Reproductive History and Cigarette Smoking as Risk Factors for Thyroid Cancer in Women: A Population-based Case-Control Study

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Abstract

A population-based case-control study was conducted in Northern Norway and Central Sweden to investigate hormonal and reproductive factors and cigarette smoking as determinants of papillary and follicular thyroid carcinoma in women. Information on 191 histologically confirmed cases and 341 age-matched controls was included. No clear association was found with regard to the number of live births, number of pregnancies, a history of incomplete pregnancies, or the use of oral contraceptives or hormonal replacement therapy. However, an early first childbirth (before 20 years of age, or less than 5 years after menarche) was associated with an increased risk of thyroid cancer.

There was an increased risk of thyroid cancer among women with a history of artificial menopause compared to those with a spontaneous menopause (odds ratio [OR], 2.52; 95% confidence interval [CI], 0.96–6.62), which was more pronounced for the papillary carcinoma and after adjustment for age at menopause and use of replacement therapy. Cigarette smokers had a decreased risk of borderline statistical significance compared to nonsmokers (OR, 0.69; 95% CI, 0.47–1.01), particularly among premenopausal women (OR, 0.60; 95% CI, 0.38–0.96). This negative association persisted after adjustment for parity, hormonal treatments, and education. Women who started smoking before the age of 15 experienced a marked reduction in risk (OR, 0.38; 95% CI, 0.18–0.80). Moreover, there was a suggestion of a dose-response effect with the amount of cigarettes smoked daily and with duration of the habit. Both the increased risk of artificial menopause and the negative association with smoking are compatible with a relation between levels of estrogens and thyroid cancer among women.

Introduction

Several lines of evidence suggest that female sex hormones play a role in the etiology of thyroid cancer. Women have a higher incidence than men in virtually all geographical areas (1) and ethnic groups (2), particularly before menopause. Moreover, pregnancy and some hormonal treatments have been associated with thyroid cancer among women (3–5). Thus far, evidence from epidemiological studies about specific hormonal components is difficult to summarize. The hormone-related factors probably act as late promoters of tumor growth, because there is no sex difference in the prevalence of subclinical tumors detected at autopsy (6). In animal models, estrogens act as promoters of thyroid tumors (7), and estrogen receptors increase in thyroid neoplasms after estrogen administration (8). Estrogen receptors have also been detected in human thyroid neoplasms, but the implications of these findings are unclear (9). Moreover, lifestyles may have biological importance among humans, as is the case for cigarette smoking, which affects the reproductive life and the hormonal milieu of women (10).

To clarify the etiology of differentiated thyroid carcinoma (papillary and follicular types) among women, we conducted a population-based case-control study. In this analysis, we focus on reproductive events and medical procedures that imply estrogenic exposure and on cigarette smoking.

Materials and Methods

Cases

The study took place in the Uppsala–Örebro Health Care Region of Sweden and in the Tromsø Health Care Region of Norway, with approval from the Ethical Advisory Boards in the respective University Hospitals. We aimed to include all cases of histologically verified papillary and follicular carcinoma of the thyroid diagnosed between January 1, 1985 and September 30, 1993 among women resident in the respective Health Care Region. Cases were eligible if alive, between 18 and 75 years of age at the time of the study (April 1993-September 1994), and in Sweden, but not in Norway, only if they were born in the country and had lived abroad for less than 5 years. The identification of cases took place in several steps, with a somewhat different sequence in the two countries.

Sweden. The incident cases of the study population were identified through the National and Regional Cancer Registers. Because there is an average delay of 3 months between clinical diagnosis and reporting to the Registers, we consider the study base completely ascertained up to June 1993. Of an initial group of 223 potential cases, 172 were eligible for the interview: 27 women were foreign-born and lived abroad for more than 5 years; 15 were found not to have papillary or follicular...
carcinoma at the histopathological review; and 9 were dead at the time of the study. The histopathological review was performed by one reviewer (L. O.) at the Department of Pathology of Uppsala University Hospital, using the WHO revised criteria for classification of thyroid tumors (11).

