Association of Tobacco Smoking With Goiter in a Low-Iodine-Intake Area

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Background: Goiter development depends on genetic and environmental factors. The major environmental factor is iodine intake, whereas diverging results have been published concerning the association between smoking and goiter.

Methods: A comparable, cross-sectional study was performed of patients from 2 areas in Denmark with mild and moderate iodine deficiency. A random sample of women and men in selected age groups from the general community was investigated; 4649 subjects participated. Smoking habits were investigated with questionnaires and interviews. Ultrasonography and clinical examination of the thyroid were performed, serum thyroglobulin was measured, and iodine concentration in spot urine samples was analyzed. Data were analyzed in linear models and logistic regression analyses.

Results: Serum thyroglobulin level and thyroid volume at ultrasonography were positively associated with smoking habits (P < .001); the association was stronger in the area with the lowest iodine intake (interaction: P < .001 for thyroglobulin, P = .04 for thyroid volume). A positive association with smoking was also found for thyroid enlargement (odds ratio, 2.9; 95% confidence interval, 2.2-3.7) and palpable goiter (odds ratio, 3.1; 95% confidence interval, 1.6-5.8). Ex-smokers had a goiter prevalence close to that of never smokers. The fraction of goiter cases attributable to smoking was 49% (95% confidence interval, 29%-65%).

Conclusions: Thyroid volume and goiter prevalence were closely associated with smoking habits, with the strongest association being found in the area with the most pronounced iodine deficiency. This may have implications for future goiter prevalences in Third World countries, with their increasing use of tobacco. Half of goiter cases in this population could be ascribed to smoking.

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Goiter is a common disorder in all populations. In an English study, palpable and visible goiter was found in 12.3% of women in the general population. The goiter prevalence is even higher in iodine-deficient areas, and more than 1.5 billion people live in such areas, including many regions in Europe. The annual costs for treatment of goiter was estimated at $1 billion (US) in 1992 in Germans with mild iodine deficiency.

Risk factors for goiter include genetic as well as environmental factors, although evidence of these environmental factors is scarce except for the important impact of iodine deficiency. Iodine deficiency undoubtedly represents the most important risk factor for the development of goiter in the world today.

Thiocyanate is abundant in cigarette smoke and exerts goitrogenic effects through competitive inhibition of iodine transport and organification. The possible impact of smoking on goiter prevalence has been investigated in a few previous studies, but these were hampered by either inaccurate methods of estimating goiter prevalence or the inclusion of small or highly selected groups of subjects. The association between tobacco smoking and goiter in these studies was contradictory, possibly because of differences in study design; however, another confounding factor might be iodine status of the populations, as the strongest association was found in iodine-deficient populations.

The purpose of our study was to determine the association between smoking, goiter, and iodine intake. This was done in a large population sample from 2 areas with different iodine intake by means of precise epidemiologic methods and high-resolution ultrasonography.
SUBJECTS AND METHODS

PARTICIPANTS

From the Danish Civil Registration System, in which all inhabitants in Denmark are registered by a unique number, a record of all subjects of Danish origin from the northern part of Copenhagen and the central part of Aalborg (a city in the western part of Denmark) was made within the following groups: women aged 18 to 22 years, 25 to 30 years, 40 to 45 years, or 60 to 65 years and men aged 60 to 65 years. These age groups were chosen to include women before, in, and after childbearing age, and postmenopausal women. A group of men were chosen in the age group with the supposed highest occurrence of thyroid abnormalities for comparison between the sexes. The 2 regions were chosen as previous studies have indicated that iodine deficiency is more severe in Aalborg than in Copenhagen. Of 40,233 subjects, a random selection of 9274 subjects were invited and 4649 participated (50.1%). The cohort has previously been described in detail.

THYROID INVESTIGATIONS

Thyroid volume was evaluated by ultrasound according to standardized criteria and was reproducible in this setup. The volumes were determined as the sum of π/6 × length × width × depth of each lobe, and thyroid enlargement was defined as a volume exceeding 18 mL for women and 25 mL for men. The ultrasonographers were blinded to the smoking status of the participants. Serum samples were analyzed for thyroglobulin (Tg) by a commercial test (LUMitest; BRAHMS Diagnostica GmbH, Berlin, Germany) with an effective working range of 1 to 500 µg/L and within-run and between-run coefficients of variation of less than 8% for Tg values above 5 µg/L. Antibodies to Tg were measured with a radioimmunoassay (DYNOtest; BRAHMS Diagnostica GmbH) with a functional assay sensitivity below 20 kU/L, and samples with Tg antibodies above 20 kU/L were excluded from statistical analyses involving serum Tg level to avoid possible analytical interference. Apart from this, Tg antibody status was not used in the analyses, as this status was not associated with thyroid volume (P = .33).

