4. Waterhouse J (ed.) *Cancer Incidence in Five Continents*. Lyon, IARC, 1982, Vol. 4, 671.
5. Kissin B, Kaley MM, Su WH, Lerner R. Head and neck cancer in alcoholics. *JAMA* 1973, **224**, 1174.
6. Luce D, Guenel P, Leclerc A, *et al.* Alcohol and tobacco consumption in cancer of the mouth, pharynx and larynx: a study of 316 female patients. *Laryngoscope* 1988, **98**, 313–316.
7. Schottenfeld D. Alcohol as a co-factor in the etiology of cancer. *Cancer* 1979, **43**, 1962–1966.
8. Tuyns AJ, Estève J, Raymond L, *et al.* Cancer of the larynx/hypopharynx, tobacco and alcohol: IARC international case-control study. *Int J Cancer* 1988, **41**, 483–491.
9. Swoboda H, Neumann H, Cartellieri M. Änderungen des Erkrankungsalters der Karzinome des Hypopharynx und des Larynx seit 1960. *HNO* 1989, **37**, 85–91.
10. Wynder EL, Bross IJ. Aetiological factors in mouth cancer. *Br Med J* 1957, **1**, 1137–1171.
11. Wynder EL, Stellman SD. Comparative epidemiology of tobacco related cancers. *Cancer Res* 1977, **37**, 4608–4622.
12. Friedl H-P. Regionale Aspekte des Rauchens. *Statistische Nachrichten* 1987, **42**, 394–397.
13. Friedl H-P. Rauchgewohnheiten und Bildungsniveau. *Statistische Nachrichten* 1987, **42**, 460–463.
14. Friedl H-P. Rauchgewohnheiten und sozioökonomische Stellung. *Statistische Nachrichten* 1987, **42**, 553–558.
15. Mader R, Mittendorfer Ch, Pavlis L, Springer A. Österreichische Trinksitten. Konsumation—Einstellung—Gefährdung. *Schriftenreihe des Ludwig-Boltzmann-Institutes für Suchtforschung*. Wien, Brüder Hollinek 1981, Vol. 4, 39.
16. Swoboda H. Epidemiology of head-and-neck cancer in Eastern Austria. In: Pfaltz CR, ed. *Advances in Oto-Rhino-Laryngology*. Basel, Karger (in press).

Eur J Cancer, Vol. 27, No. 1, pp. 85–88, 1991.
Printed in Great Britain
0277–5379/91 $3.00 + 0.00

Previous Thyroid Disease and Risk of Thyroid Cancer in Switzerland

Fabio Levi, Silvia Franceschi, Carlo La Vecchia, Eva Negri, Cristina Gulie, Germaine Duruz and Bianca Scazziga

A hospital-based case-control study of 86 cases of thyroid cancer and 317 controls was done in the Swiss Canton of Vaud. Patients with thyroid cancer tended to be better educated (odds ratio [OR] 2.1 for ≥ 14 vs. ≤ 8 years of education 95% CI 1.1–4.1) and of higher social class than controls. Cases more often had a history of benign thyroid nodules (OR 25.2, 95% CI 7.6–83.6) and non-toxic goitre (OR 5.3, 95% CI 2.5–11.2). Furthermore, patients with thyroid cancer were more likely to have resided in endemic goitre areas (OR 1.7, 95% CI 1.0–3.0) and to have had first-degree relatives affected by benign thyroid disease (OR 3.9, 95% CI 2.1–7.1). Therefore, this study offers quantitative evidence of the association between various thyroid diseases and the risk of thyroid cancer which, despite difficulties in the classification of benign and malignant thyroid diseases, is remarkably consistent in studies from different countries.
Eur J Cancer, Vol. 27, No. 1, pp. 85–88, 1991.

INTRODUCTION

THYROID CANCER is rare, causing less than 1% of cancer deaths [1], yet its epidemiology is of interest for several reasons. Upward incidence trends of thyroid cancer have been reported, in recent decades, in various registration areas (e.g. Nordic countries, Israel, USA) [2–3], although lack of increases in mortality rates [4] and changes in the definition of several areas of thyroid pathology [5–6] limit interpretation of temporal changes. Thyroid cancer is highly curable [7–8], but present treatment (e.g. thyroidectomy, lifelong high-dose thyroid hormone therapy) of small, clinically silent carcinomas, especially in young women, is a considerable burden to many countries [9].

