CLINICAL STUDY

Smoking as a risk factor for thyroid volume progression and incident goiter in a region with improved iodine supply

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Abstract

Objective: The role of smoking in the pathogenesis of thyroid enlargement is currently under debate. It has been hypothesized that the effect of smoking on increased thyroid volume is larger in regions with than in regions without iodine deficiency. The aim of this paper was to investigate the association of smoking with thyroid volume progression and incident goiter for different age-strata in a region with improved iodine supply.

Design and methods: The population-based Study of Health in Pomerania comprised 3300 subjects with complete 5-year examination follow-up. Data from 2484 participants without known history of thyroid disorder or thyroid medication were analyzed. Thyroid size was evaluated by ultrasound. Determinants of thyroid volume progression and incident goiter, i.e., newly occurred goiter between baseline and follow-up, were analyzed by linear and logistic regression respectively.

Results: Participants aged 20–39 years who were current smokers at baseline and at follow-up had a lower risk of incident goiter (odds ratio: 0.33; 95% confidence interval (CI): 0.15; 0.71; $P=0.005$). In this subpopulation, age was inversely related to thyroid volume progression. In subjects aged 60–79 years, smoking at baseline and follow-up was a risk factor for thyroid volume progression (β : 3.37; 95% CI: 0.84; 5.89; $P=0.009$). After exclusion of individuals who had actual goiter in ultrasound at baseline, this association disappeared.

Conclusion: We conclude that the inverse association between smoking and goiter in young adults and the lacking association of smoking with goiter and thyroid volume progression in adult non-goitrous subjects indicate that smoking has a declining impact on thyroid growth in the study region. Our findings mirror the improved iodine supply of Northeast Germany.

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Introduction

The role of smoking in the pathogenesis of thyroid enlargement is currently under debate. It has been hypothesized that the effect of smoking on increased thyroid volume is larger in regions with than in regions without iodine deficiency (1–4). Previous studies (5, 6), which have been conducted in iodine-deficient areas, detected smoking as a risk factor for thyroid enlargement. Other studies (7), however, did not confirm this finding. Evidence from regions with sufficient iodine supply is likewise conflicting. Some studies (8, 9) detected an association between smoking and thyroid enlargement, while others (10, 11) did not. Additionally, a twin study that recruited participants from regions with and without sufficient iodine supply detected smoking as a risk factor for goiter (12). Most of the previous studies are limited by their cross-sectional (1, 4–12) or retrospective design (13).

Methodical constraints, such as selection or recall bias, might have additionally impaired results. Only one study (3) used a prospective cohort design, but was conducted in a selected population of parous women. Therefore, we sought to investigate the association between smoking and thyroid growth in a population-based prospective cohort study.

The improved supply of iodine salt into food productions and individual salt consumption during the 1990s in the study region of Northeast Germany led us to the paradoxical situation of high goiter prevalence in a region of improved iodine supply (14). Previous studies (15) investigated the difference in thyroid growth between regions of mild and moderate iodine deficiency in different age strata. Especially, younger subjects should show more benefit from iodine improvement than elder subjects. Therefore, we investigated the association of smoking with thyroid volume progression and incident goiter in different age strata.

Materials and methods

Study subjects

The Study of Health in Pomerania (SHIP) is a population-based study in West Pomerania, a region in the north-east of Germany including the three cities Greifswald, Stralsund, Anklam, and 29 surrounding communities (16). The total population comprised 212 157 inhabitants. As in most parts of Germany, West Pomerania is a region of former iodine deficiency (14), which resulted in a high prevalence of goiter (6). During the 1990s, improved iodine supplementation has normalized this deficiency level resulting in a median iodine excretion value of 124 µg/l (14). Currently, in the KiGGS study, a German survey in children and adolescents, a median iodine excretion of 117 µg/l was detected (17). SHIP and KiGGS argue for an improvement of iodine excretion levels in Germany on a lower recommended level.

