Role of Goiter and of Menstrual and Reproductive Factors in Thyroid Cancer: A Population-based Case-Control Study in New Caledonia (South Pacific), a Very High Incidence Area

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Exceptionally high incidence rates of thyroid cancer have been reported for Melanesian women in New Caledonia (South Pacific). To investigate the occurrence of thyroid cancer in that country and to clarify the role of goiter and hormonal factors in that disease in women, a countrywide population-based case-control study was conducted in 1993–1999. The study included 293 cases, identified through pathology registers and whose thyroid cancer was verified histologically, and 354 population controls. Thyroid cancer was associated with goiter, age at menarche, irregular menstruation, and hysterectomy. There was a dose-response trend with number of full-term pregnancies (p = 0.01), with an odds ratio of 2.2 (95% confidence interval: 1.1, 4.3) for women with eight or more pregnancies. Miscarriage, particularly as an outcome of the first pregnancy, was also indicated as a risk factor. The association between voluntary abortion and thyroid microcarcinoma could be explained by enhanced medical surveillance and improved cancer detection in women undergoing abortion. Oral contraceptives and hormone replacement therapy were unrelated to thyroid cancer. The very high birth rate among Melanesian women in New Caledonia, as well as late age at menarche, may explain, in part, their elevated incidence of thyroid cancer.

case-control studies; goiter; menarche; menopause; New Caledonia; pregnancy; thyroid neoplasms

Abbreviation: OR, odds ratio.

Thyroid cancer incidence varies considerably worldwide. It is elevated in the South Pacific (1), particularly in New Caledonia, a French overseas territory located 1,500 km northeast of Australia. New Caledonia has a population of 200,000, consisting of 44 percent native Melanesians, 34 percent Europeans, and 22 percent various ethnic groups (2). Elevated rates of thyroid cancer have been reported for all ethnic groups, but an exceptionally high incidence of 35 per 100,000 person-years was observed for Melanesian women for the period 1985–1992 (3). With the exception of ionizing radiation exposure during childhood, the causes of thyroid cancer are not well established (4). In contrast to French Polynesia, no nuclear test was conducted in New Caledonia, and no known explanation for the elevated thyroid cancer incidence is available.

Because thyroid cancer is generally three times more frequent in women than in men, and because the incidence in women peaks during the reproductive years (5), hormonal changes related to the menstrual cycle, pregnancy, menopause, and hormone use have been suggested as etiologic factors. Goiter, which is intimately related to hormonal and reproductive events, may also predispose to thyroid cancer. Purposed mechanisms of carcinogenicity involve elevated levels of thyroid-stimulating hormone that stimulates thyroid hyperplasia. High levels of this hormone have been reported during puberty, pregnancy, and oral contraceptive use (6, 7). Estrogens have also been shown to promote
thyroid tumor growth via estrogen receptors present in thyroid tissue (8, 9), supporting the hypothesis that sex hormones, and therefore menstrual and reproductive events, may modify thyroid cancer risk in women.

Several epidemiologic studies have been conducted to investigate thyroid cancer risk in relation to goiter and to menstrual and reproductive factors in the United States (10–20), Europe (21–31), and Asia (32–35). Fourteen case-control studies conducted prior to 1997 (10–16, 25, 26, 28, 29, 32) were pooled in an analysis including a large number of thyroid cancer cases (2,247 women) and controls (3,699 women) (36). Goiter was strongly and consistently associated with thyroid cancer (17, 19, 21, 23, 33, 37). The associations between thyroid cancer and menstrual or reproductive factors were generally weak or nonexistent, with the exception of miscarriage as the outcome of the first pregnancy and artificial menopause (25, 38) or hysterectomy (17, 18). Parity was not associated with thyroid cancer in the pooled analysis (38), but, in recent studies, elevated risks during the 5 years postpartum have been reported (18, 20, 34). Exogenous hormone use was associated with marginally increased odds ratios in the pooled analysis (39). To investigate the remarkably high incidence of thyroid cancer and to clarify the role of certain risk factors for thyroid cancer in general, a countrywide population-based case-control study was conducted in New Caledonia. This paper reports on goiter, menstrual and reproductive events, and exogenous hormone use on the basis of the data collected on New Caledonian women.

**MATERIALS AND METHODS**

**Case selection**

All patients with papillary or follicular thyroid cancer diagnosed between January 1, 1993, and December 31, 1999, and having resided in New Caledonia for at least 5 years at the time of cancer diagnosis were eligible for the study. Only women were included in the analysis.