Except ionising radiation [1], only history of thyroid conditions (benign nodules/goitre) has been consistently associated with risk of thyroid cancer [10–18]. In aetiopathogenic terms, influence of iodine deficiency as a possible link between benign and malignant thyroid disease [10] is not established. Only few case-control studies [11–17] and two prospective investigations [18–20] have been reported on this cancer site. Switzerland offers a privileged opportunity to study thyroid cancers. First, historically it ranks among the highest mortality and incidence rates from thyroid cancer in the world [2, 21]; secondly, it has improved living standards and introduced prophylaxis against iodine deficiency (once very common in mountainous areas), therefore substantially reducing thyroid cancer deaths [22].

To explore and quantify the role of personal and family history of benign thyroid disease, sociodemographic factors and residence in endemic goitre areas in the development of thyroid cancer, we present data from our case-control study in the Canton of Vaud, Switzerland.

Correspondence to F. Levi.
F. Levi, C. Gulie and G. Duruz are at the Registre Vaudois des Tumeurs, Institut Universitaire de Médecine Sociale et Préventive, Centre Hospitalier Universitaire Vaudois, Falaises 1, 1011 Lausanne, Switzerland; S. Franceschi is at the Servizio di Epidemiologia, Centro di Riferimento Oncologico, Aviano, Italy; C. La Vecchia and E. Negri are at the Istituto di Ricerche Farmacologiche "Mario Negri", Milano, Italy; B. Scazziga is at the Unité de Thyréologie, Département de Médecine, Centre Hospitalier Universitaire Vaudois, Lausanne; and F. Levi and C. La Vecchia are also at the Institut Universitaire de Médecine Sociale et Préventive, Bugnon 17, Lausanne; Switzerland.
Revised 24 Aug. 1990; accepted 17 Oct. 1990.

SUBJECTS AND METHODS

Since January 1988, patients admitted for thyroid cancer and various other conditions to the main university hospital of the Canton of Vaud (Centre Hospitalier Universitaire Vaudois) in Lausanne, were identified (7% refused to participate) and interviewed (up to July 1990). Patients below the age of 75 with histologically confirmed thyroid cancer diagnosed within 1 year previously were considered. 86 cases (17 males and 69 females) aged 14–75 (median 42) were interviewed, and 81% of tumours were papillary (Table 1). The local cancer registry [22] was used to check recruitment of thyroid cancer cases. 81% of eligible cases were identified.

Controls were men and women admitted for acute conditions. 317 patients aged 15–75 (median 43) were interviewed. Of these, 34% had orthopaedic conditions, 19% acute surgical conditions, 12% ear, nose and throat diseases and 35% other illnesses (e.g. acute infections, eye and teeth disorders). Individuals with malignant, hormonal and gynaecological disorders were excluded. Although cases and controls were not individually matched for age, their distributions according to 5 year age groups were similar (Table 1). A standard questionnaire was used for information on sociodemographic factors, general characteristics and life-style habits, personal and family history of thyroid diseases, relevant medical conditions (i.e. metabolic and immunological disorders), diagnostic and therapeutic procedures (X-rays and radiotherapy) and history of residence in endemic goitre areas [23]. Patients were counted as having thyroid disease only if diagnosis had been made at least 1 year before cancer discovery (or at interview, for controls).

Odds ratios of thyroid cancer, with their 95% CI, were computed from data stratified for sex, 5 year age groups and current area of residence by means of the Mantel–Haenszel procedure. To account for the potential confounding effect of various risk factors, multiple logistic regression was used, with maximum likelihood fitting. Regression equations included terms for age, sex, area of current residence, education, social class (based on occupation of head of household) and history of residence in endemic goitre areas. Significance of linear trends was assessed by the Mantel method or by computing deviance of the models with and without the variable of interest. Analyses were performed separately on the largest subgroups (i.e. females and papillary thyroid cancer cases); however, very similar results were yielded.