For the SHIP baseline study, a sample from the population aged 20 to 79 years was drawn. Selection of the sample was done using population registries and performed in two steps. In Germany, all residents have to be registered. First, the three cities of the region (with 17 076–65 977 inhabitants) and 12 towns (with 1516–3044 inhabitants) were selected, and then 17 out of 97 smaller towns (with less than 1500 inhabitants) were drawn at random. Secondly, from each of the selected communities, subjects were drawn at random, proportional to the population size of each community, and stratified by age and gender. Only individuals with German citizenship and main residency in the study region were included. Finally, 7008 subjects were sampled, with 292 persons of each gender in each of the twelve 5-year age strata. The net sample (without migrated or deceased persons) comprised 6267 eligible subjects. Selected persons received a maximum of three written invitations. In case of non-response, letters were followed by a phone call or by home visits if contact by phone was not possible. The population of the baseline SHIP finally comprised 4310 participants (2117 men and 2193 women) corresponding to a final response of 68.8% (16). Baseline examinations were conducted between 1997 and 2001. Between 2002 and 2006, all participants were re-invited to take part in an examination follow-up, in which 3300 subjects took part (1589 men and 1711 women; 83.5% of all eligible subjects). The median follow-up time was 5.00 years (minimum, 4.42 years; maximum, 8.58 years; 17 314.7 person years). All participants gave informed written consent. The study followed the recommendations of the Declaration of Helsinki and was approved by the Ethics Committee of the University of Greifswald.

Among the participants, 77 (33 men and 44 women) had missing data in one or more of the variables involved in the data analysis, 717 (218 men and 499 women) had self-reported known thyroid disorders at

baseline or follow-up, and 58 (14 men and 44 women) received thyroid therapy at baseline or follow-up. We excluded these 852 individuals (265 men and 587 women) from further analysis, resulting in a study population of 2448 (1324 men and 1124 women) participants. When using incident goiter as the dependent variable, we excluded a further 801 subjects (468 men and 333 women) with goiter at baseline. This resulted in a population of 1647 participants (856 men and 791 women).

Assessments

Socio-demographic characteristics, smoking, and history of known thyroid diseases or use of antithyroid medication were assessed by computer-aided personal interviews. According to cigarette smoking status, participants were categorized into five groups (1, never smoker; 2, smoker at both baseline and follow-up; 3, smoker at follow-up but not at baseline; 4, smoker at baseline but not at follow-up; 5, nonsmoker at baseline and follow-up but former smoker). Former smokers were individuals who had smoked during their lifetime but not in the last 12 months prior to the time of the baseline examination. Pack years for current and former smokers were calculated by multiplying the duration of smoking in years with the amount of packs (20 cigarettes were defined as one pack) an individual smoked a day. Pack years were divided into three categories (1, 0 pack years; 2, # pack years < median pack years of former and current smokers; 3, # pack years > median pack years of former and current smokers). Height and weight were measured for the calculation of the body mass index: BMI=weight (kg)/height² (m²).

Iodine concentrations were measured by urine iodine excretion. Spot urine samples of the participants were collected and analyzed for iodine and creatinine concentration by photometric procedure (Photometer ECOM 6122, Eppendorf, Hamburg, Germany) with Sandell and Kolthoff reaction (18). The iodine–creatinine ratio was calculated by dividing urinary iodine by urinary creatinine concentration.

Blood samples were analyzed in one central laboratory. Serum thyrotropin (TSH), free triiodothyronine (FT₃), and free thyroxine (FT₄) levels were determined by immunochemiluminescent procedures (FT₃, LUMitest, Brahms, Berlin, Germany; TSH and FT₄, LIA-mat, Byk Sangtec Diagnostica GmbH, Frankfurt, Germany).

Thyroid ultrasonography was performed in both examinations with an Ultrasound VST-Gateway, with a 5 MHz linear array transducer (Diasonics, Santa Clara, CA, USA). The normal thyroid echo pattern was classified as homogeneous. A homogeneous echo pattern with reduced echogenicity was defined as hypoechogenic. Thyroid volume was calculated as length×width×depth×0.479 (ml) for each lobe (19). The intra- and inter-observer reliabilities were assessed before the start of the study and afterwards semi-annually during the study.

All measurements of the thyroid volume showed Spearman correlation coefficients of >0.85 and mean differences (± 2 s.d.) of the mean bias of $<5\%$ ($<25\%$). Thyroid volume progression was defined as difference between thyroid size at follow-up and baseline. Goiter was defined as a thyroid volume >18 ml in women and >25 ml in men (20).