The cases were identified from the pathology records kept by the two histopathology laboratories, one public and one private, operating in New Caledonia. All pathology reports including a diagnosis of thyroid cancer were retrieved by manual or electronic searches. The cancer diagnoses were made by the local pathologists. Most of the histologic slides were also reviewed by the Pathology Department of the Royal Prince Alfred Hospital in Sydney, Australia. The case list was cross-checked with the New Caledonia cancer registry, which collects information on cancer diagnoses from medical facilities throughout the country. However, no additional case of thyroid cancer was detected. All of the pathology reports were retrieved in order to code the histology, number, and size of the cancerous nodules. Mixed papillary-follicular cases were included in the papillary group (40). If insufficient information had been included in the initial report (e.g., unspecified tumor size), the histologic slide was reviewed to obtain the missing information. The thyroid cancer cases were classified according to histology and size of the largest cancerous nodule.

**Control selection**

Controls were selected at random from recently updated electoral rolls that included the name, address, and date of birth of all New Caledonia residents aged 18 years or older. The controls were frequency matched to the cases by gender and 5-year age group. To achieve incidence density sampling, seven control groups were selected to match the seven case groups, each group consisting of the cases diagnosed in a given year of the study period (1993–1999). Controls were allocated a year of reference equal to the year of diagnosis of the case group for which they were selected. Only those events or exposures that occurred before the reference date were considered in the analyses. Controls were excluded if they had not lived in New Caledonia for at least 5 years as of the reference date or if they had had thyroid cancer before that date. For practical reasons, prior to study initiation, the decision was made to restrict the total number of controls to 500.

Of 405 eligible controls, 51 (13 percent) did not participate because they refused (n = 19), had died (n = 11), or could not be contacted (n = 18) or for another reason (n = 3). The remaining 354 controls were included in the analyses.

**Data collection**

Trained interviewers conducted a face-to-face interview with the cases and controls at their home address, using a structured questionnaire, after having obtained informed consent. The interviewers elicited information on sociodemographic characteristics, diet, alcohol drinking, tobacco smoking, anthropometric factors, gynecologic and reproductive factors, goiter, menstrual and reproductive events, and exogenous hormone use on the basis of the data collected on New Caledonian women.

<table>
<thead>
<tr>
<th>Size of the largest malignant nodule</th>
<th>Histology</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Papillary</td>
<td>Follicular</td>
<td></td>
</tr>
<tr>
<td>(≤10 mm)</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Microcarcinoma</td>
<td>194</td>
<td>52.8</td>
<td>6</td>
</tr>
<tr>
<td>Carcinoma &gt;10 mm</td>
<td>150</td>
<td>41.4</td>
<td>34</td>
</tr>
<tr>
<td>Missing</td>
<td>2</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>255</td>
<td>100.0</td>
<td>38</td>
</tr>
</tbody>
</table>

All cases diagnosed during the 5-year period before the start of data collection in 1998 and all cases newly diagnosed up to the end of the study period in 1999 were recruited for the study. The good prognosis of differentiated thyroid tumors, and residential stability, enabled subject enrollment several years after the initial diagnosis.

Of 324 cases of thyroid cancer in women, 31 (10 percent) were not included because the subject refused to participate (n = 8), had died (n = 18), could not be contacted (n = 4), or was too ill (n = 1). The study population thus consisted of 293 cases, 255 with papillary carcinoma and 38 with follicular carcinoma (table 1). More than 54 percent of the papillary carcinomas were less than or equal to 10 mm in diameter.
history, medical conditions, medical x-ray exposure, occupational and residential history, and familial history of thyroid cancer. Benign thyroid disease history, menstrual and reproductive factors, and exogenous hormone use are reported herein. Participants were asked whether the goiter was diagnosed by a physician and how it was treated. Goiters not reported by the participants as medically confirmed were excluded. Since detection of thyroid cancer may be enhanced following diagnosis of goiter, the odds ratio for goiter may be overestimated. To minimize this potential surveillance bias, only those goiters diagnosed at least 1 year before the reference date were considered in the analyses. Different lag times between goiter and cancer, and carcinoma size, were also taken into account to assess surveillance bias, assuming that this bias would more strongly affect carcinomas less than or equal to 10 mm in diameter diagnosed shortly after goiter.

Women were considered postmenopausal if they reported that they had not menstruated for at least 1 year as of the reference date. Menopausal status was initially regarded as unknown for women who used hormone replacement therapy before the end of menstruation. To reduce the number of women of unknown menopausal status, all women older than age 55 years (90th percentile of age at menopause for women with a natural menopause) were subsequently classified as having undergone a natural menopause. Artificial menopause was defined as the cessation of menses induced by surgical removal of the ovaries or uterus.