Table 1. Distribution of 86 cases of thyroid cancer and 317 controls according to age, sex and histological type (Vaud, Switzerland 1988–1990)

	Cases		Controls	
	Males	Females	Males	Females
Age (yr)				
<35	3	28	25	72
35–54	8	25	27	97
55–74	6	16	19	77
Histological type				
Papillary	13	57		
Follicular	2	9		
Other	2	3		
Total	17	69	71	246

Table 2. Risk of thyroid cancer according to education, social class and body mass index

Variable*	Cases	Controls	OR†	95% CI
Education (yr)				
≤ 8	20	104	1	
9–13	30	122	1.2	(0.6–2.4)
≥ 14	35	90	2.1	(1.1–4.1)
χ^2_1 (trend)			4.96	$P < 0.05$
Social class‡				
High	30	66	1	
Middle	29	126	0.5	(0.3–0.9)
Low	21	92	0.5	(0.3–1.0)
Undefined	6	33	—	—
χ^2_1 (trend)§			4.49	$P < 0.05$
Body mass index (kg/m²)				
≤ 21	33	122	1	
22–26	29	141	1.0	(0.5–1.8)
≥ 27	24	54	1.6	(0.8–3.4)
χ^2_1 (trend)			3.27	$P < 0.10$

*Some strata do not add up to the total because of missing values.
†Mantel–Haenszel estimates adjusted for age, sex and current area of residence.
‡Based on the head of the household's occupation.
§Undefined excluded.

RESULTS

Patients with thyroid cancer were significantly more educated than controls (OR 2.1 for ≥ 14 years of education vs. ≤ 8, 95% CI 1.1–4.1) (Table 2). Consistently, individuals in intermediate and low social classes seemed protected from thyroid cancer relative to those in the highest social class (OR 0.5, 95% CI 0.3–1.0) (Table 2). A trend of increasing risk with increasing body mass index (BMI) was not significant (OR 1.6 for BMI ≥ 27 vs. ≤ 21, 95% CI 0.8–3.4).

Thyroid cancer was strongly related to most thyroid diseases investigated (Table 3). History of benign thyroid nodules was reported 25 fold more commonly by cases than by controls (OR 25.2, 95% CI 7.6–83.6) (Table 3). Increased thyroid cancer risk also followed diagnosis of non-toxic goitre (OR 5.3, 95% CI 2.5–11.2) and thyroiditis (OR 3.8, 95% CI 0.7–21.3), but not hyperthyroidism (recorded in only 1 case and 5 controls). Overall, history of benign thyroid disease enhanced the risk of developing thyroid cancer approximately 8 fold (Table 3). Risk increases were not restricted to thyroid disease occurring 5 years before thyroid cancer diagnosis.

Elevation of thyroid cancer risk in patients who had resided in endemic goitre areas was of borderline significance (OR 1.7, 95% CI 1.0–3.0) (Table 3). These areas, defined according to national studies, chiefly related to prevalence of goitre and other thyroid diseases in recruits and schoolchildren [24, 25], as well as standard European maps [26]. Patients reporting thyroid disease, chiefly goitre, in first-degree relatives seemed to be more likely to develop thyroid cancer (OR 3.9, 95% CI 2.1–7.1). After allowance for confounding factors (i.e. in addition to sex, age, current area of residence, education and social class), these results were not materially modified. Risk estimates for benign thyroid disease were similar in patients who had resided in endemic goitre areas and those who had not.

History of skin allergies, hay fever, autoimmune diseases, hypertension, diabetes, gallstones, hyperlipidaemia and, among

females, benign breast disease, breast cancer, ovarian cysts and fibroids was not linked to thyroid cancer risk. No significant excess of thyroid cancer was demonstrated in patients receiving radiations (generally low-dose) for therapeutic or diagnostic purposes.

DISCUSSION

In our study various benign conditions of the thyroid gland were associated with thyroid cancer. Table 4 compares relative risks for the two better defined and investigated thyroid diseases (benign nodules and goitre) in the present and in five previous case-control investigations [11–17] and one follow-up study [18]. Analysis is restricted to females, who constituted the majority of all series, and shows substantial agreement in risk estimates, despite difficulties in classifying benign thyroid disease and differences in study designs, patterns of cancer incidence and risk factors in various populations. The association between these benign thyroid conditions and thyroid cancer is therefore now firmly established.

