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# Influence of cigarette smoking on thyroid gland — an update

## Wpływ palenia papierosów na tarczycę — aktualizacja

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## Abstract

Many studies have shown that cigarette smoking exerts multiple effects on the thyroid gland. Smoking seems to induce changes in thyroid function tests, like decrease in TSH and increase in thyroid hormones. However, these alterations are usually mild. In addition, tobacco smoking may also play a role in thyroid autoimmunity. Many studies have confirmed a significant influence of smoking on Graves' hyperthyroidism and particularly on Graves' orbitopathy. Here, smoking may increase the risk of disease development, may reduce the effectiveness of treatment, and eventually induce relapse. The role of smoking in Hashimoto's thyroiditis is not as well established as in Graves' disease. Nonetheless, lower prevalence of thyroglobulin antibodies, thyroperoxidase antibiodies and hypothyroidism were found in smokers. These findings contrast with a study that reported increased risk of hypothyroidism in smokers with Hashimoto's thyroiditis. Moreover, cigarette smoking increases the incidence of multinodular goitre, especially in iodine-deficient areas. Some studies have examined cigarette smoking in relation to the risk of thyroid cancer. Interestingly, many of them have shown that smoking may reduce the risk of differentiated thyroid cancer. Furthermore, both active and passive smoking during pregnancy might modify maternal and foetal thyroid function.

This review evaluates the current data concerning the influence of cigarette smoking on thyroid gland, including hormonal changes, autoimmunity and selected diseases. These findings, however, in our opinion, should be carefully evaluated and some of them are not totally evidence-based. Further studies are required to explain the effects of smoking upon thyroid pathophysiology.

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**Key words:** *thyroid; smoking; tobacco; nicotine; thyroid hormones; TSH; TSH receptor autoantibodies; Graves' disease; Hashimoto's thyroiditis; postpartum thyroiditis*

## Streszczenie

Wyniki wielu badań dowodzą, że palenie papierosów wywiera istotny wpływ na gruczoł tarczowy. Wykazano, że nikotynizm modyfikuje parametry hormonalne tarczycy, w szczególności prowadzi do obniżenia stężenia TSH. Sugeruje się, że może również powodować nieznaczny wzrost stężenia wolnych hormonów tarczycy. Ponadto, palenie papierosów odgrywa istotną rolę w procesach autoimmunologicznych związanych z gruczołem tarczowym. Dowiedziono, że nikotynizm wywiera negatywny wpływ na przebieg choroby Gravesa i Basedowa oraz orbitopatii Gravesa i Basedowa. Palenie papierosów nie tylko zwiększa ryzyko rozwoju powyższych schorzeń, ale zmniejsza również skuteczność terapii i zwiększa ryzyko nawrotu. Wpływ palenia papierosów na chorobę Hashimoto nie jest tak jednoznacznie dowiedziony, jak w chorobie Gravesa i Basedowa. Sugeruje się, że palenie papierosów może negatywnie korelować z mianem przeciwciał przeciwko tyreoglobulinie oraz tyreoperoksydazie, zmniejszając w konsekwencji ryzyko rozwoju hipotyreozy. Palenie papierosów zwiększa ryzyko wystąpienia wola guzkowego szczególnie na obszarach niedoboru jodu. Interesująco przedstawiają się również wyniki badań nad wpływem palenia papierosów na ryzyko wystąpienia raka tarczycy. Wiele z nich dowodzi, że u palaczy ryzyko raka zróżnicowanego tarczycy jest mniejsze. Ponadto zarówno bierne, jak i czynne palenie papierosów przez kobiety ciężarne modyfikuje funkcję gruczołu tarczowego zarówno matki, jak i płodu. W pracy przedstawiono aktualny stan wiedzy dotyczący wpływu palenia papierosów na homeostazę hormonalną, procesy autoimmunologiczne oraz choroby tarczycy. W opinii autorów prezentowane wyniki badań wymagają rozważnej interpretacji, a niektóre z nich mają stosunkowo słabą siłę dowodu naukowego. Wpływ palenia papierosów na patofizjologię tarczycy powinien być przedmiotem dalszych badań. **(Endokrynol Pol 2014; 65 (1): 54–62)**

**Słowa kluczowe:** *tarczyca; palenie tytoniu; tytoń; nikotyna; hormony tarczycy; TSH; przeciwciała przeciwko receptorowi dla TSH; choroba Gravesa i Basedowa; choroba Hashimoto; poporodowe zapalenie tarczycy*

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## Introduction

Cigarette smoking has a significant impact on human health. The total number of smokers is increasing globally according to data provided by the World Health Organization (WHO). Tobacco smoke consists of several chemical substances having an impact on the endocrine system. This article reviews the influence of cigarette smoking on the thyroid gland considering current medical knowledge and results of recent studies.