Statistical analysis

Data on quantitative characteristics are expressed as median and inter-quartile range. Data on qualitative characteristics are expressed as percent values or absolute numbers, as indicated. The study population was divided into three groups according to the presence or absence of goiter at baseline and follow-up (1, presence of goiter at baseline; 2, absence of goiter at baseline and follow-up; 3, absence of goiter at baseline but presence at follow-up). Comparisons between groups were made using χ^2 test (qualitative data) or Wilcoxon test (quantitative data). Wilcoxon's signed rank test was used for paired data. Determinants of thyroid volume change and incident goiter were analyzed by linear and logistic regression respectively. All models were adjusted for age, gender, and body mass index. In the first step, both analyses were performed separately for three different age strata (20–39, 40–59, and 60–79 years). In the second step, analyses were performed for the whole population, and interactions between the smoking variables and age were tested. Interactions were kept in the models for P values <0.1 . For all interactions, the β and its s.e.m. are outlined. From linear regression models, the β and its 95% confidence interval (95% CI) and from logistic

regression, odds ratio, and its 95% CI are given. A value of $P<0.05$ was considered statistically significant. All statistical analyses were performed with SAS 9.1 (SAS Institute, Inc., Cary, NC, USA).

Results

Among the 1647 participants without goiter at baseline, 291 (151 men and 140 women) individuals developed goiter during follow-up (5-year incidence: 17.7%). Individuals who developed goiter during follow-up had lower serum TSH levels, were elder, more often overweight, less often current smokers but more often former smokers, and reported more pack years than subjects who had no goiter at baseline and follow-up (Table 1). Compared with subjects without goiter at both baseline and follow-up, individuals with goiter at baseline were elder, more often smokers, less often females, had a higher BMI and lower levels of serum TSH, but higher levels of FT₃. Current or former smokers with goiter at baseline had more pack years than smokers with no goiter at baseline and follow-up. Ever smokers at baseline had an improved risk of goiter compared with never smokers at baseline (relative risk: 1.15; 95% CI: 1.08, 1.21). In all three groups, iodine–creatinine ratio decreased during follow-up. In the whole selected population, the median iodine–creatinine ratio decreased from 133.9 $\mu\text{g/g}$ (99.8 $\mu\text{g/g}$; 179.8 $\mu\text{g/g}$) at baseline to 128.1 $\mu\text{g/g}$ (89.9 $\mu\text{g/g}$; 178.3 $\mu\text{g/g}$) at follow-up ($P<0.001$).

Table 2 shows the results of the age-specific linear regression with thyroid volume progression as outcome. Subjects who were smokers at baseline and follow-up in

Table 1 Characteristics of the study population with and without development of goiter.

	No goiter at baseline and follow-up (<i>n</i> = 1356)	Goiter at baseline (<i>n</i> = 801)	Goiter at follow-up only (<i>n</i> = 291)	<i>P</i> ^a	<i>P</i> ^b
Age (baseline) (years)	45 (32; 57)	52 (41; 64)	53 (40; 64)	<0.001	<0.001
Thyroid volume (baseline) (ml)	14.84 (12.0; 18.0)	27.40 (22.7; 32.6)	17.81 (15.8; 22.4)	<0.001	<0.001
Thyroid volume (follow-up) (ml)	15.44 (12.5; 18.6)	26.65 (21.4; 34.4)	25.43 (19.9; 27.8)	<0.001	<0.001
Urinary iodine creatinine-ratio (baseline) ($\mu\text{g/g}$)	131.0 (98.2; 176.5)	138.2 (101.4; 186.8)	138.1 (101.9; 178.5)	0.216	0.106
Δ Urinary iodine–creatinine ratio ($\mu\text{g/g}$)	−3.6 (−58.8; 44.7)	−3.9 (−57.6; 38.9)	−2.9 (−57.8; 48.3)	0.543	0.788
Body mass index (baseline) (kg/m^2)	25.71 (22.9; 28.8)	27.68 (25.0; 30.7)	27.87 (24.7; 30.5)	<0.001	<0.001
Gender (men)	705 (52.0%)	468 (58.43%)	151 (51.9%)	0.004	0.975
Cigarette smoking					
Never smoker	555 (40.9%)	252 (31.46%)	120 (41.2%)	<0.001	<0.001
Smoker before baseline	416 (30.7%)	284 (35.46%)	113 (38.8%)		
Smoker at baseline only	73 (5.4%)	52 (6.49%)	17 (5.8%)		
Smoker at follow-up only	63 (4.7%)	24 (3.00%)	9 (3.1%)		
Smoker at baseline and follow-up	249 (18.4%)	189 (23.60%)	32 (11.0%)		
Pack years	11.1 (5.5; 23.8)	17.3 (9.4; 29.0)	15.0 (6.7; 28.1)	<0.001	0.019
Serum thyrotropin (baseline) (mU/l)	0.79 (0.57; 1.10)	0.53 (0.36; 0.76)	0.61 (0.42; 0.83)	<0.001	<0.001
Free triiodothyronine (baseline) (pmol/l)	5.26 (4.72; 5.78)	5.20 (4.70; 5.80)	5.24 (4.80; 5.80)	0.680	0.709
Free thyroxine (baseline) (pmol/l)	12.40 (10.80; 13.90)	12.70 (11.10; 14.36)	12.32 (10.58; 14.20)	0.005	0.996

Data are given as numbers (percentage) or median (25th and 75th percentile). Δ Change between baseline and follow-up.