Norway. Eighty-seven living cases of thyroid cancer among women were initially ascertained through the hospitals and the two Departments of Pathology serving the Health Care Region, which are also the source of case notification to the Cancer Register in Norway. The hospitals' catchment area in Norway, particularly for the referral of oncological patients, strictly coincides with the corresponding administrative area, so that the possibility of underascertainment of cancer among residents was remote. The histopathological review also took place in the Departments of Pathology (following the same criteria as in Sweden) and led to the exclusion of three cases. The 84 remaining patients were contacted for the interview.

### Controls

**Sweden.** Two controls per case, fulfilling the same criteria concerning age, birthplace, and residence, were randomly selected from the Population Register of the administrative region and individually matched to the case by year of birth and county of residence. Due to anomalies in the selection of controls, for eight cases only one suitable control was identified.

**Norway.** Four controls per case were selected and matched by year and month of birth. The county of residence at the date of diagnosis was not included among the matching criteria.

### Data Collection

**Sweden.** Questionnaires were sent by mail, together with an explanatory letter about the general purpose of the study and the criteria for the selection of the subjects. A written reminder was sent to nonrespondents 15 to 20 days after this mailing, followed by an additional telephone reminder if necessary. The final response rate in Sweden was 84.3% (145 of 172) for cases and 71.7% (203 of 283) for the controls matched with the respondent cases. Questionnaires not adequately filled were subsequently completed through a telephone interview, a procedure followed for about 50% (197) of the questionnaires.

**Norway.** Informed consent was requested from the cases before mailing the questionnaire. Only controls matched with the 62 consenting cases were then contacted. Reminders were sent to nonrespondents as in Sweden, but there was no subsequent completion of the questionnaires by telephone interview. The response rate in Norway was 73.8% (62 of 84) among cases and 55.6% (138 of 248) among controls. In the two countries together, 48 cases (18.8%) and 189 controls (35.6%) refused participation. In addition, one control was not located, and one case died before being interviewed.

Owing to the different response rates, there were 16 cases without any respondent control. We maintained the original matched design, leaving 191 sets and a total of 532 questionnaires for the final analysis. The age distribution of the study subjects and the histopathological type of cases are given in Table 1.

### Assessment of Exposure

The study addressed several groups of potential risk factors: dietary, medical, environmental, and familial. The study instrument was designed to be identical in the two countries, apart from language and a few questions unique to each center. Fifteen questions concerned the reproductive history and the use of hormonal treatments among women. All reproductive events up to the year before the diagnosis of thyroid cancer in the case were included in the analysis. Twin births were treated as one pregnancy. Incomplete pregnancies (i.e., those interrupted before the 6th month) were recorded without specifying whether they were induced abortions or miscarriages. Questions about menopausal status did not include the type of intervention or the corresponding indication in case of surgical menopause. Exposures such as hormonal treatments and smoking habits were included in the analysis only if they started at least 1 year before diagnosis. The following treatments were considered: OCs; HRT for climacteric symptoms; hormonal treatment of infertility; and lactation suppressants.

Age at first use and duration of use were recorded, but no attempt was made to assess the pharmacological components of each treatment. Smoking history included information on whether the woman was ever a smoker, age at starting regular smoking, the total duration of the habit, and the average number of cigarettes smoked daily during that period. To control for potential confounders, we also included in the analysis the following information: education (number of completed years prior to the diagnosis); medical history of cancer prior to the diagnosis of thyroid cancer; radiation treatments and thyroid diseases (excluding 5 years prior to the diagnosis); and information about menopausal status did not include the type of intervention or the corresponding indication in case of surgical menopause. Exposures such as hormonal treatments and smoking habits were included in the analysis only if they started at least 1 year before diagnosis. The following treatments were considered: OCs; HRT for climacteric symptoms; hormonal treatment of infertility; and lactation suppressants.