Statistical analysis

The odds ratios were calculated by unconditional logistic regression (41), using SAS version 8.2 software (SAS Institute, Inc., Cary, North Carolina). All odds ratios were adjusted for age (5-year age groups) and ethnic group (European, Melanesian, other). Potential confounding between hormonal and reproductive factors was investigated in multivariate models. Nonordinal polytomous logistic regression (42) was carried out in the analyses by using two case groups defined by carcinoma size (≤10 mm or >10 mm) and histologic subtype (papillary or follicular). All of the analyses were also conducted after stratification by ethnicity and by age group (<45 years, ≥45 years). This cutpoint was chosen to categorize women according to reproductive or postreproductive age, assuming that the reproductive period may modify the relation between hormonal factors and thyroid cancer risk. Tests for trend were calculated by fitting models with continuous exposure variables, assuming a log-linear relation between exposure and cancer risk.

RESULTS

Characteristics of cases and controls

The sociodemographic characteristics of the cases and controls are shown in table 2. The distributions by age, a matching variable, were very similar for the two groups. The proportion of Melanesian women was markedly greater among the cases (75.1 percent) than among the controls (47.5 percent). No statistically significant difference between cases and controls was observed with respect to educational level or marital status.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (n = 293)</th>
<th>Controls (n = 354)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>10</td>
<td>13</td>
<td>0.65</td>
</tr>
<tr>
<td>25–29</td>
<td>24</td>
<td>24</td>
<td>0.68</td>
</tr>
<tr>
<td>30–34</td>
<td>34</td>
<td>42</td>
<td>0.11</td>
</tr>
<tr>
<td>35–39</td>
<td>32</td>
<td>38</td>
<td>0.70</td>
</tr>
<tr>
<td>40–44</td>
<td>29</td>
<td>37</td>
<td>0.10</td>
</tr>
<tr>
<td>45–49</td>
<td>36</td>
<td>32</td>
<td>0.90</td>
</tr>
<tr>
<td>50–54</td>
<td>30</td>
<td>41</td>
<td>0.16</td>
</tr>
<tr>
<td>55–59</td>
<td>40</td>
<td>37</td>
<td>0.10</td>
</tr>
<tr>
<td>60–64</td>
<td>24</td>
<td>44</td>
<td>0.12</td>
</tr>
<tr>
<td>65–69</td>
<td>18</td>
<td>19</td>
<td>0.54</td>
</tr>
<tr>
<td>≥70</td>
<td>16</td>
<td>27</td>
<td>0.65</td>
</tr>
<tr>
<td>Ethnic group</td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>European</td>
<td>32</td>
<td>110</td>
<td></td>
</tr>
<tr>
<td>Melanesian</td>
<td>220</td>
<td>168</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>41</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>Educational level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never went to school</td>
<td>22</td>
<td>20</td>
<td>0.56</td>
</tr>
<tr>
<td>≤5 years</td>
<td>151</td>
<td>177</td>
<td>0.50</td>
</tr>
<tr>
<td>6–9 years</td>
<td>74</td>
<td>94</td>
<td>0.26</td>
</tr>
<tr>
<td>≥10 years</td>
<td>22</td>
<td>44</td>
<td>0.12</td>
</tr>
<tr>
<td>Missing</td>
<td>24</td>
<td>19</td>
<td>0.15</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>35</td>
<td>42</td>
<td>0.11</td>
</tr>
<tr>
<td>Married</td>
<td>188</td>
<td>232</td>
<td>0.65</td>
</tr>
<tr>
<td>Divorced or widowed</td>
<td>70</td>
<td>77</td>
<td>0.21</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td>3</td>
<td>0.8</td>
</tr>
</tbody>
</table>

History of goiter

A history of goiter was associated with an odds ratio of 4.2 (table 3). For this association, there was no clear difference between microcarcinoma and carcinoma greater than 10 mm in diameter. The odds ratio increased with the lag time between goiter and cancer diagnosis. A more striking increase was observed for microcarcinomas than for carcinomas greater than 10 mm in diameter.

Menstrual factors

Among women aged less than 45 years, the odds ratio for those who never menstruated regularly was 3.6 (table 4).
Among older women, the corresponding odds ratio was 1.0 (interaction between irregularity of menstrual cycle and age group: \( p = 0.01 \)). The odds ratio for irregular menstruation was elevated for Melanesian women, but the interaction with ethnic group was not statistically significant. Age at menarche did not appear to be associated with thyroid cancer in the overall sample or in either of the two age groups. However, late menarche (at age \( \geq 15 \) years) increased the odds ratio to 3.4 for European and to 1.5 for Melanesian women but decreased the odds ratio to 0.2 for other ethnic groups, mainly Polynesian and Asian women (interaction between age at menarche and ethnic group: \( p = 0.01 \)).

Thyroid cancer was not associated with menopausal status or age at menopause (table 5). No association with ovariectomy was detected. A nonstatistically significant odds ratio of 1.5 that was not influenced by ovariectomy status was observed for women who had undergone a hysterectomy. This association was apparent mainly among women who were less than age 43 years when hysterectomized. Because hysterectomy was more frequent among women with irregular menstrual cycles (chi-square value = 6.8, 1 df, \( p = 0.01 \)), multivariate models including both variables were fitted, but the odds ratio for hysterectomy was not affected (results not shown).

