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.

Thérèse Truong, Laurent Orsi, Dominique Dubourdieu, Yannick Rougier, Denis Hémon, Pascal Guénel

14 January 2008, revised manuscript

Role of goiter, menstrual and reproductive factors in thyroid cancer: a population-based case-control study in New Caledonia (South Pacific), a very high incidence area

Thérèse Truong[1]

Laurent Orsi[1]

Dominique Dubourdieu[2]

Yannick Rougier[3]

Denis Hémon[1]

Pascal Guénel[1]

Abbreviations

CI, confidence intervals

hCG, human chorionic gonadotropin

HRT, hormone replacement therapy

OC, oral contraceptive

OR, odds ratio

TSH, thyroid stimulating hormone

Author's affiliations

1 INSERM, U170, IFR69, Université Paris-Sud, F-94807 Villejuif, France

2 Laboratoire d'Anatomie et de Cytopathologie – Nouméa – Nouvelle-Calédonie

3 Institut Pasteur de Nouvelle-Calédonie – Nouméa – Nouvelle-Calédonie

Address for reprints

Pascal Guénel, MD, PhD
INSERM U170
16 avenue Paul Vaillant-Couturier
94807 Villejuif Cedex
France

mail: guenel@vjf.inserm.fr

Running head: Thyroid cancer in New Caledonia

ABSTRACT

Exceptionally high incidence rates of thyroid cancer have been reported for Melanesian women in New Caledonia (South Pacific). In order to investigate the occurrence of thyroid cancer in that country, and 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 histologically verified cases of thyroid cancer, identified through pathology registers, and 354 population controls. Thyroid cancer was associated with goiter, age at menarche, irregular menstruations, and hysterectomy. There was a dose-response trend with the number of full-term pregnancies (p=0.01), with an odds ratio of 2.2 (95% confidence interval: 1.1, 4.3) in 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.

Word count: 192

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

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 north east 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.

Since 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 etiological factors. Goiter, which is intimately related to hormonal and reproductive events, may also predispose to thyroid cancer. Purported mechanisms of carcinogenicity involve elevated levels of thyroid stimulating hormone (TSH) that stimulates thyroid hyperplasia. High levels of TSH have been reported during puberty, pregnancy and oral contraceptive (OC) 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 epidemiological studies have been conducted to investigate thyroid cancer risk in relation to goiter and menstrual and reproductive factors in the US (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 non-existent, 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 post partum have been reported (18, 20, 34). Exogenous hormone use was associated with marginally

increased odds ratios (OR) in the pooled analysis (39). In order to investigate the remarkably high incidence of thyroid cancer and 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 the pathology reports with a diagnosis of thyroid cancer were retrieved by manual or electronic searches. The cancer diagnoses were made by the local pathologists. Most of the histological 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 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 histological slide was reviewed to obtain the missing information. The thyroid cancer cases were classified according to histology and size of the largest cancerous nodule.

All the 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 enrolment several years after the initial diagnosis.

Out 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 to

participate (n=1). The study population thus consisted of 293 cases, of which 255 cases of papillary carcinoma and 38 cases of follicular carcinoma (table 1). Over 54 percent of the papillary carcinomas had a diameter less than or equal to 10 mm.

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 over. The controls were selected to frequency-match the cases by gender and 5-year age groups. In order 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 events or exposures that occurred before the reference date were considered in the analyses. Controls were excluded it they had not lived in New Caledonia for at least 5 years on the reference date, or if they had had thyroid cancer before that date. For practical reasons, prior to study initiation, the decision was taken to restrict the total number of controls to 500.

Out of 405 eligible female controls, 51 (13 percent) did not participate because they refused (n=19), had died (n=11), 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 of the cases and controls at their home address, using a structured questionnaire, after having obtained informed consent. The interviewers elicited information on socio-demographic characteristics, diet, alcohol drinking, tobacco smoking, anthropometric factors, gynecological and reproductive 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 doctor, 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, overestimation of the odds ratio for goiter may occur. In order to minimize this potential surveillance bias, only goiters diagnosed at least one 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 ≤10 mm diagnosed shortly after goiter.