Cigarette smoking is regarded as an independent risk factor for Graves' orbitopathy and multinodular goitre in iodine-deficient area. On the other hand, smoking may reduce the risk of thyroid cancer [1–3]. However, the exact pathophysiological mechanisms responsible for these relations are the subject of debate.

The effect of cigarette smoking on thyroid hormones and thyroid autoantibodies (Abs) is discussed in the first part of this review. The second part focuses on the relations between cigarette smoking and thyroid gland diseases. The third part sums up the impact of smoke exposure on maternal and foetal thyroid gland during pregnancy and postpartum period.

## Influence of cigarette smoking on serum concentration of thyrotropine (TSH), thyroxine (T4), triiodothyronine (T3)

Recent studies have found that TSH serum concentration is lower in smokers [4-8]. Belin et al. conducted a population-based cross-sectional study in the United States: the Third National Health and Nutrition Examination Survey (NHANES III). Smoking status was estimated using serum cotinine level and self-reported questionnaire [8]. The study revealed that active smokers (serum cotinine > 15 ng/mL) had TSH concentrations shifted toward lower values. A similar trend was observed among subjects with mild smoke exposure (serum cotinine 0.05–15 ng/mL). Mild smoke exposure was associated with 40% lower odds of elevated TSH levels compared to individuals with undetectable cotinine (OR [95% CI] = 0.6 [0.4–0.7]). The trend remained after adjustments for age, gender, race/ethnicity and iodine status, however it was not statistically significant (OR [95% CI] = 0.8 [0.6–1.0]). Moreover, the prevalence of TSH elevation above 4.5 mU/L was statistically lower in smokers compared to nonsmokers (OR [95% CI] = 0.6 [0.5–0.6]) after adjustment for confounders.

Jorde and Sundsfjord performed a cross-sectional study and also found that TSH level adjusted for sex, age and BMI was lower in smokers (females and males) compared to nonsmokers [7]. Moreover, the authors evaluated the influence of smoking on TSH concentration among smokers in relation to use of levothyroxine medication. TSH concentration was significantly higher in female smokers who used levothyroxine than in female smokers who did not use this medication.

Mehran et al. analysed an Iranian population in which adults were classified into ever smokers and never smokers according to self-administered questionnaires [4]. Although the study did not distinguish active smoking status from prior smoke exposure, lower TSH level was established among ever smoker males compared to never smoker males [4].

Some authors evaluated the association between dose of smoke exposure and TSH concentration. Belin et al. in NHANES III found that the increase in cotinine level of 10 ng/mL is associated with a 1.4% decrease of OR of having TSH level above 4.5 mU/L after adjustment for age, gender, iodine status and race/ethnicity. Moreover, every 10 ng/mL increase in serum cotinine was associated with an approximately 2% increased odds of having TSH level of 0.1–0.4 mU/L (adjusted OR [95% CI] = 1.02 [1.01–1.03]) [8]. Asvold et al. analysed the correlation between the number of cigarettes smoked daily and TSH level [6]. They found that heavier smoking was associated with lower TSH concentration, but smoking 12 or more cigarettes per day did not cause any further decrease of TSH concentration [6]. On the contrary, Jorde and Sundsfjord did not find a correlation between the number of cigarettes smoked daily and TSH serum concentration [7]. In this study, a decrease of TSH level was found even in subjects who smoked fewer than six cigarettes per day.