**Reproductive history**

The odds ratio for parous women aged less than 45 years, versus nulliparous women, was 1.8, whereas no association with parity was apparent for older women (odds ratio (OR) = 0.8). In the total sample, the odds ratio increased with the number of full-term pregnancies (\( p \) for trend = 0.01), reaching 2.2 for eight or more pregnancies (table 6). The trend toward an increase in risk with the number of full-term pregnancies was most apparent for younger women, although the odds ratio decreased for eight or more pregnancies in this age group. Conversely, no indication of an increase in risk with the total number of full-term pregnancies was observed for women over age 45 years (interaction between age group and number of pregnancies: \( p = 0.10 \)).

When parous women were compared with nulliparous women by time since the last full-term pregnancy, no clear pattern emerged (table 6). However, when time since the last full-term pregnancy was analyzed for uniparous women only, the odds ratios were increased in the 5-year period after childbirth and decreased noticeably thereafter, although the trend was not statistically significant (\( p = 0.13 \)).

A history of miscarriage was associated with an odds ratio of 1.4 (table 6) that reached 2.3 for miscarriage during the first pregnancy. Voluntary abortion was associated with an odds ratio of 3.1. Voluntary abortion was more strongly associated with papillary microcarcinoma (OR = 4.1) than with larger tumors (OR = 1.7) (table 7). Seven cases and no controls had had a voluntary abortion in the 5-year period before the reference date. Because a history of voluntary abortion was related to the number of full-term pregnancies, multivariate models including both variables were fitted, but the odds ratios were not modified by mutual adjustment (results not shown).

**Exogenous hormone use**

Thyroid cancer was not associated with use of oral contraceptives or with duration of oral contraceptive use (table 8). Hormone replacement therapy in women 45 years of age or older was not associated with thyroid cancer, and no trend with duration of use was detected.

**DISCUSSION**

This study provides evidence that a history of goiter, irregular menstruation, high parity, miscarriage, and voluntary abortion are related to thyroid cancer, especially in women of reproductive age. Although these associations may indicate a causal link, they may also reflect an
etiology shared by those factors and thyroid cancer (e.g., a hormonal etiology) or a surveillance bias. Because the incidence of thyroid cancer among Melanesian women in New Caledonia is exceptionally high (3), identification of highly prevalent risk factors in this group is of particular interest.

**Strengths and limitations of the study**

The methodological strengths of the study are a population-based design, exhaustive identification of cases over the study period, and high response rates among cases (90 percent) and controls (87 percent). Another important feature is a thorough review of the histologic diagnoses and of tumor

| TABLE 4. Odds ratios of thyroid cancer associated with irregular menstrual cycle and age at menarche, by age group (reproductive period) and ethnic group, New Caledonia, South Pacific, 1993–1999 |
|---|---|---|---|---|---|
| Age group* | Total sample | European | Melanesian | Other | Ca/Co† (293/354) OR 95% CI |
| <45 years | 241/307 | 1.0 Reference | 99/139 | 1.0 Reference | 0.4, 1.5 |
| 45–60 years | 113/151 | 1.0 Reference | 51/70 | 1.0 Reference | 0.7, 1.5 |
| >60 years | 129/169 | 1.0 Reference | 52/68 | 1.0 Reference | 0.8, 1.6 |

* Odds ratios were adjusted for age and ethnic group.
† Ca, number of cases; Co, number of controls; OR, odds ratio; CI, confidence interval.
‡ Some numbers do not add to the total because of missing values.
§ Menopausal status shared by those factors and thyroid cancer (e.g., a hormonal etiology) or a surveillance bias. Because the incidence of thyroid cancer among Melanesian women in New Caledonia is exceptionally high (3), identification of highly prevalent risk factors in this group is of particular interest.

**Strengths and limitations of the study**

The methodological strengths of the study are a population-based design, exhaustive identification of cases over the study period, and high response rates among cases (90 percent) and controls (87 percent). Another important feature is a thorough review of the histologic diagnoses and of tumor