Women were considered post-menopausal if they reported that they had not menstruated for at least one year at the reference date. Menopausal status was initially regarded as unknown for women who used hormone replacement therapy (HRT) before the end of menstruations. In order to reduce the number of women with unknown menopausal status, all women aged over 55 years (90^{th} percentile of age of menopause for women with a natural menopause) were subsequently classified as having had 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 (SAS institute Inc., Cary, NC, USA). All odds ratios are 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. Non-ordinal polytomous logistic regression (42) was carried out in the analyses using two case groups defined by carcinoma size (≤10 mm or >10 mm) and histological subtype (papillary or follicular). All 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 post-reproductive 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 relationship between exposure and cancer risk.

RESULTS

Characteristics of cases and controls

The socio-demographic 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.

History of goiter

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

Menstrual factors

Among women aged less than 45 years, those who never menstruated regularly had an odds ratio of 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 in Melanesian women, but the interaction with the 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 (≥15 years) increased the odds ratio to 3.4 in European and to 1.5 in Melanesian women, but decreased the odds ratio to 0.2 in 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 non-statistically significant odds ratio of 1.5 was observed for women with hysterectomy that was not influenced by ovariectomy status. This association was mainly apparent in women who were less than 43 years old when hysterectomized. Since hysterectomy was more frequent in women with irregular menstrual cycles (chi-square=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

Parous women aged less than 45 years, versus nulliparous women, had an odds ratio of 1.8, whereas no association with parity was apparent in older women (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 in 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 in women over 45 years (interaction between age group and number of pregnancies: p=0.10). No association with age at first or last birth was observed in either age group (results not shown).

When parous women were compared to nulliparous women by time since the last full-term pregnancy, no clear pattern emerged (table 6). However, when time since last full-term pregnancy was analyzed in 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 control had had a voluntary abortion in the 5 year period before 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 the use of OC or with duration of OC use (table 8). HRT in women ≥45 years of age 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), the 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, an exhaustive identification of the cases over the study period, a thorough review of the histological diagnoses, and of the tumor size, which to our knowledge, was determined for the first time in a case-control study, and high response rates among cases (90 percent) and controls (87 percent). The study also has some limitations. Electoral rolls may not be a perfect population register for the recruitment of 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 radiations during childhood, one of the few recognized risk factor. This exposure, however, 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 to declare goiter than the controls. Only taking into account 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, lead 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 the size of carcinoma to study hormonal and reproductive risk factors permitted to assess a possible effect of a surveillance bias.

History of benign thyroid disease

Goiter was associated with a four-fold 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, 14, 17, 19), Japan (33) and China (32), that reported odds ratios ranging from 4 to 7 in 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, i.e. in 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 by surveillance bias, and thus provide further evidence that goiter predisposes to thyroid cancer.

Menstrual factors

The relationship 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 the 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 (>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 in other ethnic groups, including Polynesian and Asian women (OR=0.2). It is possible that ethnic-specific risk factors of thyroid cancer also influencing age at menarche, such as dietary or genetic factors, explain the different odds ratios in 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 the menarche occurred noticeably later in Melanesian women than in other ethnic groups (46 percent of Melanesian and 13 percent of European control women had menarche at age 15 years or later).

Irregular menstruation. Women aged less than 45 years who had never menstruated regularly had an odds ratio of 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 CI: 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 CI: 1.4, 2.4), but the types of surgical procedure, 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 two-fold excess risk of thyroid cancer was reported for hysterectomy. This association may be related to surveillance bias, since 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 CI: 0.9, 3.6), whereas parity did not increase the risk in older women. An association between thyroid cancer and parity has been reported in some (13, 14, 22, 31-33, 48) but not in all studies (11, 15, 17, 18, 20, 24-27, 29), 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 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 control women 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 in 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 two-fold in 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 estrogens, human chorionic gonadotropin (hCG), and TSH 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 in women of reproductive age. A time-dependent risk pattern after a live birth, with increased risk over the first years post partum, followed by a downward trend, has also been reported in several studies (18, 20, 31, 34, 48). In New Caledonia, this pattern was observed in 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 on 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 a 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 epidemiological 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. This finding, however, 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 OC or HRT in New Caledonian women, and do not confirm the weak association observed for current OC 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 to European women. High parity, in particular may explain, in part, the high thyroid cancer incidence observed among Melanesian women in New Caledonia.

