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Risk Factors for Thyroid Cancer in Northern Italy

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We conducted a hospital based case-control study of 245 cases of thyroid cancer (62 males and 183 females) and 411 controls in three areas of Northern Italy. Subjects with thyroid cancer more often had a history of benign thyroid nodules (18 cases versus 0 controls, lower 95% confidence limit = 7.84), goitre (RR = 5.61, 95% confidence interval (CI): 2.13–14.77) and residence in endemic goitre areas (RR for residence longer than 20 years = 2.29, 95% CI: 1.23–4.29). Heavy (>1000 rads) irradiation of the neck was reported only by seven cases (lower 95% confidence limit: 2.45). Among 31 food items considered, a few showed direct association, including starchy foods and various sources of animal fats or proteins, whereas frequent consumption of other foods, including major sources of dietary iodine (such as fish, green vegetables and fruit) gave significant protection. When analysis was restricted to various subgroups of patients (ie, different histological types, sexes and major groups of hospital controls), it yielded similar results.

Thyroid cancer is a relatively rare cancer that occurs more frequently among females than males.[1] In many industrialized countries such as the US and Great Britain, increases in incidence, but not in mortality, were apparent in the last decades,[1,2] partly as a consequence of increasing diagnosis of occult lesions, especially in young women.[1] Survival rates have improved over time and also account for the diverging incidence and mortality rates seen in some countries.[2]

In Italy, where only mortality rates are available for the whole nation, an increasing trend was apparent for cohorts of men and women born up to the 1930s.[3] Endemic goitre has been reported till recently in some parts of Italy,[4] particularly in the mountainous areas (Alps and Appenines[4]) where mortality rates from thyroid cancer are double the national average.[5]

The best known risk factor for thyroid cancer is irradiation of the head and neck, particularly during childhood.[6-11] Such practice in the treatment of benign conditions has been largely abandoned. Other potential determinants of thyroid cancer such as prior benign thyroid conditions,[11-13] iodine deficiency,[14,15] and dietary habits[13,16,17] are still poorly understood, particularly in relation to cancer of different histological types (papillary, follicular etc).[18]

The present case-control study investigates the potential risk factors mentioned above using three areas of Northern Italy including both high and low risk areas for thyroid cancer.

SUBJECTS AND METHODS

Since January 1986 we have been conducting a case-control study on thyroid cancer in three areas of Northern Italy (1) The provinces of Pordenone and Udine, which constitute the continental part of Friuli-Venezia Giulia region, bordering Austria and Yugoslavia. (2) The province of Padua, in Veneto region, where the largest Medical School in north-eastern Italy is located, and (3) the greater Milan area. In each area one trained interviewer (AM and SV and a professional nurse) identified and questioned patients admitted for thyroid cancer and for a wide spectrum of other conditions to university and general hospitals in the areas under surveillance. Relevant medical staff granted permission for the interview. Less than 3% of patients refused to participate.

The cases considered were (i) below the age of 75 with histologically confirmed thyroid cancer diagnosed within two years prior to interview (ie, since February 1984 for subjects interviewed in January 1986, and so on); (ii) admitted as inpatients or referred for follow-up to the outpatient clinics of the study hospitals. A total of

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245 cases (62 males and 183 females) aged 14 to 72 (median age 45) were interviewed (Table 1). The three areas under study were not covered by cancer registries and it was not possible to estimate the proportion of thyroid cancer cases interviewed. The study hospitals, however, included all the diagnostic and therapeutic facilities available in the areas under surveillance and, therefore, the great majority of thyroid cancer cases will have been referred there. In the light of differences in prognosis and, perhaps, risk factors,[19] an attempt was made to differentiate histological types. Critical to the segregation of papillary from follicular carcinomas was the presence of (1) ground-glass nuclei, (2) well-formed papillae, and (3) psammoma bodies.[19] Seventy-seven per cent of tumours were classified as papillary or mixed papillary and follicular. The series included 16 undifferentiated thyroid carcinomas but no medullary carcinoma (Table 1).

Controls were individuals of both sexes admitted for acute conditions to the study hospitals. The catchment areas of hospitals where cases and controls were interviewed were comparable (ie control subjects would have been referred, if affected by thyroid cancer, to the hospitals where cases were contacted, and comparability of cases and controls by place of residence was checked). Controls had diseases other than malignant, hormonal or gynaecological diagnosed within two years prior to interview. A total of 411 controls, aged 13 to 75 (median age 46) were interviewed. Of these 21% were admitted for orthopaedic conditions, (mostly low back pain and disc disorders), 18% for skin diseases, 16% for ear, nose and throat diseases, 18% for traumatic conditions (mostly fractures and sprains), 5% for eye diseases, and 22% had other illnesses such as infections and acute surgical conditions (mostly abdominal). Although cases and controls were not individually matched for age, their distribution according to five-year age groups were comparable. A standard questionnaire was used to obtain information on sociodemographic factors, general characteristics and lifestyle, past history and family history of thyroid diseases, other potentially relevant medical conditions (ie metabolic and immunological disorders), diagnostic therapeutic procedures (x rays and radiotherapy), and history of residence in endemic-goitre areas.[20] The dietary part of the questionnaire included 31 food items representing the major sources of starch, proteins, fats, fibres, vitamin A and C in the Italian diet. The subjects were asked to describe their weekly intake of every food item during the year preceding the first symptoms of the disease. They were also asked to recall any major change in frequency of intake of the same food during the ten years preceding diagnosis but, since changes in diet were infrequently reported, and no significant difference emerged between cases and controls, for all analytical purposes only information on recent diet was considered.