| TABLE 5. Odds ratios* of thyroid cancer for menopausal status, ovariectomy, and hysterectomy, New Caledonia, South Pacific, 1993–1999 |
|---|---|---|---|---|---|
| Menopausal status | Ca/Co† (293/354) OR 95% CI |
| Premenopausal | 162/180 | 1.0 Reference |
| Natural menopause | 99/131 | 0.7 0.4, 1.5 |
| Artificial menopause | 22/25 | 1.1 0.5, 2.7 |
| Undetermined§ | 6/11 | 0.6 0.2, 1.9 |
| Age at menopause (years)¶ | 35/50 | 1.0 Reference |
| <48 | 42/41 | 1.3 0.6, 2.8 |
| 48–51 | 27/44 | 0.8 0.4, 1.6 |
| Ever had an ovariectomy | 271/320 | 1.0 Reference |
| No | 26/27 | 1.5 0.8, 2.8 |
| Unilateral | 6/12 | 0.9 0.3, 2.8 |
| Bilateral | 16/13 | 1.5 0.7, 3.3 |
| Ever had a hysterectomy | 260/320 | 1.0 Reference |
| No | 10/10 | 1.8 0.7, 4.8 |
| <43 | 10/11 | 1.8 0.7, 4.8 |
| 43–48 | 7/8 | 1.3 0.4, 3.9 |
| ≥49 | 5/7 | 0.9 0.3, 3.2 |

* Adjusted for age and ethnic group.
† Ca, number of cases; Co, number of controls; OR, odds ratio; CI, confidence interval.
‡ Some numbers do not add to the total because of missing values.
§ Menopausal status could not be determined according to the criteria defined in the text.
¶ For all postmenopausal women (natural and artificial menopause).
# Categories for age are based on approximate tertiles of the distribution among controls.
TABLE 6. Odds ratios* of thyroid cancer associated with selected reproductive factors, for the total sample and by age group (reproductive period), New Caledonia, South Pacific, 1993–1999

<table>
<thead>
<tr>
<th>Factor</th>
<th>Total sample</th>
<th>&lt;45 years</th>
<th>≥45 years</th>
<th>Interaction p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ca/Co‡</td>
<td>OR‡</td>
<td>95% CI‡</td>
<td>Ca/Co‡</td>
</tr>
<tr>
<td>Ever had a full-term pregnancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>35/49 1.0 Reference 16/32 1.0 Reference 19/17 1.0 Reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>258/305 1.2 0.7, 1.9 113/122 1.8 0.9, 3.6 145/183 0.8 0.4, 1.6</td>
<td>0.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of full-term pregnancies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>35/49 1.0 Reference 16/32 1.0 Reference 19/17 1.0 Reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>36/55 1.0 0.5, 1.9 23/25 1.8 0.8, 4.4 13/30 0.5 0.2, 1.2</td>
<td>0.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>31/77 0.7 0.4, 1.4 22/42 1.2 0.5, 2.8 9/35 0.3 0.1, 0.9</td>
<td>0.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>42/47 1.4 0.7, 2.6 26/22 2.3 1.0, 5.5 16/25 0.8 0.3, 2.1</td>
<td>0.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4–5</td>
<td>50/61 1.1 0.6, 2.1 24/19 2.2 0.9, 5.5 26/42 0.6 0.2, 1.4</td>
<td>0.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6–7</td>
<td>38/29 1.6 0.8, 3.3 14/8 2.8 0.9, 8.6 24/21 0.9 0.4, 2.4</td>
<td>0.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥8</td>
<td>61/36 2.2 1.1, 4.3 4/6 1.1 0.2, 4.8 57/30 1.5 0.6, 3.5</td>
<td>0.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time since last full-term pregnancy (years)§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>35/49 1.0 Reference 16/32 1.0 Reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2</td>
<td>38/38 1.3 0.6, 2.6 38/38 1.7 0.8, 3.7</td>
<td>0.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3–5</td>
<td>35/30 1.5 0.8, 3.1 30/29 2.0 0.9, 4.6</td>
<td>0.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6–9</td>
<td>21/28 0.9 0.4, 2.0 14/22 1.2 0.5, 3.2</td>
<td>0.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥10</td>
<td>157/203 1.1 0.6, 1.9 30/33 2.2 0.9, 5.4</td>
<td>0.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time since full-term pregnancy for uniparous women (years)§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>35/49 1.0 Reference 16/32 1.0 Reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2</td>
<td>6/5 2.5 0.6, 11.1 6/5 2.7 0.6, 11.8</td>
<td>0.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3–5</td>
<td>7/5 2.2 0.5, 8.5 7/5 2.6 0.7, 10.1</td>
<td>0.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6–9</td>
<td>3/5 2.0 0.2, 12.0 3/5 2.1 0.4, 12.0</td>
<td>0.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥10</td>
<td>20/39 0.6 0.3, 1.3 7/10 1.2 0.3, 5.1</td>
<td>0.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome of first pregnancy§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulligravid</td>
<td>27/46 1.0 Reference 15/30 1.0 Reference 12/16 1.0 Reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full-term pregnancy</td>
<td>242/285 1.4 0.8, 2.5 105/111 1.8 0.9, 3.7 137/174 1.0 0.4, 2.3</td>
<td>0.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miscarriage</td>
<td>19/15 2.3 1.0, 5.6 7/8 2.1 0.6, 7.4 12/7 2.2 0.6, 8.0</td>
<td>0.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voluntary abortion</td>
<td>4/7 1.5 0.4, 6.2 2/4 2.1 0.3, 13.6 2/3 0.8 0.1, 6.7</td>
<td>0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever had a miscarriage¶</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>208/253 1.0 Reference 93/104 1.0 Reference 115/149 1.0 Reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>58/55 1.4 0.9, 2.1 21/20 1.3 0.6, 2.5 37/35 1.5 0.8, 2.7</td>
<td>0.74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever had a voluntary abortion¶</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>238/293 1.0 Reference 97/115 1.0 Reference 141/178 1.0 Reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>28/15 3.1 1.5, 6.2 17/9 3.3 1.3, 8.4 11/6 2.4 0.8, 7.2</td>
<td>0.56</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Adjusted for age and ethnic group.
† Interaction between age group (<45 years, ≥45 years) and the risk factor.
‡ Ca, number of cases; Co, number of controls; OR, odds ratio; CI, confidence interval.
§ Some numbers do not add to the total because of missing values.
¶ Among ever pregnant women.
size, which, to our knowledge, was determined for the first time in a case-control study. The study also has some limitations. Electoral rolls may not be a perfect population register to use to recruit population controls. However, the rolls were updated just before study initiation and were believed to be almost complete. We did not take into account exposure to ionizing radiation during childhood, one of the few recognized risk factors. However, this exposure was probably too low to affect the risk of thyroid cancer at a detectable level and to confound the reported associations. Recall bias may have occurred, particularly for previous thyroid disorders such as goiter, if cases were more prone than controls to declare goiter. Taking into account only those goiters reported by the participant as medically confirmed should have minimized this potential bias. Another problem, referred to below as surveillance bias, may have occurred if diagnosis of goiter, or another medical condition, led to intensive cancer screening and diagnosis of thyroid carcinomas that would otherwise have remained undetected. The elevated proportion of papillary microcarcinomas in our case group (over 54 percent vs. 17–24 percent in a cancer-registry-based study (43)) may reflect high screening levels in New Caledonia and indicate that some degree of surveillance bias did occur. Stratification on size of the carcinoma to study hormonal and reproductive risk factors permitted assessment of a possible effect of a surveillance bias.