Word count: 3971

Acknowledgements

This study was supported by Fondation de France ; Association pour la Recherche contre le Cancer (ARC) ; Ministère de l'Environnement (Programme Environnement Santé); Ministère des DOM-TOM (CORDET). The authors wish to gratefully acknowledge Michèle Reynier for her invaluable help in data collection in New Caledonia.

References

1. Blot WJ, Le Marchand L, Boice JD, Jr. et al. Thyroid cancer in the Pacific [letter]. J.Natl.Cancer Inst. 1997;89:90-1.

2. ITSEE-INSEE. Recensement de la population de Nouvelle-Calédonie, principaux tableaux 1996. Nouméa: ITSEE-INSEE(Institut Territorial de la Statistique et des Etudes Economiques - Institut National de la Statistique et des Etudes Economiques), 1997.

3. Ballivet S, Salmi LR, Dubourdieu D et al. Incidence of thyroid cancer in New Caledonia, South Pacific, during 1985-1992. Am.J.Epidemiol. 1995;141:741-6.

4. Thyroid cancer. In: Stewart BW, Kleihues P, eds. World Cancer Report. Lyon: IARC, 2003:257-60.

5. Parkin DM et al. Cancer Incidence in Five Continents, vol. VII. Lyon: IARC, 1997.

6. Glinoer D, de Nayer P, Bourdoux P et al. Regulation of maternal thyroid during pregnancy. J.Clin.Endocrinol.Metab 1990;71:276-87.

7. Henderson BE, Ross RK, Pike MC et al. Endogenous hormones as a major factor in human cancer. Cancer Res. 1982;42:3232-9.

8. Manole D, Schildknecht B, Gosnell B et al. Estrogen promotes growth of human thyroid tumor cells by different molecular mechanisms. J.Clin Endocrinol Metab 2001;86:1072-7.

9. Kawabata W, Suzuki T, Moriya T et al. Estrogen receptors (alpha and beta) and 17beta-hydroxysteroid dehydrogenase type 1 and 2 in thyroid disorders: possible in situ estrogen synthesis and actions. Mod.Pathol. 2003;16:437-44.

10. McTiernan AM, Weiss NS, Daling JR. Incidence of thyroid cancer in women in relation to previous exposure to radiation therapy and history of thyroid disease. J.Natl.Cancer Inst. 1984;73:575-81.

11. McTiernan AM, Weiss NS, Daling JR. Incidence of thyroid cancer in women in relation to reproductive and hormonal factors. Am.J.Epidemiol. 1984;120:423-35.

12. McTiernan A, Weiss NS, Daling JR. Incidence of thyroid cancer in women in relation to known or suspected risk factors for breast cancer. Cancer Res. 1987;47:292-5.

13. Preston-Martin S, Bernstein L, Pike MC et al. Thyroid cancer among young women related to prior thyroid disease and pregnancy history. Br.J.Cancer 1987;55:191-5.

14. Ron E, Kleinerman RA, Boice JDJ et al. A population-based case-control study of thyroid cancer. J.Natl.Cancer Inst. 1987;79:1-12.

15. Kolonel LN, Hankin JH, Wilkens LR et al. An epidemiologic study of thyroid cancer in Hawaii. Cancer Causes Control 1990;1:223-34.

16. Goodman MT, Kolonel LN, Wilkens LR. The association of body size, reproductive factors and thyroid cancer. Br.J.Cancer 1992;66:1180-4.

17. Mack WJ, Preston-Martin S, Bernstein L et al. Reproductive and hormonal risk factors for thyroid cancer in Los Angeles County females. Cancer Epidemiol.Biomarkers Prev. 1999;8:991-7.

18. Rossing MA, Voigt LF, Wicklund KG et al. Reproductive factors and risk of papillary thyroid cancer in women. Am.J.Epidemiol. 2000;151:765-72.