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<table>
<thead>
<tr>
<th>Table 1</th>
<th>Cases of papillary and follicular thyroid carcinoma among women by histology and age at diagnosis and matched controls, Sweden and Norway</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Papillary carcinoma</td>
</tr>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>17-24</td>
<td>14</td>
</tr>
<tr>
<td>25-29</td>
<td>16</td>
</tr>
<tr>
<td>30-34</td>
<td>24</td>
</tr>
<tr>
<td>35-39</td>
<td>12</td>
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<tr>
<td>40-44</td>
<td>31</td>
</tr>
<tr>
<td>45-49</td>
<td>13</td>
</tr>
<tr>
<td>50-54</td>
<td>16</td>
</tr>
<tr>
<td>55-59</td>
<td>14</td>
</tr>
<tr>
<td>60-69</td>
<td>21</td>
</tr>
<tr>
<td>All cases</td>
<td>161</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>42.47 (13.59)</td>
</tr>
</tbody>
</table>
reference age); and some occupations that might have entailed exposure to radiation. We also analyzed an indicator variable for the method of the data collection in the Swedish study (whether the subject underwent a telephone interview to complete the questionnaire).

Statistical Analysis

All quantitative variables were analyzed both in the categorized and continuous form. Unless there were clear reasons to choose a specific different categorization, the categories for the quantitative variables were chosen as quantiles of the distribution among controls. Separate analyses were performed, when feasible, for the subsets of papillary and follicular carcinoma, for the two countries, and for pre- and postmenopausal women.

The logistic regression model was used in both univariate and multivariate analyses. As the study design was matched, the model parameters were estimated using conditional maximum likelihood (12). These estimates were used to calculate odds ratios with corresponding 95% CI. Wald tests were used to assess statistical significance. Multivariate models were used to adjust simultaneously for potential confounders. Interaction between two variables was investigated by adding a product term to a model already containing the two main effects.

Results

Reproductive History. Women with at least one pregnancy had risks comparable to those who were never pregnant (data not shown), and the same was true for parous and nulliparous women. However, among parous women, there was an increase in risk with each additional birth after adjustment for age at first full-term pregnancy in continuous form (Table 2). This effect was mainly due to the excess risk in the groups of women with very high parity (four children or more).

Incomplete pregnancies did not confer any increase in risk; women who had at least one miscarriage or induced abortion had, if anything, a decreased risk compared to women without such a history, i.e., nulligravidae and women who had only full-term pregnancies (OR, 0.76; 95% CI, 0.49–1.17). This risk pattern however, was confined to premenopausal women (OR, 0.36–1.38). The outcome of the first pregnancy did not affect the risk of thyroid cancer (OR for women whose first pregnancy was incomplete compared to those who carried to term, 0.81; 95% CI, 0.49–1.17). The analysis of risks associated with the total number of pregnancies did not add substantial information to that obtained by the separate analysis of full-term and incomplete pregnancies.

A first childbirth before the age of 20 years carried an increased risk compared to nulliparous women (Table 3), but this excess risk was confined to premenopausal subjects (OR, 2.52; 95% CI, 0.98–6.51; data not shown). This risk decreased for women giving birth for the first time at an age of 20 to 24 years, while no clear association was seen with an older age at the birth of the first child. The same pattern was evident with age at first pregnancy and with the interval between menarche.
Table 4  Relative risk (OR) of thyroid cancer by use of some hormonal treatments: a matched case-control study, Norway and Sweden