^a χ^2 test (qualitative data) and Wilcoxon test (quantitative data) for row one and two.

^b χ^2 test (qualitative data) and Wilcoxon test (quantitative data) for row one and three.

Table 2 Risk factors for thyroid volume progression.

	20–39 years β (95% confidence interval)	40–59 years β (95% confidence interval)	60–79 years β (95% confidence interval)
Smoker at baseline and follow-up	–0.54 (–1.18; 0.08)	–0.46 (–1.42; 0.50)	3.37 (0.84; 5.89)*
Smoker at baseline only	0.12 (–0.88; 1.12)	0.48 (–1.06; 2.03)	–0.31 (–3.10; 2.47)
Smoker at follow-up only	–0.47 (–1.55; 0.62)	–0.75 (–2.61; 1.10)	–0.69 (–5.22; 3.83)
Smoker only before baseline	–0.25 (–0.93; 0.44)	0.62 (–0.20; 1.45)	0.93 (–0.43; 2.29)
Age (years)	–0.10 (–0.15; –0.05)*	0.01 (–0.05; 0.07)	0.03 (–0.06; 0.12)
Gender (ref. female)	0.34 (–0.18; 0.86)	–0.56 (–1.26; 0.14)	0.20 (–1.13; 1.52)
Body mass index (kg/m ²)	0.06 (–0.01; 0.12)	0.05 (–0.02; 0.12)	0.12 (–0.01; 0.26)

Linear regression for thyroid volume progression as outcome. Reference group for smokers: non-smokers. * $P < 0.05$.

the elder subgroup (60–79 years) had a higher risk of thyroid volume progression than nonsmokers. However, after exclusion of individuals with goiter at baseline, this association disappeared (β : 1.64; 95% CI: –1.20, 4.48; $P = 0.256$). An interaction between smoking and age ≥ 60 years was detected after including two dichotomous age variables (I, 4–59 vs < 40 years; II, ≥ 60 vs < 40 years) and their interaction terms with smoking into the model ($\beta = 3.50$, S.E.M. = 0.97, $P = 0.001$).

Table 3 outlines the results of the logistic regression with incident goiter as outcome for the three age strata. In the population < 40 years, smoking at baseline and follow-up was inversely associated with goiter. Considering one logistic model over the whole population revealed an interaction between age and smoking ($\beta = 0.03$, S.E.M. = 0.02, $P = 0.055$). For clarifying this interaction, a logistic model with two dichotomous age variables (I, 40–59 vs < 40 years; II, ≥ 60 vs < 40 years) was performed. This calculation revealed significant interactions of smoking and age of 40–59 years ($\beta = 1.10$, S.E.M. = 0.47, $P = 0.019$) and age of ≥ 60 years ($\beta = 1.71$, S.E.M. = 0.70, $P = 0.014$) respectively.

For taking the lifetime amount of tobacco consumption into account, we repeated all analyses for pack years as exposition variable. Among the 2448 individuals, there were 308 former or current smokers (160 men and 148 women), for which pack years could not be calculated due to missing values. Thus, 2140 subjects (1164 men and 976 women) were available for analysis on the association between pack years and thyroid volume progression, and 1423 subjects (740 men and 683 women) for the association between pack years and goiter respectively. Linear regression revealed

a significant inverse association between pack years and thyroid volume progression in subjects aged 20–39 years (β : –1.82; 95% CI: –2.16, –0.96, $P < 0.001$). Other significant associations between lifetime amount of smoking and thyroid enlargement were not detected (data not shown).

Discussion

In the present study, we investigated the association of smoking with incident goiter and thyroid volume progression in a region of improved iodine supply. We detected age-dependent effects of smoking on the dependent variables. While there was an inverse association between smoking and goiter in younger subjects, a positive association was found between smoking and thyroid volume progression in older subjects.

West Pomerania is a region with former iodine deficiency. In the middle of the 1990s, the iodine supply was increased by means of iodized salt in food productions and individual salt consumption. This led to an increase in urinary iodine concentration (21) and to a decrease in goiter prevalence in adolescents living in the study region (22). Because sufficient iodine supply was only available for the past decade in West Pomerania, we observed the paradoxical situation of a high prevalence of goiter and other iodine deficiency-related disorders in a region of improved iodine supply (14). The results of the iodine monitoring in the KiGGS study (17) among children and adolescents demonstrated that Germany meanwhile has an improved

Table 3 Risk factors for incident goiter.