19. Iribarren C, Haselkorn T, Tekawa IS et al. Cohort study of thyroid cancer in a San Francisco Bay area population. Int.J.Cancer 2001;93:745-50.

20. Sakoda LC, Horn-Ross PL. Reproductive and menstrual history and papillary thyroid cancer risk: the San Francisco Bay Area thyroid cancer study. Cancer Epidemiol.Biomarkers Prev. 2002;11:51-7.

21. Franceschi S, Fassina A, Talamini R et al. Risk factors for thyroid cancer in Northern Italy. Int.J.Epidemiol. 1989;18:578-84.

22. Franceschi S, Fassina A, Talamini R et al. The influence of reproductive and hormonal factors on thyroid cancer in women. Rev.Epidemiol.Sante Publique 1990;38:27-34.

23. Levi F, Franceschi S, La Vecchia C et al. Previous thyroid disease and risk of thyroid cancer in Switzerland. Eur.J.Cancer 1991;27:85-8.

24. Akslen LA, Nilssen S, Kvale G. Reproductive factors and risk of thyroid cancer. A prospective study of 63,090 women from Norway. Br.J.Cancer 1992;65:772-4.

25. Levi F, Franceschi S, Gulie C et al. Female thyroid cancer: the role of reproductive and hormonal factors in Switzerland. Oncology 1993;50:309-15.

26. Wingren G, Hatschek T, Axelson O. Determinants of papillary cancer of the thyroid. Am.J.Epidemiol. 1993;138:482-91.

27. Hallquist A, Hardell L, Degerman A et al. Thyroid cancer: reproductive factors, previous diseases, drug intake, family history and diet. A case-control study. Eur.J.Cancer Prev. 1994;3:481-8.

28. D'Avanzo B, La Vecchia C, Franceschi S et al. History of thyroid diseases and subsequent thyroid cancer risk. Cancer Epidemiol.Biomarkers Prev. 1995;4:193-9.

29. Galanti MR, Hansson L, Lund E et al. Reproductive history and cigarette smoking as risk factors for thyroid cancer in women: a population-based case-control study. Cancer Epidemiol.Biomarkers Prev. 1996;5:425-31.

30. Zivaljevic V, Vlajinac H, Jankovic R et al. Case-control study of female thyroid cancer - menstrual, reproductive and hormonal factors. Eur.J.Cancer Prev. 2003;12:63-6.

31. Kravdal O, Glattre E, Haldorsen T. Positive correlation between parity and incidence of thyroid cancer: new evidence based on complete Norwegian birth cohorts. Int.J.Cancer 1991;49:831-6.

32. Preston-Martin S, Jin F, Duda MJ et al. A case-control study of thyroid cancer in women under age 55 in Shanghai (People's Republic of China). Cancer Causes Control 1993;4:431-40.

33. Takezaki T, Hirose K, Inoue M et al. Risk factors of thyroid cancer among women in Tokai, Japan. J.Epidemiol. 1996;6:140-7.

34. Memon A, Darif M, Al Saleh K et al. Epidemiology of reproductive and hormonal factors in thyroid cancer: evidence from a case-control study in the Middle East. Int.J.Cancer 2002;97:82-9.

35. Memon A, Varghese A, Suresh A. Benign thyroid disease and dietary factors in thyroid cancer: a case-control study in Kuwait. Br.J.Cancer 2002;86:1745-50.

36. Negri E, Ron E, Franceschi S et al. A pooled analysis of case-control studies of thyroid cancer. I. Methods. Cancer Causes Control 1999;10:131-42.

37. Franceschi S, Preston-Martin S, Dal Maso L et al. A pooled analysis of case-control studies of thyroid cancer. IV. Benign thyroid diseases. Cancer Causes Control 1999;10:583-95.

38. Negri E, Dal Maso L, Ron E et al. A pooled analysis of case-control studies of thyroid cancer. II. Menstrual and reproductive factors. Cancer Causes Control 1999;10:143-55.