Possible sources of bias are unlikely to have distorted the results, since: (i) subjects interviewed were representative of all incident cases; (ii) participation rate was almost total; and (iii) the catchment area of cases and controls was similar. In relation to confounding, results were virtually unmodified after allowing for potential distorting factors, including major sociodemographic indicators. A limitation of the study, however, was the small sample size, which allowed meaningful inference for a restricted number of well-defined and strong risk factors only.

Thyroid nodules (adenomas) are usually associated with the highest relative risks (around or above 10). Transition from adenoma to carcinoma has been shown experimentally [27] and a substantial proportion of carcinomas discovered at necropsy are considered to have developed from pre-existing adenomas [28]. Lower relative risks (from 3 to 7) were reported after history of goitre. Elevated risk following hyperthyroidism or hypothyroidism seemed smaller and inconsistent in this and previous studies [11–14, 16, 20]. However, the range of conditions in such diagnostic categories and the complexity of evaluation and interpretation of thyroid dysfunction [29] are likely to introduce substantial misclassification.

Artefacts (e.g. accidental diagnosis of benign thyroid disease in the course of diagnostic procedures for cancer or recall bias) seem an unlikely explanation for the positive association in consideration of time required to have elapsed from benign disease to thyroid cancer (at least 1 year in our study), and consistency of these results with those from follow-up studies [18].

Patients with a history of both thyroid disease in the family, and, to a lesser extent, residence in endemic goitre areas, had an increased probability of developing thyroid cancer. Although high endemicity for goitre is not an indispensable condition for elevated rates of thyroid carcinoma (see, as exceptions, Iceland [30] and Hawaii [31]), high incidence rates in European mountainous areas (e.g. Switzerland and Austria) [21] lend support to the positive association between iodine deficiency and thyroid cancer risk. Our findings agree with results of a similar case-control study in Northern Italy [16].

In our study, thyroid cancer showed a positive sociocultural gradient. Previous data is scanty, inconsistent and probably confounded by ethnic differences. In Los Angeles County [32], doctors, engineers, salesmen and managers had above average thyroid cancer incidence; in Hawaii, however, the highest incidence rates of thyroid cancer were found not only in groups such as Chinese, who rank among the highest ethnic groups in socio-cultural indicators, but also in Filipino and Hawaiian populations who do not fit this pattern [31]. In contrast with present results, a negative social class gradient emerged in Switzerland for thyroid cancer mortality [33]. Since in our series

Table 3. Risk of thyroid cancer by previous thyroid disease, residence in endemic goitre areas and family history

Variable	No. (%) of patients with the disease		ORs (95%)	
	Cases	Controls	M-H*	MLR†
Benign nodules	9 (10.5)	2 (0.6)	25.2 (7.6–83.6)	22.6 (4.7–109.7)
Non-toxic goitre	16 (18.6)	14 (4.4)	5.3 (2.5–11.2)	6.1 (2.7–13.7)
Hyperthyroidism	1 (1.2)	5 (1.6)	0.8 (0.1–8.1)	0.8 (0.1–7.1)
Thyroiditis	3 (3.5)	3 (0.9)	3.8 (0.7–21.3)	4.4 (0.8–23.9)
Any of the above	27 (31.4)	22 (6.9)	7.7 (4.1–14.6)	8.5 (4.3–16.9)
History of residence in endemic goitre areas‡	58 (68.2)	173 (56.2)	1.7 (1.0–3.0)	1.9 (1.1–3.3)
Family history of thyroid disease	22 (25.6)	28 (9.0)	3.9 (2.1–7.1)	3.7 (1.9–7.0)

*Mantel–Haenszel (M–H) estimates adjusted for age, sex and current area of residence. Subjects who did not report the variable of interest were considered as reference category.
†Estimates from multiple logistic regression (MLR) equations including terms for age, sex, area of current residence, education and social class.
‡Defined on the basis of national studies [24, 25] as well as of standard European maps [26].