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cases</th>
<th>Controls</th>
<th>OR*</th>
<th>95% CI</th>
<th>OR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral contraceptives’</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never users</td>
<td>81</td>
<td>154</td>
<td>Ref</td>
<td></td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>All users</td>
<td>98</td>
<td>180</td>
<td>0.95</td>
<td>0.60–1.50</td>
<td>0.94</td>
<td>0.59–1.49</td>
</tr>
<tr>
<td>Short-term users (≤2 yr)</td>
<td>33</td>
<td>52</td>
<td>1.16</td>
<td>0.67–2.02</td>
<td>1.12</td>
<td>0.63–1.97</td>
</tr>
<tr>
<td>Long-term users (&gt;2 yr)</td>
<td>64</td>
<td>127</td>
<td>0.79</td>
<td>0.48–1.32</td>
<td>0.80</td>
<td>0.48–1.33</td>
</tr>
<tr>
<td>Per each additional year of use’</td>
<td>0.98</td>
<td>0.91–1.05</td>
<td>0.98</td>
<td>0.91–1.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HRT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never users</td>
<td>48</td>
<td>86</td>
<td>Ref</td>
<td></td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>All users</td>
<td>13</td>
<td>24</td>
<td>0.80</td>
<td>0.34–1.88</td>
<td>0.98</td>
<td>0.39–2.46</td>
</tr>
<tr>
<td>Short-term users (≤2 yr)</td>
<td>10</td>
<td>19</td>
<td>0.71</td>
<td>0.26–1.96</td>
<td>0.91</td>
<td>0.30–2.73</td>
</tr>
<tr>
<td>Long-term users (&gt;2 yr)</td>
<td>3</td>
<td>5</td>
<td>1.06</td>
<td>0.25–4.55</td>
<td>1.15</td>
<td>0.25–5.28</td>
</tr>
</tbody>
</table>

* Among all women.
+ Among all women, adjusted for number of full-term pregnancies.
' Figures do not add up to the total because of missing values.
* Ref. reference category.
$ Duration of OC use and number of full-term pregnancies in continuous form.
% Among postmenopausal women.
‘ Among postmenopausal women, adjusted for age at menopause.

Table 5  Relative risk (OR) of thyroid cancer by age at menopause and type of menopause: a matched case-control study, Norway and Sweden

<table>
<thead>
<tr>
<th>Age at menopause’</th>
<th>Cases</th>
<th>Controls</th>
<th>OR*</th>
<th>95% CI</th>
<th>OR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premenopausal women</td>
<td>122</td>
<td>227</td>
<td>Ref</td>
<td></td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>All postmenopausal women</td>
<td>62</td>
<td>110</td>
<td>1.48</td>
<td>0.55–4.01</td>
<td>1.37</td>
<td>0.49–3.81</td>
</tr>
<tr>
<td>≤48 yr</td>
<td>16</td>
<td>35</td>
<td>2.30</td>
<td>0.56–9.49</td>
<td>2.64</td>
<td>0.82–8.50</td>
</tr>
<tr>
<td>49–51 yr</td>
<td>17</td>
<td>31</td>
<td>1.99</td>
<td>0.51–7.78</td>
<td>2.02</td>
<td>0.71–5.71</td>
</tr>
<tr>
<td>≥52 yr</td>
<td>23</td>
<td>38</td>
<td>1.87</td>
<td>0.47–7.42</td>
<td>2.44</td>
<td>0.84–7.33</td>
</tr>
<tr>
<td>Per year of increasing age’</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Type of menopause’</td>
<td></td>
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</tr>
<tr>
<td>Premenopausal women</td>
<td>122</td>
<td>227</td>
<td>Ref</td>
<td></td>
<td>Ref</td>
<td></td>
</tr>
<tr>
<td>Spontaneous menopause</td>
<td>43</td>
<td>95</td>
<td>0.87</td>
<td>0.28–2.66</td>
<td>0.97</td>
<td>0.31–2.99</td>
</tr>
<tr>
<td>Iatrogenic menopause</td>
<td>18</td>
<td>35</td>
<td>2.37</td>
<td>0.79–7.06</td>
<td>3.30</td>
<td>0.89–12.2</td>
</tr>
</tbody>
</table>