39. La Vecchia C, Ron E, Franceschi S et al. A pooled analysis of case-control studies of thyroid cancer. III. Oral contraceptives, menopausal replacement therapy and other female hormones. Cancer Causes Control 1999;10:157-66.

40. Hedinger C, Williams ED, Sobin LH. Histological typing of thyroid tumours. New York - Berlin - Heidelberg: Springer-Verlag, 1988.

41. Breslow N.E., Day NE. Statistical methods in cancer research. Volume I - The analysis of case-control studies. Lyon: IARC Scientific Publications, 1980.

42. Hosmer D, Lemeshow S. Applied logistic regression. New York: John Wiley and Sons, Inc, 1989.

43. Verkooijen HM, Fioretta G, Pache JC et al. Diagnostic changes as a reason for the increase in papillary thyroid cancer incidence in Geneva, Switzerland. Cancer Causes Control 2003;14:13-7.

44. Krassas GE. Thyroid disease and female reproduction. Fertil.Steril. 2000;74:1063-70.

45. Doufas AG, Mastorakos G. The hypothalamic-pituitary-thyroid axis and the female reproductive system. Ann.N.Y.Acad.Sci. 2000;900:65-76.

46. Hegedus L, Karstrup S, Rasmussen N. Evidence of cyclic alterations of thyroid size during the menstrual cycle in healthy women. Am.J.Obstet.Gynecol. 1986;155:142-5.

47. Luoto R, Grenman S, Salonen S et al. Increased risk of thyroid cancer among women with hysterectomies. Am.J.Obstet.Gynecol. 2003;188:45-8.

48. Galanti MR, Lambe M, Ekbom A et al. Parity and risk of thyroid cancer: a nested case-control study of a nationwide Swedish cohort. Cancer Causes Control 1995;6:37-44.

49. Lambe M, Hsieh C, Trichopoulos D et al. Transient increase in the risk of breast cancer after giving birth. N.Engl.J.Med. 1994;331:5-9.

50. Liu Q, Wuu J, Lambe M et al. Transient increase in breast cancer risk after giving birth: postpartum period with the highest risk (Sweden). Cancer Cause Control 2002;13:299-305.

51. Ron E, Curtis R, Hoffman DA et al. Multiple primary breast and thyroid cancer. Br.J.Cancer 1984;49:87-92.

52. Chen AY, Levy L, Goepfert H et al. The development of breast carcinoma in women with thyroid carcinoma. Cancer 2001;92:225-31.

53. Hankinson S, Hunter D. Breast Cancer. In: Adami HO, Hunter D, Trichopoulos D, eds. Textbook of Cancer Epidemiology. New York: Oxford University Press, 2002:301-39.

TABLE 1. Number of cases by histology and size of carcinoma. Thyroid cancer study New Caledonia, South Pacific, 1993-1999.

Size of the largest malignant nodule	Histology			
	Papillary		Follicular	
	n	%	n	%
Microcarcinoma (≤10 mm)	139	*54.5*	6	*15.8*
Carcinoma >10 mm	114	*44.7*	32	*84.2*
Missing	2	*0.8*	0	*0.0*
Total	**255**	*100.0*	**38**	*100.0*

TABLE 2. Selected socio-demographic characteristics of cases and controls. Thyroid cancer study, New Caledonia, South Pacific, 1993-1999.

	Cases (n = 293)		Controls (n = 354)		
	n	***%***	**n**	***%***	***p-value***
Age (year)					
<25	10	*3.4*	13	*3.7*	
25-29	24	*8.2*	24	*6.8*	
30-34	34	*11.6*	42	*11.9*	
35-39	32	*10.9*	38	*10.7*	
40-44	29	*9.9*	37	*10.4*	
45-49	36	*12.3*	32	*9.0*	
50-54	30	*10.2*	41	*11.6*	
55-59	40	*13.6*	37	*10.4*	
60-64	24	*8.2*	44	*12.4*	
65-69	18	*6.1*	19	*5.4*	
≥70	16	*5.5*	27	*7.6*	*p = 0.65*
Ethnic group					
European	32	*10.9*	110	*31.0*	
Melanesian	220	*75.1*	168	*47.5*	
Other	41	*14.0*	76	*21.5*	*p < 0.01*
Education level					
Never went to school	22	*7.5*	20	*5.6*	
≤5 years education	151	*51.5*	177	*50.0*	
6-9 years education	74	*25.3*	94	*26.5*	
≥10 years education	22	*7.5*	44	*12.4*	
Missing	24	*8.2*	19	*5.4*	*p = 0.15*
Marital status					
Single	35	*11.9*	42	*11.9*	
Married	188	*64.2*	232	*65.5*	
Divorced or widowed	70	*23.9*	77	*21.7*	
Missing	0	*0.0*	3	*0.8*	*p = 0.41*