Table 4. Relative risk of thyroid cancer in females by history of benign nodules and goitre

Ref.	Design	Benign nodules	Goitre
11–13	Population-based case-control	10.5	
14	Population-based case-control	12.0	6.6
15	Population-based case-control	33.3	5.6
16	Hospital-based case-control	*	9.6
17 (USA data)	Hospital-based case-control	19.0	
17 (Chinese data)	Hospital-based case-control	9.0	
18	Historical follow-up	11.7	2.6
Our study	Hospital-based case-control	18.3	3.8

*No control subjects reported the disease.

early papillary carcinomas represent the majority, it can be hypothesised that easier access to health-care results in diagnosis of a greater number of early cancers in the more educated and affluent strata of the population.

Our study confirms the importance of benign thyroid disease in the aetiology of thyroid cancer, and supports the possibility that residence in endemic goitre areas may still represent, even in now wealthy areas, a detectable risk factor.

1. Ron E, Modan B. Thyroid. In: Schottenfeld D, Fraumeni JF Jr, eds. *Cancer Epidemiology and Prevention*. Philadelphia, WB Saunders, 1982, 837–854.
2. Muir CS, Waterhouse JAH, Mack T, Powell J, Whelan S. *Cancer Incidence in Five Continents*. Lyon, International Agency for Research on Cancer, 1987, Vol. V. (IARC Scientific Publications No. 88).
3. Pottern LM, Stone BJ, Day NE, Pickle L, Fraumeni J, Jr. Thyroid cancer in Connecticut, 1935–1975: an analysis by cell type. *Am J Epidemiol* 1980, **112**, 764–774.
4. Kerr DJ, Burt AD, Brewin TB, Boyle P. Divergence between mortality and incidence rates of thyroid cancer in Scotland. *Lancet* 1985, **ii**, 149.
5. Rigaud C. Le carcinome papillaire de la thyroïde: évolution des critères histologiques du diagnostic. *Ann Pathol* 1988, **8**, 211–219.
6. Hedinger C, Williams ED, Sobin LH. The WHO histological classification of thyroid tumors: a commentary on the second edition. *Cancer* 1989, **63**, 908–911.
7. The Cancer Registry of Norway. *Survival of Cancer Patients*. Oslo, The Norwegian Cancer Society, 1975, 154–157.
8. Thoresen SO, Akslen LA, Glattre E, Haldorsen EV, Lund EV, Schoultz M. Survival and prognostic factors in differentiated thyroid cancer—a multivariate analysis of 1,055 cases. *Br J Cancer* 1989, **59**, 231–235.
9. Baldet L, Manderscheid JC, Glinoer D, Jaffiol C, Coste-Seignowert B, Percheron C. The management of differentiated thyroid cancer in Europe in 1988. Results of an international survey. *Acta Endocrinol* 1989, **120**, 547–558.
10. Cuello C, Correa P, Eisenberg H. Geographic pathology of thyroid carcinoma. *Cancer* 1969, **23**, 230–239.
11. McTiernan AM, Weiss NS, Daling JR. Incidence of thyroid cancer in relation to reproductive and hormonal factors. *Am J Epidemiol* 1984, **120**, 423–435.
12. 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**, 575–581.
13. McTiernan AM, 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**, 292–295.
14. Preston-Martin S, Bernstein L, Pike MC, Maldonado AA, Henderson BE. Thyroid cancer among young women related to prior thyroid disease and pregnancy history. *Br J Cancer* 1987, 55, 191–195.
15. Ron E, Kleinerman RA, Boice JD, LiVolsi VA, Flannery JT, Fraumeni JF. A population-based case-control study of thyroid cancer. *J Natl Cancer Inst* 1987, **79**, 1–12.
16. Franceschi S, Fassina A, Talamini R, *et al.* Risk factors for thyroid cancer in Northern Italy. *Int J Epidemiol* 1989, **18**, 578–584.
17. Preston-Martin S, Jin F. Risk factors for thyroid cancer among women under age 55 in Shanghai and Los Angeles (Abstr. No. 260). International Epidemiological Association, Twelfth Scientific Meeting, Los Angeles, 1990.
18. Goldman MB, Monson RR, Maloof F. Cancer mortality in women with thyroid disease. *Cancer Res* 1990, **50**, 2283–2289.
19. Thoresen SO, Myking O, Glattre E, Rootwelt K, Andersen A, Foss OP. Serum thyroglobulin as preclinical tumour marker in subgroups of thyroid cancer. *Br J Cancer* 1988; **57**, 105–108.
20. Glattre E, Thomassen Y, Thoresen S, *et al.* Prediagnostic serum selenium in a case-control study of thyroid cancer. *Int J Epidemiol* 1989, **18**, 45–49.
21. Levi F, Maisonneuve P, Filiberti R, La Vecchia C, Boyle P. Cancer incidence and mortality in Europe. *Soz Praeventivmed* 1989, **34**(Suppl. 2), S3–S84.
22. Levi F, Franceschi S, Te VC, Negri E, La Vecchia C. Descriptive epidemiology of thyroid cancer in the Swiss canton of Vaud. *J Cancer Res Clin Oncol* 1990, **116**, 693–647.
23. Report of the Subcommittee for the Study of Endemic Goitre and Iodine Deficiency of the European Thyroid Association: Goitre and iodine deficiency in Europe. *Lancet* 1986, i, 1289–1293.
24. Von Merke F. Die Eiszeit als primordiale Ursache des endemischen Kropfes. *Schweiz Med Wschr* 1965, **95**, 1183–1192.
25. Dind E. Endémie goitreuse et prophylaxie par le sel iodé dans le canton de Vaud. Thèse médicale. Université de Lausanne, 1939.
26. Kelly FC, Snedden WW. Fréquence et répartition géographique du goitre endémique. In: Clements FW, De Moerloose, J, De Smet MP, *et al.*, eds. *Le Goitre Endémique*. Genève, OMS, 1962, 97–99.
27. Meissner WA, Warren S. Tumors of the thyroid gland (Fascicle No. 4 Second series). Washington DC, Armed Forces Institute of Pathology, 1969.
28. Silverberg SG, Vidone RA. Adenoma and carcinoma of the thyroid. *Cancer* 1966, **19**, 1053–1062.
29. Surks MI, Chopra IJ, Mariash CN, Nicoloff JT, Solomon DH. American Thyroid Association guidelines for use of laboratory tests in thyroid disorders. *JAMA* 1990, **263**, 1529–1532.
30. Hrafnkelsson J, Jonasson JG, Sigurdsson G, Sigvaldason H, Tulinius H. Thyroid cancer in Iceland 1955–1984. *Acta Endocrinol* 1988, **118**, 566–572.
31. Goodman MT, Yoshizawa CN, Kolonel LN. Descriptive epidemiology of thyroid cancer in Hawaii. *Cancer* 1988, **61**, 1272–1281.
32. Preston-Martin S, Mench HR. The epidemiology of thyroid cancer in Los Angeles county. *West J Med* 1979, **131**, 369–372.
33. Levi F, Negri E, La Vecchia C, Te VC. Socioeconomic groups and cancer risk at death in the Swiss Canton of Vaud. *Int J Epidemiol* 1988, **17**, 711–717.