* Among all women.
+ Adjusted for type of menopause among postmenopausal women.
' Figures do not add up to the total because of missing values.
* Ref. reference category.
$ Age at menopause in continuous form.
‘ Adjusted for age at menopause and use of HRT among postmenopausal women.

and birth of the first child. Women who delivered their first child less than 5 years after menarche had an increased risk compared to those who delivered 5 to 10 years after menarche (Table 3) and to nulliparous women (data not shown). The association was weakened, but still apparent, after adjustment for the number of pregnancies. Women with a first full-time pregnancy more than 10 years after menarche had risks comparable to nulliparous women. No association was found with age at last pregnancy or at last livebirth.

Use of Exogenous Hormones. ORs for users of oral contraceptives were close to unity, even after adjustment for the number of full-term pregnancies, and among users, also for age at first use. No trend with increasing duration of use was detected (Table 4).

Among postmenopausal women, HRT for climacteric symptoms was also not associated with thyroid cancer, both with and without control for age at menopause (Table 4). A further adjustment for type of menopause (data not shown) suggested a decreased risk for users compared to nonusers, but the estimate was very imprecise and compatible with chance (OR, 0.56; 95% CI, 0.18–1.73). Duration of HRT use did not show any association with risk.

No clear association emerged with a history of treatments to stop lactation or to enhance fertility; the latter condition was reported by very few women (five cases and nine controls).

Menstrual Cycling. No significant association was found between the risk of thyroid cancer and the characteristics of menstrual cycling, although there was a suggestion of an increased risk for menarche at age 15 years or later versus 12 years or earlier (OR, 1.49; 95% CI, 0.87–2.53) and for menopause after 48 years of age versus both premenopausal status and an earlier menopause (Table 5). However, the risk estimates of age at menopause were imprecise, and the effect was markedly reduced when the analysis was restricted to women with spontaneous menopause.

There was a more than 2-fold increase in risk of thyroid cancer among women whose menstrual cycles ceased after a medical intervention, compared to premenopausal women (Table 5). The association became even stronger when women with a natural menopause were chosen as the reference category (OR = 2.52; 95% CI, 0.96–6.62; data not shown in the table). Controlling for age at menopause among postmenopausal women only slightly altered the magnitude of the association (OR, 2.44; 95% CI, 0.77–7.74), while this was strengthened after further adjustment for use of HRT (Table 4). When the analysis was restricted to papillary carcinoma, the relative risk
of artificial menopause compared to a spontaneous one was somewhat higher (OR, 4.20; 95% CI, 0.93–18.92), adjusted for age at menopause and use of HRT.

**Cigarette Smoking.** Cigarette smoking was associated with a decreased risk of thyroid cancer (Table 6). Although the estimates were not always statistically significant, risk decreased with increasing cigarette consumption, at least up to 15 cigarettes per day, both compared to nonsmokers and to smokers in the lowest category of consumption. Adjusting the quantity of cigarettes by duration of the habit among smokers did not substantially change the results (Table 6), nor did the adjustment for educational levels (data not shown). A negative association was also present between duration of smoking and risk of thyroid cancer, although it was less pronounced after adjustment for educational levels (data not shown). A negative association was also present between duration of smoking and risk of thyroid cancer, although it was less pronounced after adjustment for use of OCs and of any exogenous hormones (Table 6). In this group, the negative association was strengthened after adjustment for the number of children (Table 6). The risk for women who had smoked for 11 to 20 years was almost halved compared to never smokers (OR, 0.55; 95% CI, 0.31–0.97), but a duration of 21 years or more did not further reduce the risk. Women who started cigarette smoking early in life (before the age of 15) experienced a marked reduction in risk compared to nonsmokers, but the inverse association was progressively less evident for women who took up the habit at an older age (Table 6).