TABLE 3. Odds ratio* of thyroid cancer associated with goiter, by size of carcinoma. Thyroid cancer study, New Caledonia, South Pacific, 1993-1999

	Total sample			Thyroid carcinomas by size†					
				≤10 mm			>10 mm		
	Ca/Co‡ (293/354)	**OR‡**	**95% CI‡**	**Ca/Co (145/354)**	**OR**	**95% CI**	**Ca/Co (146/354)**	**OR**	**95% CI**
History of goiter									
No	263/344	**1.0**	Ref	130/344	**1.0**	Ref	131/344	**1.0**	Ref
Yes	30/10	**4.2**	2.0, 9.1	15/10	**4.2**	1.8, 10.0	15/10	**4.4**	1.8, 10.5
Period of goiter diagnosis									
1-5 years before cancer diagnosis	11/4	**2.7**	0.8, 9.0	3/4	**1.6**	0.3, 7.4	8/4	**3.9**	1.1, 13.9
> 5 years before cancer diagnosis	19/6	**5.5**	2.0, 14.6	12/6	**6.6**	2.3, 19.1	7/6	**4.3**	1.3, 13.8

* Adjusted for age and ethnic group
† Two cases with missing value for size of carcinoma are not included
‡ Ca, number of cases; Co, number of controls; OR, odds ratio; 95% CI, 95% confidence interval

TABLE 4. Odds ratio for thyroid cancer associated with irregular menstrual cycle and age at menarche, by age group (reproductive period) and ethnic group. Thyroid cancer study, New Caledonia, South Pacific, 1993-1999

	Total sample*			Age group*						Ethnic group†								
				<45 years			≥45 years			European			Melanesian			Other		
	Ca/Co‡ (293/354)	OR‡	95%CI‡	Ca/Co (129/154)	OR	95% CI	Ca/Co (164/200)	OR	95% CI	Ca/Co (32/110)	OR	95% CI	Ca/Co (220/168)	OR	95% CI	Ca/Co (41/76)	OR	95% CI
Irregular menstrual cycles§																		
No	241/307	**1.0**	Ref	99/139	**1.0**	Ref	142/168	**1.0**	Ref	23/90	**1.0**	Ref	183/153	**1.0**	Ref	35/64	**1.0**	Ref
Yes	44/39	**1.9**	1.2, 3.2	30/13	**3.6**	1.7, 7.4	14/26	**1.0**	0.5, 2.2	8/19	**1.6**	0.6, 4.5	30/9	**3.0**	1.3, 6.7	6/11	**0.9**	0.3, 2.7
Age at menarche (year)§																		
≤12	42/76	**1.0**	Ref	22/32	**1.0**	Ref	20/44	**1.0**	Ref	7/38	**1.0**	Ref	17/17	**1.0**	Ref	18/21	**1.0**	Ref
13-14	113/151	**1.0**	0.6, 1.6	51/70	**0.7**	0.4, 1.5	62/81	**1.3**	0.6, 2.5	15/57	**1.4**	0.5, 4.1	80/66	**1.2**	0.6, 2.6	18/28	**0.6**	0.3, 1.6
≥15	120/109	**1.2**	0.7, 1.9	52/50	**0.9**	0.4, 1.8	68/59	**1.5**	0.7, 3.0	9/14	**3.4**	1.0, 12.0	106/70	**1.5**	0.7, 3.3	5/25	**0.2**	0.1, 0.7