A clinical examination of the thyroid was performed by a physician (N.K. or I.B.) without knowledge of the result of the ultrasonography, and thyroid size at the clinical examination was recorded according to World Health Organization criteria as 0 (no enlarged thyroid), Ia (palpable and enlarged, but not visible thyroid), Ib (palpable and enlarged thyroid, visible with extended neck), and 2 and 3 (visible goiter). In the analyses, subjects with grades 2 and 3 goiter were included in group Ib.

DEFINITION OF SMOKING STATUS

Smoking was evaluated from questionnaires and, in case of ambiguous or missing answers, also from the subsequent interviews. Participants were asked about present or previous smoking, daily or occasional smoking, amount of tobacco consumed, type of smoking (cigarettes, cheroots, cigars, or pipe tobacco), years of smoking, years since cessation of smoking, inhalation, and exposure to passive smoking. Most of the smokers were solely cigarette smokers, and as no significant differences were found for the association of smoking with thyroid disease between smokers of cigarettes (33.1% of participants), cheroots (1.0%), cigars (0.2%), and pipe tobacco (2.6%), the different types of smoking were combined in the calculations.

RESULTS

There was a strong association between smoking and serum Tg level (P for trend < .001) (Figure 1). The association was strongest in the area with the lowest iodine intake (P for interaction < .001). A similar association was found between smoking and thyroid volume (P for trend < .001) (Figure 2). The overall interaction term for region and smoking was not significant (P = 1.5), but a significant interaction was found between region and never smoking vs heavy smoking (P = .04), indicating that the influence of at least heavy smoking on thyroid volume is more pronounced in moderate than in mild iodine deficiency. A similar interaction was found if participants were divided according to iodine concentration in spot urine samples. The association between smoking and thyroid volume tended to be stronger in participants with a urinary iodine concentration less than 50 µg/L (P for interaction = .07).

For thyroid enlargement and clinically detectable goiter, no significant differences between the 2 regions were found for the effect of smoking. Consequently, the re-

Table 1. Frequency of Daily Smoking Among 4644 Unselected Subjects From a Danish Cohort From 2 Areas of Denmark*
Further analyses. To combine the different types of tobacco, cigarettes were regarded as 1 g of tobacco, cheroots as 2 g, and cigars as 3 g. Participants were classified as never smokers (never daily use of tobacco), ex-smokers (previous daily use of tobacco), moderate smokers (1-19 g/d), and heavy smokers (≥20 g/d), or simply as smokers or nonsmokers, depending on the context. Familial occurrence of thyroid disease among first-degree relatives and consumption of alcohol were also reported in the questionnaires.

IODINE STATUS

Iodine excretion was measured in casual urine samples with a ceric-arsenite method as previously described.21,22 Median iodine excretion was 68 µg/L in Copenhagen and 53 µg/L in Aalborg; after exclusion of subjects taking individual iodine supplementation in the form of iodine-containing vitamin tablets, the excretion was 61 µg/L and 45 µg/L, respectively. According to World Health Organization criteria,4 the Copenhagen area is mildly iodine deficient and the Aalborg area, moderately iodine deficient.

ETHICS

The study was approved by the regional ethics committee in Copenhagen and Northern Jutland, and all participants gave written informed consent.

STATISTICS

All data processing was done with SPSS 8.0 software (SPSS Inc, Chicago, Ill). For the association of serum Tg level and thyroid volume to smoking, linear models were applied after logarithmic transformation, as the distribution of these variables was skewed toward higher values. For thyroid enlargement and clinical goiter, a logistic regression model was applied.

The frequency of smoking was significantly different in the 2 regions and in the different age and sex groups (Table 1). Consequently, region of inhabitance and age and sex group were included in all regression models. Thus, with the use of multivariate statistics, possible differences in thyroid volume owing to different distribution on age and sex of the different smoking groups were adjusted for. Alcohol consumption and familial occurrence of thyroid disease were also tested in the models but could be excluded, as they had no influence on the estimates for the association of smoking with serum Tg level, thyroid volume, or goiter. Likewise, iodine concentration in the spot urine samples was not different in the 4 smoking groups (P=.98) and iodine excretion could be excluded from the regression models.

Interactions between region of inhabitance and smoking were investigated in all models to describe a possible difference in the impact of smoking on goiter prevalence between the regions; where significant interactions were found, a new variable was constructed with all combinations of region and smoking to provide separate estimates. Generally, smoking as a continuous covariate showed a linear relation to the different estimates of thyroid volume and goiter, but data are presented for the grouped variable with 4 levels of smoking to include nonsmokers and ex-smokers in a comprehensive view.

The population attributable fraction (AF) was computed as follows: \( AF = \frac{p(RR - 1)}{p(RR - 1) + 1} \), where \( p \) is the fraction of smokers in the cohort and \( RR \) is the relative risk.23 Relative risks were replaced by odds ratios from the logistic regression analysis to obtain adjusted estimates.