The influence of smoking cessation on TSH concentration was also investigated. Asvold et al. suggested that smoking may have a reversible effect on thyroid gland function. They ascertained that TSH concentration was similar in former female smokers 5–10 years after quitting smoking and in females who have never smoked [6]. However, the length of cessation time in former male smokers was at least 18 years in order to have TSH level similar to males who have never smoked [6]. Cho et al. found that TSH level in former male smokers was lower than in males who have never smoked, but the correlation between the total amount of smoked cigarettes (pack-years) and TSH concentration was not established [5]. When interpreting this finding, it is important to consider that the duration of quitting smoking in 30% of former smokers was shorter than one year.

An analysis of the relationship between smoking status, TSH level and thyroid structure showed interesting results. Vejbjerg et al. found a correlation between smoking status and lower TSH only in smokers with multinodular thyroid goitre and diffuse goitre ($p < 0.001$). This was in contrast to smokers with solitary thyroid nodule, where no association was reported ($p = 0.64$) [9].

Moreover, this study found that the influence of cigarette smoking on mean TSH concentration did not differ before and after iodisation.

The influence of smoking on free thyroxine (fT4) and free triiodothyronine (fT3) concentrations has been found to be more controversial. Jorde and Sundsfjord reported higher levels of fT4 and fT3 in smokers compared to nonsmokers [7]. Knudsen et al. performed a study in an iodine-deficient region and revealed lower TSH concentration and higher fT4 concentration in smokers compared to nonsmokers [10]. However, there was no impact of smoking status on fT3 level [10]. Vejbjerg et al. evaluated the same population in an iodine- deficient period and after iodisation of salt. The impact of cigarette smoking on the level of TSH and fT4 did not differ before and after iodisation. Concentration of fT4 was higher in smokers than in nonsmokers regardless of iodine status [9]. The authors also reported that before mandatory iodisation of salt there was no influence of cigarette smoking on the concentration of fT3. However, investigation of an iodine-sufficient area revealed that fT3 was higher in smokers. Vejbjerg et al. suggested that this finding may be caused by the application of different analytic methods for determination of fT3 concentration before and after iodisation.

Although most studies showed a stimulatory effect of smoking on the thyroid gland, some have revealed different findings. Cho et al. did not find a statistically significant difference in fT4 between smokers and nonsmokers [5]. Soldin et al. revealed that both active and passive smoke exposure were associated with lower levels of T4 and T3 in females compared to nonsmokers [11].

In conclusion, studies showing an increase of free thyroid hormones in smokers are in line with investigations revealing lower TSH levels in this group of patients.

## Influence of cigarette smoking on thyroperoxidase antibodies (TPO-Abs), thyroglobulin antibodies (Tg-Abs), TSH receptor antibodies (TSHR-Abs)

The effect of cigarette smoking on TPO-Abs and Tg-Abs is controversial. Some studies have proved that cigarette smoking is associated with a lower prevalence of TPO-Abs and Tg-Abs [8, 12]. Belin et al. established that the increase in cotinine concentration in smokers is correlated with a decrease of TPO-Abs and Tg-Abs titres. Effraimidis et al. performed a prospective cohort study in a population of women who were relatives of patients diagnosed with autoimmune thyroid disease. The main finding of this study was that smoking cessation increased the risk of occurrence of TPO-Abs and/or Tg-Abs [13]. Pedersen et al. reported a negative association between smoking and the presence of Tg-Abs in a survey performed in a moderate and mild iodine-deficient population. In this study, a weak association between smoking and TPO-Abs was also found. The risk for having thyroid Abs was similar in moderate and heavy smokers. Comparison between former and never smokers also did not reveal any difference in the risk of having thyroid Abs [14]. But Cho et al. failed to establish an association between smoking status and the level of TPO-Abs [5].

Quadbeck et al. determined that smokers had a higher level of TSHR-Abs than nonsmokers [15]. The same difference between TSHR-Abs for smokers and nonsmokers was assessed after the treatment of Graves' disease with antithyroid drugs (ATDs).