**TABLE 7.** Odds ratios* of thyroid cancer for incomplete pregnancy, by histology and size of carcinoma, New Caledonia, South Pacific, 1993–1999

<table>
<thead>
<tr>
<th></th>
<th>Papillary</th>
<th>follicular</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤10 mm</td>
<td>&gt;10 mm</td>
</tr>
<tr>
<td></td>
<td>Ca/Co</td>
<td>OR†</td>
</tr>
<tr>
<td>Ever had a miscarriage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>102/253</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>26/55</td>
<td>1.2</td>
</tr>
<tr>
<td>Ever had a voluntary abortion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>111/293</td>
<td>1.0</td>
</tr>
<tr>
<td>Yes</td>
<td>17/15</td>
<td>4.1</td>
</tr>
</tbody>
</table>

* Adjusted for age and ethnic group, among ever pregnant women.
† Ca, number of cases; Co, number of controls; OR, odds ratio; CI, confidence interval.

**TABLE 8.** Odds ratios* of thyroid cancer associated with exogenous hormone use, New Caledonia, South Pacific, 1993–1999

<table>
<thead>
<tr>
<th></th>
<th>Ca/Co†</th>
<th>OR†</th>
<th>95% CI†</th>
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</thead>
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<tr>
<td>Oral contraceptive use</td>
<td></td>
<td></td>
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<tr>
<td>Never</td>
<td>194/213</td>
<td>1.0</td>
<td>Reference</td>
</tr>
<tr>
<td>Ever</td>
<td>96/138</td>
<td>1.1</td>
<td>0.8, 1.7</td>
</tr>
<tr>
<td>Duration of use of oral contraceptives (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>194/213</td>
<td>1.0</td>
<td>Reference</td>
</tr>
<tr>
<td>&lt; 2</td>
<td>21/24</td>
<td>1.0</td>
<td>0.5, 1.9</td>
</tr>
<tr>
<td>2–4</td>
<td>25/25</td>
<td>1.7</td>
<td>0.9, 3.3</td>
</tr>
<tr>
<td>≥5</td>
<td>44/82</td>
<td>1.1</td>
<td>0.6, 1.8</td>
</tr>
<tr>
<td>HRT† use§</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>146/178</td>
<td>1.0</td>
<td>Reference</td>
</tr>
<tr>
<td>Ever</td>
<td>10/19</td>
<td>0.9</td>
<td>0.4, 2.2</td>
</tr>
<tr>
<td>Duration of use of HRT (years)§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>146/178</td>
<td>1.0</td>
<td>Reference</td>
</tr>
<tr>
<td>&lt; 2</td>
<td>5/7</td>
<td>1.6</td>
<td>0.4, 6.0</td>
</tr>
<tr>
<td>2–4</td>
<td>2/3</td>
<td>0.8</td>
<td>0.1, 6.0</td>
</tr>
<tr>
<td>≥5</td>
<td>2/5</td>
<td>1.1</td>
<td>0.2, 6.3</td>
</tr>
</tbody>
</table>