In this study of a large cohort representing an unselected part of the population from 2 regions of Denmark, we demonstrate a highly significant positive association between smoking and goiter. Both thyroid enlargement on ultrasonography and clinically detected goiter were included, as ultrasonography represents a reproducible and precise estimate of thyroid size, whereas goiter at the clinical examination may be regarded as clinically more relevant. Furthermore, serum Tg level was included as a sensitive but nonspecific marker of thyroid abnormalities. All of these different expressions gave concordant positive associations with smoking.

The modest participation rate may introduce bias in the analyses; the nonresponder problem has previously been discussed.17 The bias is, however, more important in descriptive statistics, whereas estimates of relative risks or odds ratios as in these analyses are less affected by se-
The association between smoking and serum thyroglobulin level in 2 regions of Denmark with different degrees of iodine deficiency (ID). Data are from 3764 unselected subjects, as subjects with thyroglobulin antibodies or previous thyroid disease were excluded. The curves represent mean serum thyroglobulin levels after correction for age and sex in a linear model with logarithmic transformation of thyroglobulin values. Vertical bars are 95% confidence intervals for the mean. Differences are as follows: a, \( P = .24 \) vs never smokers; b, \( P = .20 \) vs never smokers; c, \( P = .004 \) vs ex-smokers and \( P < .001 \) vs never smokers; d, \( P < .001 \) vs ex-smokers and \( P = .001 \) vs never smokers; e, \( P < .001 \) vs all other groups; and f, \( P = .008 \) vs moderate smokers and \( P < .001 \) vs other groups.

The association between smoking and serum thyroglobulin level in 2 regions of Denmark with different degrees of iodine deficiency (ID). Data are from 4412 subjects, as subjects previously treated for thyroid disease were excluded. The curves represent mean thyroid volume determined with ultrasound after correction for age and sex in a linear model with logarithmic transformation of thyroglobulin values. Vertical bars are 95% confidence intervals for the mean. Differences are as follows: a, \( P = .51 \) vs never smokers; b, \( P = .03 \) vs never smokers; c, \( P < .001 \) vs ex-smokers and never smokers; d, \( P = .003 \) vs ex-smokers and \( P < .001 \) vs never smokers; e, \( P = .06 \) vs moderate smokers and \( P < .001 \) vs other groups; and f, \( P = .006 \) vs moderate smokers and \( P < .001 \) vs other groups.

Figure 1. The association between smoking and serum thyroglobulin level in 2 regions of Denmark with different degrees of iodine deficiency (ID). Data are from 3764 unselected subjects, as subjects with thyroglobulin antibodies or previous thyroid disease were excluded. The curves represent mean serum thyroglobulin levels after correction for age and sex in a linear model with logarithmic transformation of thyroglobulin values. Vertical bars are 95% confidence intervals for the mean. Differences are as follows: a, \( P = .24 \) vs never smokers; b, \( P = .20 \) vs never smokers; c, \( P = .004 \) vs ex-smokers and \( P < .001 \) vs never smokers; d, \( P < .001 \) vs ex-smokers and \( P = .001 \) vs never smokers; e, \( P < .001 \) vs all other groups; and f, \( P = .008 \) vs moderate smokers and \( P < .001 \) vs other groups.

Figure 2. Association between thyroid volume and smoking in 2 regions of Denmark with different degrees of iodine deficiency (ID). Data are from 4412 subjects, as subjects previously treated for thyroid disease were excluded. The curves represent mean thyroid volume determined with ultrasound after correction for age and sex in a linear model with logarithmic transformation of thyroid volume. Vertical bars are 95% confidence intervals for the mean. Differences are as follows: a, \( P = .51 \) vs never smokers; b, \( P = .03 \) vs never smokers; c, \( P < .001 \) vs ex-smokers and never smokers; d, \( P = .003 \) vs ex-smokers and \( P < .001 \) vs never smokers; e, \( P = .06 \) vs moderate smokers and \( P < .001 \) vs other groups; and f, \( P = .006 \) vs moderate smokers and \( P < .001 \) vs other groups.