## Influence of cigarette smoking on thyroid gland diseases

### *Graves' disease (GD) and Graves' orbitopathy (GO)*

The negative influence of cigarette smoking on GD is well established [16, 17]. In a meta-analysis performed by Vestergaard, the risk for GD was higher in current smokers than in nonsmokers. Another important finding of the meta-analysis was that previous smoking did not increase the risk of GD [16]. This particular study also revealed that the relationship between smoking and GD was similar in iodine-replete and iodine-deficient areas. This finding may suggest that smoking acts independently of iodine status. Quadbeck et al. showed a significantly higher relapse rate of GD in smokers compared to nonsmokers [15]. Cigarette smoking is considered to be one of the environmental risk factors that might impact upon GD development, but in some studies there was no difference in GD prevalence between smokers and nonsmokers [18]. However, one study found a higher proportion of smokers among patients with GD compared to those with toxic multinodular goitre and solitary toxic adenoma. Lantz et al. analysed three populations of people living in an urban area of southern Sweden: people born in Sweden, born in Europe but outside Sweden, and born outside Europe. Interestingly, the lowest proportion of smokers was observed in people born outside Europe with the highest share of GD [19]. This finding supports the hypothesis that many factors, other than smoking, are involved in the development of GD.

The strong association between cigarette smoking and GO is also well established [17, 20, 21]. Cigarette smoking increases the risk of GO (OR [95% CI] = 7,7 [4,3–13,7]) [22]. Childhood GO is also considered to have a strong link with tobacco smoke exposure [23]. Some

researchers have proved that current smoking status is a stronger risk factor than a history of smoking [17]. In contrast, many investigators did not find a difference in risk of GO occurrence between former and current smokers. However, the risk of GO is increased also in former smokers compared to never smokers.

There are still some investigators who did not find the association between smoking status, prevalence and severity of GD [24, 25]. However, Chen et al. found an association between smoking habit and GO [24]. It should be considered that these contradictory results are derived from investigations carried out on relatively small numbers of Asian subjects. Moreover, it has to be mentioned that risk of GO due to smoking cigarettes was found to be lower in Asians than in Europeans [26]. Population-based prospective studies assessing the influence of cigarette smoking on both GD and GO for Asians are needed to explain those relationships.

Cigarette smoking is considered to be an independent risk factor for progression of GO after radioiodine (RAI). Smoking increases the risk of development or worsening of GO regardless of treatment with RAI or ATDs [27]. Quadbeck et al. found that cigarette smoking was associated with a higher risk of relapse of GD and GO independently of high TSHR-Abs level [15]. Smoking also decreased the initial response to immunosuppressive therapy with glucocorticosteroids (GCC) or radiotherapy [28, 29]. Eckstein et al. revealed better response 1.5–7.5 months after the beginning of therapy in nonsmokers but did not find the difference in proptosis between smokers and nonsmokers after 12 months of treatment. However, clinical activity score (CAS) and motility estimated 12 months after the beginning of therapy were statistically worse in smokers than in nonsmokers. Bartley et al. investigated a group of 120 patients with GO and did not find a difference in long-term outcome of GO therapy between smokers and nonsmokers [30].

It seems that smoking has a certain effect on short-term response to therapy of GO, but the long-term influence of smoking is still unclear and requires prospective studies. It is possible that smoking delays the response to treatment.

There is still a question whether a smoking dose has an influence on GO outcome. There have been several studies measuring smoke exposure with different methodological tools. The most frequently assessed parameter was the number of cigarettes smoked per day. Pfeilschifter and Ziegler estimated that the risk of diplopia and proptosis was statistically higher among smokers and it was correlated with smoking severity (measured as cigarettes smoked per day and total number of cigarettes smoked in a lifetime) [31]. Some investigators classify the extent of smoking using more measurable parameters like cotinine level or N-2- hydroxyethylvaline (HEV) level [29, 32]. Eckstein et al. established that an initial improvement of clinical symptoms (CAS and motility but not proptosis) in patients with GO treated with anti-inflammatory drugs was inversely correlated with HEV level.

The mechanism by which cigarette smoking exacerbates GO requires further research. Tobacco compounds are suspected to act in several possible ways. They may have immunomodulatory effect. This hypothesis is supported by the results that smoking worsens early response to anti-inflammatory therapy of GO with GCC or radiotherapy [29]. But cigarette smoking may lead to direct damage of thyroid tissue and it could stimulate the production of Abs. Similar situation is observed when TSHR-Abs level rises after RAI treatment of GD, probably due to thyroid damage and release of thyrotropine receptors [33]. A case report about GD and GO caused by percutaneous ethanol injection has been reported [34]. It showed that autoimmune response might be triggered by mechanical damage of thyroid tissue. Szucs-Farcas et al. performed magnetic resonance imaging (MRI) scans of 110 orbits and found that the amount of intraorbital connective tissue was correlated with cumulative smoking (calculated as the total number of cigarettes smoked per day and smoking period in days) for patients with GO. Extraocular muscle volumes were not influenced by smoking in this study [35].