* Odds ratios adjusted on age and ethnic group
† Odds ratios adjusted on age only
‡ Ca, number of cases; Co, number of controls; OR, odds ratio; 95% CI, 95% confidence interval
§ Some figures do not add up to the total because of missing values

TABLE 5. Odds ratios* of thyroid cancer for menopausal status, ovariectomy and hysterectomy. Thyroid cancer study, New Caledonia, South Pacific, 1993-1999

	Ca/Co† (293/354)‡	OR†	95% CI†
Menopausal status			
Pre-menopausal	162/180	**1.0**	Ref
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**,††			
< 48 years	35/50	**1.0**	Ref
48-51 years	42/41	**1.3**	0.6, 2.8
≥ 52 years	27/44	**0.8**	0.4, 1.6
Ever had an ovariectomy			
No	271/320	**1.0**	Ref
Unilateral	6/12	**0.9**	0.3, 2.8
Bilateral	9/15	**1.1**	0.4, 2.6
Ever had a hysterectomy			
No	260/320	**1.0**	Ref
Yes	26/27	**1.5**	0.8, 2.8
Without ovariectomy	16/13	**1.5**	0.7, 3.3
With unilateral ovariectomy	3/4	**1.6**	0.3, 8.7
With bilateral ovariectomy	7/10	**1.5**	0.5, 4.5
Age at hysterectomy††			
No hysterectomy	260/320	**1.0**	Ref
< 43 years	10/10	**1.8**	0.7, 4.8
43-48 years	7/8	**1.3**	0.4, 3.9
≥ 49 years	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; 95% CI, 95% confidence interval
‡ Some figures do not add up to the total because of missing values
§ Menopausal status cannot be determined according to the criteria defined in the text
** For all postmenopausal women (natural and artificial)
†† 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). Thyroid cancer study, New Caledonia, South Pacific, 1993-1999.

	Total sample			Age group						Interaction†
				<45 years			≥45 years			
	Ca/Co‡ (293/354)	OR‡	95%CI‡	Ca/Co (129/154)	OR	95% CI	Ca/Co (164/200)	OR	95% CI	p-value
Ever had a full-term pregnancy										
No	35/49	**1.0**	Ref	16/32	**1.0**	Ref	19/17	**1.0**	Ref	
Yes	258/305	**1.2**	0.7, 1.9	113/122	**1.8**	0.9, 3.6	145/183	**0.8**	0.4, 1.6	*p = 0.11*
Number of full-term pregnancies										
0	35/49	**1.0**	Ref	16/32	**1.0**	Ref	19/17	**1.0**	Ref	
1	36/55	**1.0**	0.5, 1.9	23/25	**1.8**	0.8, 4.4	13/30	**0.5**	0.2, 1.2	
2	31/77	**0.7**	0.4, 1.4	22/42	**1.2**	0.5, 2.8	9/35	**0.3**	0.1, 0.9	
3	42/47	**1.4**	0.7, 2.6	26/22	**2.3**	1.0, 5.5	16/25	**0.8**	0.3, 2.1	
4-5	50/61	**1.1**	0.6, 2.1	24/19	**2.2**	0.9, 5.5	26/42	**0.6**	0.2, 1.4	
6-7	38/29	**1.6**	0.8, 3.3	14/8	**2.8**	0.9, 8.6	24/21	**0.9**	0.4, 2.4	
≥ 8	61/36	**2.2**	1.1, 4.3	4/6	**1.1**	0.2, 4.8	57/30	**1.5**	0.6, 3.5	*p = 0.10*
Time since last full-term pregnancy§										
Nulliparous	35/49	**1.0**	Ref	16/32	**1.0**	Ref				
≤ 2 years	38/38	**1.3**	0.6, 2.6	38/38	**1.7**	0.8, 3.7				
3-5 years	35/30	**1.5**	0.8, 3.1	30/29	**2.0**	0.9, 4.6				
6-9 years	21/28	**0.9**	0.4, 2.0	14/22	**1.2**	0.5, 3.2				
≥ 10 years	157/203	**1.1**	0.6, 1.9	30/33	**2.2**	0.9, 5.4				
Time since full-term pregnancy in uniparous women										
Nulliparous	35/49	**1.0**	Ref	16/32	**1.0**	Ref				
≤ 2 years	6/5	**2.5**	0.6, 11.1	6/5	**2.7**	0.6, 11.8				
3-5 years	7/5	**2.2**	0.5, 8.5	7/5	**2.6**	0.7, 10.1				
6-9 years	3/5	**2.0**	0.2, 12.0	3/5	**2.1**	0.4, 12.0				
≥ 10 years	20/39	**0.6**	0.3, 1.3	7/10	**1.2**	0.3, 5.1				
Outcome of first pregnancy§										
Nulligravid	27/46	**1.0**	Ref	15/30	**1.0**	Ref	12/16	**1.0**	Ref	
Full-term pregnancy	242/285	**1.4**	0.8, 2.5	105/111	**1.8**	0.9, 3.7	137/174	**1.0**	0.4, 2.3	
Miscarriage	19/15	**2.3**	1.0, 5.6	7/8	**2.1**	0.6, 7.4	12/7	**2.2**	0.6, 8.0	
Voluntary abortion	4/7	**1.5**	0.4, 6.2	2/4	**2.1**	0.3, 13.6	2/3	**0.8**	0.1, 6.7	*p > 0.50*
Ever had a miscarriage**										
No	208/253	**1.0**	Ref	93/104	**1.0**	Ref	115/149	**1.0**	Ref	
Yes	58/55	**1.4**	0.9, 2.1	21/20	**1.3**	0.6, 2.5	37/35	**1.5**	0.8, 2.7	*p = 0.74*
Ever had a voluntary abortion**										
No	238/293	**1.0**	Ref	97/115	**1.0**	Ref	141/178	**1.0**	Ref	
Yes	28/15	**3.1**	1.5, 6.2	17/9	**3.3**	1.3, 8.4	11/6	**2.4**	0.8, 7.2	*p = 0.56*