Figure 3. Association between smoking and goiter in a Danish population study. Figures are odds ratios adjusted for age, sex, and region of inhabitance in a logistic regression analysis with 95% confidence intervals. Never smokers constitute the reference group. Thyroid enlargement was defined as a thyroid volume on ultrasound exceeding 18 mL for women and 25 mL for men.\(^ {10} \) Odds ratios are significantly different from the reference if the 95% confidence interval does not include 1.

smoking\(^ {7,8} \) and 1 did not.\(^ {9} \) In an Italian study investigating highly selected subjects with no indication of iodine status, no association between goiter and smoking was detected.\(^ {11} \) This discrepancy may be due to the inaccuracy of palpation of the thyroid.\(^ {23} \) Four studies have used ultrasonic thyroid volume measurements to determine the association with smoking; in 2 studies from mildly iodine-deficient areas, a marked association was found,\(^ {10,12} \) whereas no association was found in a small study from an iodine-sufficient area.\(^ {13} \) A small Greek study with no indication of iodine status found a small impact of smoking on thyroid volume, but only among subjects with familial predisposition to goiter.\(^ {14} \) In our study, familial occurrence of goiter had no influence on the relationship between smoking and thyroid volume. In a recent twin study from an area with mild iodine deficiency, an insignificant association between smoking and nontoxic goiter was found, but the power of the study was limited.\(^ {11} \)

The different effects of smoking reported from areas with different iodine intake is in accordance with our finding of an interaction between smoking and inhabitance of regions with different iodine intake. This interaction, indicating a more profound association between smoking and thyroid enlargement in more severe iodine deficiency, was significant, even though there was only a relatively small difference in iodine excretion between the regions. This difference supports the hypothesis that thiocyanate is the important goitrogen in cigarette smoke.\(^ {25} \) Thiocyanate is a competitive inhibitor of iodine transport and organification, and a more severe effect in iodine deficiency could be anticipated.

We have previously shown that the major increase in goiter prevalence takes place between the ages of 30 and 40 years in areas of mild and moderate iodine deficiency.\(^ {17} \) The major impact of smoking was also seen in this vulnerable period, possibly by accelerating iodine deficiency–induced thyroid enlargement.

Ex-smokers had only a slightly increased risk of thyroid enlargement and goiter compared with never smokers and much less than present smokers. The impact of
smoking thus seems to be reversible to a large extent, emphasizing the importance and benefits of smoking cessation for goitrous subjects. Two studies have investigated goiter prevalence among ex-smokers and found prevalences comparable with those of never smokers,7,8 but goiter was evaluated only by palpation. The public health consequences of smoking were addressed by the population attributable fraction. A prerequisite for the estimation of a population attributable fraction is a causal relationship. For serum Tg level, thyroid volume, thyroid enlargement, and goiter, a dose-response relationship was demonstrated, supporting a causal relationship. Furthermore, the concordance with previous investigations from iodine-deficient areas, a plausible experimental basis for the association, and little confounding from other factors in the analyses support a causal relation. We estimated that 49% of clinically detectable goiters were related to smoking, and as goiter is common in areas of low iodine intake, smoking may be causing large numbers of goiters. Many European countries are exposed to some degree of iodine deficiency, and the cost of goiter treatment is considerable; hence, this is a problem not only for the individual but also for the health care system. With an ongoing increase in smoking prevalence in the developing countries, which are in many cases iodine deficient,9 goiter prevalence may be increasing substantially in the coming years, along with the expected increase in cardiovascular diseases, lung diseases, and cancer.

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Table 2. Odds Ratios for Thyroid Enlargement in the Different Age Strata of the Cohort Comprising 4412 Subjects With No Known Thyroid Disease*

<table>
<thead>
<tr>
<th></th>
<th>Never Smokers</th>
<th>Ex-Smokers</th>
<th>Moderate Smokers</th>
<th>Heavy Smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women 18-22 y</td>
<td>1 (Reference)</td>
<td>1.1 (0.3-3.9)</td>
<td>1.3 (0.7-2.4)</td>
<td>1.5 (0.5-4.6)</td>
</tr>
<tr>
<td>Women 25-30 y</td>
<td>1 (Reference)</td>
<td>1.0 (0.5-2.8)</td>
<td>1.7 (1.0-3.0)</td>
<td>2.4 (1.2-4.8)</td>
</tr>
<tr>
<td>Women 40-45 y</td>
<td>1 (Reference)</td>
<td>2.9 (1.7-4.9)</td>
<td>4.4 (2.8-7.0)</td>
<td>7.1 (4.4-11.6)</td>
</tr>
<tr>
<td>Women 60-65 y</td>
<td>1 (Reference)</td>
<td>0.9 (0.6-1.4)</td>
<td>2.1 (1.4-3.2)</td>
<td>1.7 (0.9-2.9)</td>
</tr>
<tr>
<td>Men 60-65 y</td>
<td>1 (Reference)</td>
<td>1.5 (1.0-2.4)</td>
<td>1.8 (1.0-2.5)</td>
<td>2.4 (1.4-3.8)</td>
</tr>
</tbody>
</table>

*Thyroid enlargement was defined as a thyroid volume on ultrasound exceeding 18 ml for women and 25 ml for men.9 Values were obtained from a logistic regression analysis including an interaction term. Data are odds ratios (95% confidence intervals).

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