### *Hashimoto's thyroiditis*

Fukata et al. found that smoking increased the risk of hypothyroidism development among smokers with Hashimoto's thyroiditis [36]. On the other hand, a meta-analysis did not confirm an association between smoking and hypothyroidism [16]. In sharp contrast to these results, other studies have shown that smoking may decrease the risk of development of TPO-Abs and hypothyroidism [6, 8]. Cho et al. found that subclinical hypothyroidism was inversely associated with current smoking status in female smokers [5]. This study suggested that the protective effect of smoking on hypothyroidism development is linked with iodine-related mechanism rather than direct immunological modulation. However, as mentioned previously, cigarette smoking may decrease TPO-Abs titre. Therefore, it may be suggested that protective role of smoking on hypothyroidism development is due to the immune system.

The influence of smoking cessation on the risk of overt hypothyroidism was also investigated in recent studies. In a population-based case-control study performed by Carle et al., the risk of hypothyroidism was increased within the first two years after quitting smoking (OR [95% CI] = 6.53 [3.03–14.10]) [37].

### *Diffuse goitre, multinodular goitre and solitary nodule*

It is well established that the prevalence of nontoxic goitre is higher among smokers than nonsmokers [16, 18]. The influence of smoking is stronger among female smokers than male smokers. Goitrogenic effect of smoking was more pronounced in iodine-deficient areas which may suggest thiocyanate ($SCN^-$) role as a competitive inhibitor of iodine uptake [39]. Ittermann et al. performed a prospective study in a region with improved iodine supply [40]. Cigarette smoking was found to have no impact on thyroid growth among young subjects (under 40) during a five-year follow-up. The association between smoking and thyroid volume progression was reported only in subjects aged 60 plus presenting goitre in the beginning of the follow-up. This was a population of subjects who had been living in an iodine-deficient region previously. It is worth stressing that subjects who developed goitre during follow-up were older, more often former smokers, and reported more pack-years than subjects who did not develop goitre. Therefore, a declining impact of smoking on thyroid volume in iodine-sufficient areas was suggested. Vejbjerg et al. also studied the influence of smoking on thyroid volume in relation to higher iodine intake in the population [9]. The results were compared to findings from a cross-sectional study in the same area before iodisation of salt. Risk of thyroid enlargement was increased in smokers regardless of iodine status. However, the influence of smoking on thyroid volume was lower in iodine-sufficient area. A positive association between smoking and thyroid volume was reported only among women aged 40–45 with low urinary iodine concentration, which indicates an iodine- dependent mechanism.

Cigarette smoking is regarded as a risk factor for multinodular thyroid gland in iodine-deficient regions. Knudsen et al. described the prevalence of multinodular goitre as two times higher in smokers than in nonsmokers (16.5% *v.* 7.6%) [41]. In contrast, there was no influence of smoking status on prevalence of solitary thyroid nodules. A stronger association between smoking and multinodular goitre was seen in areas with more pronounced iodine deficiency, however it was not statistically significant. On the other hand, a study conducted in an iodine-sufficient region revealed equal distribution of smokers among the three types of hyperthyroidism (GD 24% of hyperthyroid smokers (HS), toxic multinodular goitre 21% of HS, and solitary toxic adenoma 24% of HS) [42]. According to Vejbjerg et al., there was no correlation between smoking and the occurrence of multiple thyroid nodules in men after mandatory iodisation. This cross-sectional study also failed to reveal an association between smoking and solitary thyroid nodule regardless of iodine status [9].