* Adjusted for age and ethnic group.
† Ca, number of cases; Co, number of controls; OR, odds ratio; CI, confidence interval; HRT, hormone replacement therapy.
‡ Some numbers do not add to the total because of missing values.
§ Among women aged ≥45 years.

was probably too low to affect the risk of thyroid cancer at a detectable level and to confound the reported associations. Recall bias may have occurred, particularly for previous thyroid disorders such as goiter, if cases were more prone than controls to declare goiter. Taking into account only those goiters reported by the participant as medically confirmed should have minimized this potential bias. Another problem, referred to below as surveillance bias, may have occurred if diagnosis of goiter, or another medical condition, led to intensive cancer screening and diagnosis of thyroid carcinomas that would otherwise have remained undetected. The elevated proportion of papillary microcarcinomas in our case group (over 54 percent vs. 17–24 percent in a cancer-registry-based study (43)) may reflect high screening levels in New Caledonia and indicate that some degree of surveillance bias did occur. Stratification on size of the carcinoma to study hormonal and reproductive risk factors permitted assessment of a possible effect of a surveillance bias.

**History of benign thyroid disease**

Goiter was associated with a fourfold increase in the risk of thyroid cancer in New Caledonian women. This finding is in line with the results of previous studies conducted in Italy (21, 28), Switzerland (23), the United States (10, 13, 17, 19), Japan (33), and China (32) that reported odds ratios ranging from 4 to 7 for women with a history of goiter. In a pooled analysis of 12 case-control studies, the odds ratio was 5.9 (37). These findings may support the assumption that goiter facilitates thyroid tumor growth, or they may reflect an upward bias of the odds ratio due to surveillance bias. Two studies have reported that the association between goiter and thyroid cancer is particularly elevated if the cancer is diagnosed shortly after goiter, that is, during a period when cancer screening is more active (17, 37), suggesting some surveillance bias. In contrast, the New Caledonian study showed a higher odds ratio when goiter was diagnosed 5 or more years before cancer than when it occurred closer to the time of cancer diagnosis. Furthermore, microcarcinomas, which are unlikely to be detected without screening,
were as strongly associated with goiter as large thyroid tumors. If surveillance bias were acting fully, a stronger association with small carcinomas would be expected. These findings suggest that the reported odds ratio cannot be entirely accounted for by surveillance bias and thus provide further evidence that goiter predisposes to thyroid cancer.

Menstrual factors

The relation between thyroid function and menstruation, puberty, and menopause has long been recognized (44, 45). The thyroid gland enlarges during the menstrual cycle (46), and it has been shown that estrogen 17β-estradiol has a growth-promoting effect on thyroid tumor cells, mainly via estrogen receptors present in thyroid tissue (8, 9).

Age at menarche. Late menarche was weakly associated with thyroid cancer (OR = 1.2) in a pooled analysis of 14 case-control studies conducted worldwide (38). In New Caledonia, late menarche (age >15 years) was strongly associated with thyroid cancer in European women (OR = 3.4) and, to a lesser degree, in Melanesian women (OR = 1.5), whereas an inverse association was observed for other ethnic groups, including Polynesian and Asian women (OR = 0.2). It is possible that ethnic-specific risk factors for thyroid cancer also influencing age at menarche, such as dietary or genetic factors, explain the different odds ratios for the various ethnic groups. If late menarche increases the risk of thyroid cancer in Melanesian women, it may play a role in the elevated incidence observed in this group because menarche occurred noticeably later in Melanesian women than in other ethnic groups (for 46 percent of Melanesian and 13 percent of European controls, age at menarche was ≥15 years).

Irregular menstruation. For women aged less than 45 years who had never menstruated regularly, the odds ratio was 3.6. Because this association did not change with cancer size, surveillance bias was not a likely explanation. No data on menstrual disorders were reported in the pooled analysis (38). An odds ratio of 2.2 (95 percent confidence interval: 0.9, 6.1), consistent with the present finding, was observed for women aged less than 35 years in a US study (17). Again, a link between menstrual disorders and thyroid dysfunction (44) may explain the observed association.