The protective effect of smoking was even more pronounced among premenopausal women (OR, 0.60; 95% CI, 0.38–0.96). In this group, the negative association was strengthened after adjustment for use of OCs and of any exogenous hormones but was little altered after adjustment for the number of pregnancies or childbirths. A study of interactions revealed a significant product term for smoking and total number of pregnancies in continuous form ($\chi^2$, 4.18; $P = 0.041$), with a significant negative trend per each pregnancy among smokers (OR, 0.71; 95% CI, 0.53–0.93), but not among nonsmokers (OR, 1.16; 95% CI, 0.92–1.46). Investigation of effect modification of smoking by gravidity (total number of pregnancies) was hampered by the paucity of observations in each stratum. No interaction was detected between smoking and the number of full-term pregnancies, use of OCs, or replacement therapy after menopause.

All of the main associations described above did not show appreciable differences when separate analyses were carried out for Norwegian and Swedish women or after restriction to the papillary carcinoma. Similarly, results were not altered after the exclusion of 18 women (6 cases and 12 controls) with a history of cancer prior to the date of thyroid cancer diagnosis, of women with previous radiation treatment (5 cases and 6 controls), with occupational exposure to radiation (5 cases and 16 controls), or with previous thyroid disorders (12 cases and 15 controls). The adjustment for the method of interview in the Swedish study did not modify the results.

**Discussion**

In this population-based case-control study, no clear associations emerged between the risk of papillary and follicular thyroid carcinoma in women and their main menstrual and reproductive characteristics. There were no suggestions that exogenous hormones or incomplete pregnancies affected risk, but an artificial menopause did seem to confer an increased risk. Cigarette smoking had a protective effect, particularly among premenopausal women.

The weak association with parity in this study is generally consistent with previous findings. In fact, although some studies reported that risk increased with the number of children (4, 5, 13), this was not confirmed in later, larger analyses (14, 15). The lack of association with incomplete pregnancies is far more unexpected, since several authors reported a remarkably increased risk associated with a history of miscarriages, especially among young women (5), or as outcome of a first pregnancy (4, 16–18). We did not collect information regarding the
reason for pregnancy interruption to avoid differential misclassification due to recall bias (19). Having pooled all incomplete pregnancies together, however, cannot explain the lack of association in this study. To conceal a positive association with miscarriages, induced abortions should have conferred a decreased risk, just the reverse of what could be expected on the basis of the hormonal characteristics of spontaneously and electively terminated pregnancy. It has been suggested (16) that the association between subfertility and thyroid cancer may not be etiological but rather indicative of underlying thyroid disorders, possibly caused by iodine deficiency or excess. This may be one explanation for the lack of association with incomplete pregnancies in our study, since clinically evident iodine deficiency disorders, such as goiter, are no longer a reality in Sweden (20). Discrepancies, however, can be partly explained by different patterns of fertility between countries and time periods.

At odds with other investigations (13, 15, 21), an early first pregnancy (at age younger than 20 years) and a short interval between menarche and birth of the first child entailed an increased risk, suggesting, as in a previous study from Sweden (22), an adverse effect of childbearing close to puberty. However, these findings must be interpreted with caution, because of the inverse correlation between parity and timing of the first pregnancy.

Our negative findings regarding oral contraception and HRT at menopause are well in accord with many previous studies, which reported absence of a clear association between thyroid cancer and use of OCS or HRT (5, 13, 16, 17). Few women in our study used HRT, and for most of them, the length of follow up might have been too short to reveal any effect. These women may also suffer most severely from menopausal estrogen deprivation and, therefore, represent a group with a low background risk of thyroid cancer.

In this study, two findings suggest, although indirectly, a linkage between risk of thyroid cancer in women and sex hormone levels. Women with an iatrogenically induced menopause (mostly ablation of uterus and/or ovaries) showed an increased risk of thyroid cancer. In another study, where a similar association was detected (17), a bias due to a closer medical surveillance of women who underwent a hysterectomy and/or ovariectomy was proposed as the most plausible explanation. However, the effect of surveillance bias in this study is likely to be limited, since the exclusion from the analysis of women with previous neoplastic diseases, where this issue is of real concern, did not alter the association. We suggest an alternative explanation for these findings, i.e., confounding by indication: uterine fibroids, a common indication for hysterectomy, has been linked to hyperestrogenism.