$SCN^-$ is a compound of cigarette smoke considered to be a goitrogenic factor. A study conducted in an area with significant air pollution as a $SCN^-$ source suggested that it is an independent cofactor for goitre development in smokers and nonsmokers [43]. Thyroid volume enlargement and goitre were also associated with increased dietary intake of $SCN^-$ from cabbage in Sicily [44]. However, the influence of cigarette smoking on thyroid volume seems to decline due to mandatory iodisation. Thus, further studies are required to reveal the impact of tobacco smoking on thyroid volume according to improved iodine supply.

### *Thyroid gland cancer*

A reduced risk of thyroid gland cancer due to cigarette smoking status has been found in several studies [1–3, 45]. Mack et al. performed an international pooled analysis of 14 case-control studies and found 40% reduction in risk of papillary and follicular thyroid cancers among current smokers compared to never smokers. Some studies established decreased risk of thyroid cancer associated with current smoking status compared to former tobacco consumption [2, 3].

A different pooled analysis of 14 case-control studies revealed a decreased risk of medullary thyroid cancer in current smokers, with no gender related difference [46].

Kabat et al. analysed data concerning smoking habits and thyroid cancer prevalence among women who participated in a large, multi-centre study: The Women's Health Initiative (WHI) [47]. Current active smoking status was associated with reduced risk of all thyroid cancers (Hazard Ratio (HR) [95% CI] = 0.54 [0.29–1.0]) and papillary thyroid cancer (HR [95% CI] = = 0.34 [0.15–0.78]). A pooled analysis of five prospective studies conducted in the United States revealed that current smokers had reduced risk of thyroid cancer (HR [95% CI] = 0.68 [0.55–0.85]) compared to never smokers [48]. However, some cohort studies did not find influence of tobacco smoking on thyroid cancer prevalence [49, 50].

The influence of daily tobacco dose on the reduced risk of thyroid cancer remains unclear. Guingard et al. did not report any correlation between age at starting smoking, daily tobacco consumption, smoking duration and reduction of the risk of thyroid cancer [51]. However, Kitahara et al. found positive correlations between smoking intensity, duration, pack-years and risk reduction among former and current smokers [48].

TSH plays a role in growth and differentiation of thyroid cells. Previously discussed decrease of TSH concentration in smokers may hypothetically explain the reduced risk of differentiated thyroid cancer compared to nonsmokers. The mechanism of suggested inverse relationship of cigarette smoking and medullary thyroid cancer requires further research.

## Influence of cigarette smoking on maternal and foetal thyroid gland function

Thyroid hormones are essential for the development of the foetus. Changes in thyroid function are modulated by several factors related to physiological pregnancy, such as: influence of human chorionic gonadotropin, activity of placental deiodinases, increased iodine renal clearance and changes in thyroid hormone binding protein concentration. The exact influence of cigarette smoking on maternal and foetal thyroid function is not clearly established. Shields et al. analysed TSH, fT3, fT4 concentrations and TPO-Abs titre in two independent cohorts of pregnant women: one during the first trimester (n = 1,428), and one during the beginning of the third trimester (n = 927). TSH, fT3, fT4 were also measured in cord blood of newborns born to women from the third trimester cohort [52]. The authors found that maternal TSH concentration was lower and maternal fT3 concentration was higher in smokers than in nonsmokers. No association was determined between maternal fT4 concentration and cigarette smoking. The prevalence of TPO-Abs positive women was similar in smokers and in nonsmokers in both cohorts. TPO-Abs titre was measured only in the third trimester cohort and was higher in smokers. The authors of this study also examined the influence of the number of cigarettes smoked per day on maternal TSH, fT4, fT3 concentrations: they did not find any dose-related effect. In the third trimester cohort, cessation of smoking in the first trimester of pregnancy led to reversal of smoking-related changes in thyroid hormones. In both cohorts, TSH and fT3 concentrations were similar between women who stopped smoking during pregnancy and women who had never smoked. Concentration of fT4 was lower in women who stopped smoking compared to women who had never smoked (first trimester cohort). TSH concentration measured in cord blood of newborns born to mothers who smoked during pregnancy was lower than of those born to nonsmokers. No correlations were found for fT4 and fT3.