	20–39 years odds ratio (95% confidence interval)	40–59 years odds ratio (95% confidence interval)	60–79 years odds ratio (95% confidence interval)
Smoker at baseline and follow-up	0.33 (0.15; 0.71)*	1.17 (0.62; 2.21)	2.29 (0.67; 7.77)
Smoker at baseline only	1.03 (0.41; 2.57)	2.19 (0.89; 5.39)	0.49 (0.10; 2.33)
Smoker at follow-up only	0.57 (0.19; 1.74)	0.96 (0.31; 3.00)	0.68 (0.07; 6.30)
Smoker before baseline	0.88 (0.47; 1.64)	1.12 (0.69; 1.83)	1.41 (0.77; 2.58)
Age (years)	1.02 (0.97; 1.07)	1.00 (0.97; 1.04)	1.01 (0.97; 1.06)
Gender (ref. female)	0.73 (0.43; 1.23)	0.73 (0.48; 1.13)	1.09 (0.60; 1.99)
Body mass index (kg/m ²)	1.12 (1.06; 1.19)*	1.06 (1.02; 1.11)*	1.10 (1.04; 1.16)*

Logistic regression for the incidence of goiter as outcome. Reference group for smokers: non-smokers. * $P < 0.05$.

iodine supply at a lower recommended level. The present analysis revealed similar results. Due to the large study population, the slight decrease in the iodine–creatinine ratio over time attained statistical significance. Iodine excretion at follow-up, however, was still on a lower recommended level.

Smoking was inversely related with goiter in subjects <40 years and positively associated with thyroid volume progression in subjects ≥60 years. Previous studies on the prevalence of goiter from formerly or currently iodine-deficient areas (1, 2, 5, 23) reported smoking as a risk factor for goiter whereas others did not (7, 24, 25). The fact that the latter studies (7, 24, 25) were only based on bivariate comparisons between smoking and goiter might have resulted in false conclusions because confounders (e.g. age) were not considered. Furthermore, our analysis that used lifetime amount of tobacco smoking as exposition variable confirmed the inverse association between increased amount of pack years and thyroid volume progression in the population <40 years. An association with goiter was not present in this subgroup. In the age group ≥60 years, no interaction between pack years and thyroid enlargement was detected, which argues for an absence of an association between lifetime amount of tobacco smoking and goiter at older ages.

In line with these results, other studies (10, 11) conducted in an iodine-replete region did not detect any association between smoking and thyroid enlargement. This endorses the hypothesis that the association between smoking and thyroid enlargement is present in regions of iodine deficiency rather than in areas with sufficient iodine supply (4). In our analysis, smoking was a risk factor for thyroid volume progression only in the population ≥60 years and, within this, only for those with goiter at baseline. After exclusion of these subjects, the association between smoking and thyroid change was no longer present. This finding suggests that individuals ≥60 years are only affected by thyroid volume progression, if they already have developed goiter during time of iodine deficiency.

The goitrogenous effect of cigarette smoking can be partly explained by elevated plasma cyanate (CN[−]) concentrations in smokers (26). Univalent anions with sizes similar to iodide, such as CN[−], are able to competitively inhibit the transport of iodide into the thyroid gland. Our findings support the notion, that in regions with iodine deficiency this cohesion might fortify the development of goiter in smokers, whereas in regions with sufficient iodine supply smokers might be not that greatly affected (27).

In subjects <40 years, age was inversely associated with thyroid volume progression, but was not related to the risk of goiter. This finding supports the notion that, in general, younger individuals are less strongly affected by iodine deficiency than older individuals (14) and that this subpopulation particularly benefits from iodine fortification programs.

The definition of known thyroid disorders by self-report, which was used as exclusion criterion, was certainly one limitation of the present study. Due to the vague symptoms of most thyroid diseases, the participant might be self-reported healthy, but suffer from biochemical thyroid disease. Therefore, we cannot fully rule out a certain misclassification in the chosen exclusion criterion.

We conclude that the inverse association between smoking and goiter in young adults and the lacking association of smoking with goiter and thyroid volume progression in adult non-goitrous subjects indicate that smoking has a declining impact on thyroid growth in the study region. Our findings mirror the improved iodine supply of Northeast Germany.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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