* 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; 95% CI, 95% confidence interval
§ Some figures do not add up to the total because of missing values
** Among ever pregnant women

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

	Papillary						Follicular		
	≤10 mm			>10 mm					
	Ca/Co†	OR†	95% CI†	Ca/Co	OR	95% CI	Ca/Co	OR	95% CI
Ever had a miscarriage									
No	102/253	**1.0**	Ref	80/253	**1.0**	Ref	25/253	**1.0**	Ref
Yes	26/55	**1.2**	0.7, 2.1	25/55	**1.6**	0.9, 2.8	7/55	**1.5**	0.6, 4.0
Ever had a voluntary abortion									
No	111/293	**1.0**	Ref	98/293	**1.0**	Ref	28/293	**1.0**	Ref
Yes	17/15	**4.1**	1.8, 9.0	7/15	**1.7**	0.7, 4.7	4/15	**4.3**	1.2, 15.7

* Adjusted for age and ethnic group, among ever pregnant women
† Ca, number of cases; Co, number of controls; OR, odds ratio; 95% CI, 95% confidence interval

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

	Ca/Co† (293/354)‡	OR†	95% CI†
Oral contraceptives			
Never	194/213	**1.0**	Ref
Ever	96/138	**1.1**	0.8, 1.7
Duration of OC use			
Never	194/213	**1.0**	Ref
< 2 years	21/24	**1.0**	0.5, 1.9
2-4 years	25/25	**1.7**	0.9, 3.3
≥ 5 years	44/82	**1.1**	0.6, 1.8
HRT use§			
Never	146/178	**1.0**	Ref
Ever	10/19	**0.9**	0.4, 2.2
Duration of HRT use§			
Never	146/178	**1.0**	Ref
< 2 years	5/7	**1.6**	0.4, 6.0
2-4 years	2/3	**0.8**	0.1, 6.0
≥ 5 years	2/5	**1.1**	0.2, 6.3

* Adjusted for age and ethnic group
† Ca, number of cases; Co, number of controls; OR, odds ratio; 95% CI, 95% confidence interval
‡ Some figures do not add up to the total because of missing values
§ Among women ≥45 years