The second line of evidence concerns the decreased risk of thyroid cancer for smokers compared to nonsmokers. This was most evident among premenopausal women and for women who took up the habit as adolescents, but there was no indication of a different effect in the two histopathological types. The association remained after adjustment for parity, use of hormonal treatments, and education. Moreover, there were indications of dose-response effects, both with daily consumption of cigarettes and with duration of smoking.

The measurements regarding cigarette smoking in our study were not refined, because we did not collect a complete lifetime history of the habit. Some misclassification is, therefore, possible but would likely be nondifferential and bias the point estimates toward unity. We are not aware of professional exposures or lifestyles that might have introduced a negative confounding in the association with smoking. Our findings are also supported by some previous studies: one reported a higher proportion of women smokers among controls than among cases (3), whereas in the other two studies (16, 23), a decreased risk of thyroid cancer was associated with smoking among women but not among men.

There are different mechanisms by which cigarette smoking may reduce the risk of thyroid cancer. Studies suggest that thyroid-stimulating hormone levels are lower in smokers (24); the possible protective effect might thus result from reduced pituitary stimulation. However, in this case, one would expect an equally decreased risk in the two sexes.

An additional pathway, which could account for a reduced risk confined to women, rests in the antiestrogenic effect of smoking among women, for which there is consistent epidemiological evidence (25), although the mechanism is not clear. Smoking seems not to affect the plasma levels of natural estrogens (26, 27), whereas achieved levels are lower among women taking oral estrogens (28, 29). During pregnancy (30), smokers have lower serum levels of estrogens but also of human chorionic gonadotropin, which has a thyrotropic activity (31). In this study, there was a statistically significant interaction between smoking and total number of pregnancies but not between smoking and other reproductive factors or hormonal treatments. A more detailed analysis of these effects was hampered by the limited information and by the size of the study; the interpretation at the biological level is, therefore, difficult.

The effect of smoking in lowering body weight could be the most relevant common mechanism, since adipose tissue is an important source of estrogens, at least after menopause (32). An increased risk of thyroid cancer was indeed associated in previous studies with elevated body mass index and/or weight gain among women (5, 18, 33). We did not compile this information from our study subjects and are, therefore, unable to comment on this possibility further.

The drawbacks of this study include the limited information available on some exposures, a limitation needed to achieve completion of the self-administered questionnaires. Another concern is the low response rate among controls and, therefore, the possibility of a self-selection conditionally on some exposures. We maintained the original matched design to obtain the most efficient adjustment for age (assuming this as one of the most important factors conditioning the respondent status). The smoking habits recorded among control persons in this study were comparable to those in the study populations (34, 35), and the same was true for the fertility features (36). More importantly, the explanation of a selection bias for our findings is, as already discussed, unlikely.

On the other hand, our study had several strengths; we used a population-based design and uniform histopathological review. To avoid dealing with small subsets of biologically different histopathological types, only cases of papillary and follicular carcinoma were enrolled. The substantial stability of the results in the two countries also strengthens the validity of this study.

It suggests that the role of the most reproductive and hormonal factors on the risk of papillary and follicular thyroid carcinoma among women is of moderate importance. However, events close to puberty deserve further attention. In addition, the influence of reproductive life and hormonal treatments may be modified by other factors, if they interfere with the levels and/or peripheral utilization of sex steroids, in particular of estrogens. Cigarette smoking is an example of such factors. Its concomitant effect on the regulation of thyroid function and energy metabolism of women is not well known and is of potential importance.
interest also in understanding the etiology of other hormone-related cancers.

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