exposures) or certain occupational exposures (pesticides or solvents). Conducting studies within populations in which the incidence of benign or malignant thyroid tumors is high, should be encouraged. Examples include populations where endemic goiter persists despite sufficient iodine intake [68] or populations with incidence rate of thyroid cancers not entirely explained by increased screening, as is the case in New Caledonia [2]. Conducting studies in Western populations presenting high levels of pollution by industrial pollutants is also a lead to explore. Taking into account multiple or concomitant exposures to thyroid function disruptors is also of major interest, because the effects of exposure to each of them, even at low doses, could be multiplied by the presence of other factors. Finally, it is useful to take into account the interactions
between exposure to environmental pollutants and other risk factors of thyroid diseases such as hormonal, dietary, or genetic factors.

Conflict of statement

The authors have not declared any conflict of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found at http://www.sciencedirect.com and doi:10.1016/j.respe.2010.05.005.

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