Menopausal status. No evidence that thyroid cancer was associated with menopausal status or with age at menopause emerged in our data. There was some evidence that hysterectomy, but not ovariectomy, was related to thyroid cancer, particularly when hysterectomy occurred at a young age. In the pooled analysis (38), artificial menopause was associated with an odds ratio of 1.8 (95 percent confidence interval: 1.4, 2.4), but the types of surgical procedures, hysterectomy or bilateral ovariectomy, were not distinguished. In two recent case-control studies (17, 18), and in a cohort study of hysterectomized women (47), an approximately twofold excess risk of thyroid cancer was reported for hysterectomy. This association may be related to surveillance bias because women undergoing surgical procedures may be more carefully monitored for thyroid disorders. However, it has also been suggested that hysterectomy may be an indicator of prolonged menstrual disturbances that may share a common etiology with thyroid cancer (47). For example, uterine fibroma, which induces hyperestrogenism, is an indication for hysterectomy (38). The higher risk of thyroid cancer associated with hysterectomy at a younger age reported herein may reflect more serious menstrual disorders.

Reproductive factors

Parity. Parity among women aged less than 45 years was associated with an odds ratio of 1.8 (95 percent confidence interval: 0.9, 3.6), whereas parity did not increase the risk for older women. An association between thyroid cancer and parity has been reported in some (13, 14, 22, 31–33, 48) but not all (11, 15, 17, 18, 20, 24–27, 29) studies, resulting in an approximately 20 percent increased odds ratio for parous versus nulliparous women in the pooled analysis (38), making a conclusion difficult. The very high birth rates observed in our study population, particularly among Melanesian women, provided a unique opportunity to investigate the effect of high parity on thyroid cancer. For example, 18 percent of the European and 48 percent of the Melanesian controls had had at least four full-term pregnancies. A statistically significant 8 percent increase in risk (p = 0.01) for each additional pregnancy was observed, resulting in a 2.2-fold increase for women having had eight or more pregnancies. The trend was also more marked among women of reproductive age, although not statistically significant. These findings are in line with the results of a previous case-control study in Kuwait in which the risk was increased approximately twofold for women having had 11 or more pregnancies (34). They strongly support the existence of a link between parity and thyroid cancer.

Time-dependent factors. High levels of estrogen, human chorionic gonadotropin, and thyroid-stimulating hormone during pregnancy are responsible for direct thyroid stimulation and may promote tumor growth (6–8). This mechanism may account for an increased risk of thyroid cancer in the period following delivery and is compatible with our observation of an increased risk for women of reproductive age. A time-dependent risk pattern after a livebirth, with increased risk over the first years postpartum, followed by a downward trend, has also been reported in several studies (18, 20, 31, 34, 48). In New Caledonia, this pattern was observed for uniparous women, although the transient increase in risk following delivery and the downward trend thereafter were not statistically significant.

Interestingly, a transient increase in risk after the first childbirth, attributed to increased cell proliferation during pregnancy, was reported for breast cancer (49, 50). There is also evidence that women with a thyroid carcinoma have a greater than expected risk of developing breast carcinoma, particularly young premenopausal women (51, 52), suggesting that breast and thyroid cancers may share common etiologic factors. Although several factors such as parity or age at menarche seem to have opposite effects on thyroid and breast cancers (53), the transient increase in risk following childbirth is a common feature that might explain a link between the two tumors.

Miscarriage and abortion. New Caledonian women with miscarriage as the outcome of the first pregnancy had...
a marked increased risk of thyroid cancer (OR = 2.3). This factor was consistently associated with thyroid cancer in previous epidemiologic studies (13, 15, 25, 32, 38). The mechanism leading from miscarriage during the first pregnancy to thyroid cancer has not been elucidated, but it is possible that miscarriage may be induced by thyroid disorders or hormonal dysfunction (44).

This study demonstrated a clear association between voluntary abortion and thyroid cancer. However, this finding may reflect a surveillance bias, since women undergoing voluntary abortion may be more actively screened for thyroid disorders. This hypothesis is supported by a strong association with microcarcinomas and by the short lag time between abortion and cancer diagnosis.

**Exogenous hormone use.** Our results do not show an association with the use of oral contraceptives or hormone replacement therapy in New Caledonian women. In addition, they do not confirm the weak association observed for current oral contraceptive users in the pooled analysis (39).

**Conclusion**

This study provides additional evidence that factors related to hormonal, menstrual, or reproductive life in women are associated with thyroid cancer. The development of thyroid carcinoma may share common mechanisms with goiter, miscarriage, or conditions leading to hysterectomy that might explain the observed associations between these factors and thyroid cancer. Alternatively, the association between voluntary abortion and thyroid cancer could be explained by an increased detection of thyroid cancer in women undergoing that surgical procedure. High parity and late menarche are of particular interest, since they are both associated with thyroid cancer risk and are highly prevalent among Melanesian women compared with European women. High parity in particular may explain, in part, the high thyroid cancer incidence observed among Melanesian women in New Caledonia.

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**REFERENCES**