A recent study from Finland on 4,837 euthyroid mothers showed different results [53]. Smoking before pregnancy or during first trimester caused an increase in fT3 concentration, but a decrease in fT4 concentration compared to non-smoking women. Smoking in the second trimester caused similar changes, except fT4 concentration which remained unchanged. All these alterations might be explained by smoking-related changes in peripheral metabolism of thyroid hormones. Interestingly, TSH concentration was similar in smokers and nonsmokers, regardless of pregnancy period. Samples taken from this cohort were also assayed for Tg-Abs (lower prevalence in smokers) and TPO-Abs (similar prevalence in smokers). Based on their results, the authors hypothesised that lower fT4 concentration in smoking mothers might be a risk factor for hypothyroidism in the future. However, this cohort analysed 20 years later had a similar prevalence of hypothyroidism compared to nonsmokers.

Chen and Kelly showed in a study on thyroid function in neonatal rats that maternal nicotine exposure did not alter the total T4 level, T3 uptake and the calculated fT4 index in the offspring [54]. The authors hypothesised that the smoking-related alterations in TSH and thyroid hormones levels might be caused by other substances in cigarette smoke, but not the nicotine itself. Similar results were presented by Colzani et al. who studied the effect of nicotine on thyroid function in non-pregnant rats [55].

Chanoine et al. investigated the influence of maternal smoking on neonatal thyroid volume [56]. The study was conducted in an area of borderline iodine intake (median maternal urinary iodine: 315 nmol/L). Authors used cord serum $SCN^-$ as an index of maternal smoking and found a positive correlation between $SCN^-$ concentration and neonatal thyroid volume. This finding was not accompanied by alterations in TSH, fT4 and fT3 levels which remained within the normal range in all newborns.

Postpartum thyroiditis (PPT) is defined as thyroiditis diagnosed within 12 months since childbirth. The association of smoking with increased risk of PPT and other postpartum autoimmune disorders has been presented in some studies [16, 57–59]. The contradictory results of other researchers are probably due to differences in study design, sample size, and definitions of cigarette smoke exposure [60, 61].

## Discussion

There is a relatively large amount of data on the influence of cigarette smoking on the thyroid gland. This influence is exerted through different mechanisms and modified by several factors such as age, sex, ethnicity and iodine status. Contradictory results of some studies may arise from those complex relationships, but also from various methodological tools used by investigators.

Many researchers have used self-reported smoking status questionnaires. Some investigators did not distinguish between former and current smokers. Belin et al. defined 'smoker' using serum cotinine concentration. Eckstein et al. estimated smoking status via determination of N-2-hydroxyethylvaline (HEV). Laboratory parameters enable the avoidance of misclassifying passive smokers as nonsmokers.

Based on this, estimation of smoking status using biochemical testing might be especially important for

investigations carried out on children and teenagers. In those subjects, laboratory measurements are the only reliable tool for determination of tobacco smoke exposure. They enable to precisely assess the dose of smoke exposure and should be used in further prospective studies. Estimating the severity of smoking according to the number of cigarettes smoked per day seems to be insufficient and can lead to misleading results.

The results of TSH, fT4 and fT3 evaluation in smokers quoted in our review suggest that the concentration of TSH in serum is decreased in most smokers. It should be noted that the same authors or others in the same time found the concentration of fT4 and fT3 in smokers to be elevated [4–10]. In our opinion, as correlation between concentration of TSH and fT4 is generally accepted, the decreased concentration of TSH may be much more related to elevated fT4 than to smoking itself. The problem as to whether the effect of smoking primarily affects concentration of thyrotropin or formation of fT4 requires further study.

Cigarette smoking may have a deteriorating impact on many autoimmune diseases, such as rheumatoid arthritis, Crohn's disease, and systemic lupus erythematosus [62, 63]. In sharp contrast, cigarette smoking seems to improve ulcerative colitis and Behçet disease [62]. It could be hypothesised that the main influence of cigarette smoking on Hashimoto's thyroiditis and GD results from immune modulation. The exact pathogenic mechanisms of these autoimmune disorders have not been sufficiently revealed. Investigations on the effects of cigarette smoking on immunity have shown that both the cell-mediated and the humoral immune response is affected in smokers. Interestingly, cigarette smoking has both pro-inflammatory and immuno-suppressive effects. Nicotine, hydroquinone and carbon monoxide are the main compounds of cigarette smoke with suggested suppressive influence on the immune system [62]. Obviously, the influence of nicotine or other cigarette smoke compounds on the immune system is regulated by many factors, but cigarette smoke exposure is believed to inhibit Th1 cytokine production and may lead to enhancement of Th2 response [62]. Since Hashimoto's thyroiditis is regarded as a predominantly Th1 disease, the suppressive effect of cigarette smoking on Th1 response may explain the decreased risk of this disease among smokers [64, 65]. The increase in risk of GD and GO in smokers may be caused by the Th2 cytokines involvement and enhancement of Th2 response, which is also considered as one of the main factors in pathogenesis of GD and GO. Cigarette smoking may also increase oxidative stress in patients with GO and this might also be responsible for the higher risk of GO in smokers.