Acknowledgements—We thank the following hospital doctors as well as their medical and nursing staff for their assistance: P. Burckhardt, G. Chapuis, N. De Tribolet, E. Frenk, S. Krupp, S. Leyvraz, J.-J. Livio, P. Magnenat, R. Mirimanoff, R. Mosimann, M. Savary (Centre Hospitalier Universitaire Vaudois, Lausanne), Cl. Gailloud and L. Zografos (Hôpital Ophtalmique, Lausanne), A. Balmer, P. de Werra, S. Dettwiler, M. Duc, S. Meyer, C.-A. Richon, S. Stephanov (Hôpital Régional Herens Conthey, Sion); the following practitioners: J.-Ph. Bonjour, M. Cikes, S. Cuttelod, A. Flattet, G. Gross, Ph. Haldy, F.-G. Henry, E. Heraïeff, B. Mivelaz, F. Pellet, P. Rosselet, J. Saladino, E. Simon, S. Vecerina, P.-D. Viredaz, C. Waeber, J. Wyss. We also thank the Vaud Cancer Registry's staff (Ms F. Golay, Mrs N. Menoud and Dr V.-C. Te).

This work was partly supported by the Swiss National Science Foundation Grant No. 3.950–0.87. The contribution of the Swiss League Against Cancer is gratefully acknowledged. S.F. was the recipient of an ICRETT award (No. 173).