In conclusion, since the pathogenesis of HT and GD is still uncertain, it is difficult to explain the basis of the influence of cigarette smoking on thyroid autoimmunity. On the other hand, experimental investigations concerning the influence of cigarette smoke compounds on thyroid autoimmunity may provide new insights into the pathogenesis of these disorders.

An inverse relationship between cigarette smoking and thyroid cancer risk seems to be well established. However, the existing data on the mechanisms of this association is definitely insufficient. Among many factors involved in the pathogenesis of thyroid cancer, only a few have been found to be modified by smoking. TSH as a major growth factor for thyroid nodules has long been hypothesised to play a crucial role in thyroid carcinogenesis [66]. Cigarette smoking is associated with decreased serum TSH concentration, which may limit cancer growth. To date, this is the most convincing hypothesis linking cigarette smoking with a decreased risk of thyroid cancer.

It has long been known that the incidence of thyroid cancer is significantly higher among women, which may be due to the metabolism of oestrogens. There is strong evidence that oestrogens may directly stimulate thyroid cells, through oestrogen receptors (ORs). The action of oestrogens on thyroid cells is rather complex and may involve several genomic and non-genomic components, with a major effect on cell function modulation and proliferation [67]. Smoking has been shown to have anti-oestrogenic effect, thus may have the potential to inhibit growth of oestrogen- dependent cancers.

Several studies have shown that patients with higher BMI tend to suffer from thyroid cancer more frequently [68]. This phenomenon might be explained by the fact that adipose tissue is an important secondary source of circulating oestrogens. Numerous studies have shown that BMI is lower in smokers than in non-smokers and it might be an additional component modifying the risk of thyroid cancer development, although this has yet to be confirmed [69].

Despite opposite action on thyroid cancer development, cigarette smoking is one of the major causes of carcinogenesis. This action is exerted through direct genotoxicity, but also through epigenetic (nongenotoxic) effects. Cigarette smoke is a mixture of several hundreds of substances, of which more than 60 considered carcinogenic act on mechanisms involving all steps of carcinogenesis [70]. Based on studies on smoking-related cancers, many genes and regulatory pathways have been discovered to play a role in smoking-induced carcinogenesis [71]. Interestingly, some of these elements may also be involved in thy-

roid cancer development. Genetic alterations differ according to its histological type (papillary, follicular, medullary, anaplastic) and their detailed description is not a subject of this review. However, some major genetic alterations, common for smoking-related cancers and thyroid cancers should be listed here. These are mutations in such genes like: BRAF, RAS, PI3K/AKT, PTEN, TP53. Nonetheless, mechanisms of acquisition and persistence of given mutations may have some tissue specificity and probably differ according to the organs. The exact aetiology of these mutations in thyroid cancer depending on smoking status is unknown and definitely deserves further research.

To summarise, investigations on the influence of several compounds of cigarette smoke on the thyroid gland may give a better understanding of the results from epidemiological studies which frequently provide contradictory data. On the other hand, for some thyroid diseases there is strong evidence for the effect of smoking. In GD and especially in GO, smoking cessation is effective in primary, secondary and tertiary prevention. In thyroid gland cancer, cigarette smoking seems to have opposite effects.

However, it should never be considered as a protective agent in medical practice, because of the huge number of deleterious effects on other organs and whole systems. Altogether, the possible effects of smoking on thyroid pathophysiology is not fully elucidated. Some data suggesting beneficial results of smoking on Hashimoto's thyroiditis or thyroid cancer should be considered as requiring further, more comprehensive, studies.

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