TABLE 1 *Distribution of 245 cases of thyroid cancer according to age, sex, and histological type. Northern Italy, 1986–87*

	Males	Females
	No. (%)	No. (%)
Age (yrs)		
<30	9 (15)	39 (21)
30–39	10 (16)	31 (17)
40–49	15 (24)	41 (22)
50–59	14 (23)	44 (24)
≥60	14 (23)	28 (15)
Histological type		
Papillary	40 (65)	132 (72)
Follicular	12 (19)	29 (16)
Mixed papillary/follicular	3 (5)	13 (7)
Other	7 (11)	9 (5)

Data Analysis and Controls of Confounding:
Frequencies of food item consumption were (i) considered separately and (ii) used to derive indices of retinoids (preformed vitamin A), carotenoids (provitamin A) and ascorbic acid (vitamin C) intake, using tables of nutrient values issued by the Italian Ministry of Agriculture[21] or, in the absence of Italian data, standard American tables.[22] Food item consumption and micronutrient intake were then subdivided into three levels (ie low, intermediate and high) each including, as far as possible, the same number of cases and controls combined (approximate tertiles). Pasta, rice, bread, polenta (ie porridge made from maize) and potatoes were also analysed jointly (starchy foods).

Relative risks (RR) of thyroid cancer, together with their 95% approximate confidence intervals (CI),[23] were first computed from data stratified for sex, five-year age groups and area of residence by means of the Mantel-Haenszel procedure.[24] With small expected values, the exact method[25] was used for CI. Significance was assessed by the linear trends described by Mantel.[26]

In order to account simultaneously for the potential confounding effect of various risk factors, multiple logistic regression was used, with maximum likelihood fitting.[27] Regression equations included terms for age, sex, geographical area, history of residence in endemic goitre areas, smoking habits, plus selected dietary factors which emerged as significantly related to thyroid cancer risk. The significance of the linear trends in risk was assessed in the usual way, by computing the differ-

TABLE 2 *Risk of thyroid cancer by prior thyroid disease. Northern Italy, 1986–87*

Thyroid disease		Thyroid cancer (N = 245)	Controls (N = 411)	Relative risk* (95% CI)
Benign nodules	no	227	411	1
	yes	18	0	∞ (7.84–∞)
Goitre	no	228	406	1
	yes	17	5	5.61 (2.13–14.77)
Hyperthyroidism	no	239	408	1
	yes	6	3	2.34 (0.58–9.45)
Thyroid disease (any of above plus unspecified)	no	207	404	1
	yes	38	7	9.61 (4.79–19.31)
Family history of goitre	no	214	375	1
	yes	31	36	1.44 (0.85–2.43)

*Mantel-Haenszel estimates adjusted for age, sex and geographical area.

ence between the deviance of the models with and the variance of the models without the variable of interest.[23]

All analyses were performed on males and females and different histological types (papillary and mixed papillary and follicular versus follicular and other) separately, generally reaching very similar results, when not otherwise stated.

RESULTS

Prior Thyroid Disease and Residence in Endemic Goitre Areas

Thyroid cancer was strongly related to all thyroid diseases investigated (Table 2). Cases were counted as having thyroid disease only if diagnosis had been made at least two years before cancer diagnosis. Past history of benign thyroid nodules was reported only by cases and therefore RR estimate was infinity (lower 95% confidence limit: 7.48). Goitre was also more commonly reported by cases than controls (RR = 5.61, 95% CI: 2.13–14.77), whereas family history for goitre was not significantly related to thyroid cancer risk (RR = 1.46, 95% CI: 0.87–2.48). Hypothyroidism and thyroiditis were reported only by one case each. Overall, previous history of thyroid disease enhanced the risk of developing thyroid cancer approximately ten-fold. Although all benign thyroid diseases were more commonly reported by females than males, they seemed to enhance the risk of thyroid cancer equally in both sexes (not shown in table). Furthermore, the association between prior thyroid disease and thyroid cancer was not restricted to any histological type.

The risk of thyroid cancer increased significantly in subjects who had ever resided in endemic goitre areas, if they had lived there for 20 years or longer (RR = 2.29, 95% CI: 1.23 and 4.29) or in childhood or youth (RR = 2.37, 95% CI: 1.30–4.30) (Table 3). This tendency was stronger in females than in males. When different histological types were considered, the association between history of residence in endemic goitre areas in one's childhood or youth and follicular histotype was not substantially stronger (RR = 2.73, 95% CI: 1.08–6.91) as compared to papillary and mixed papillary and follicular types (RR = 1.85, 95% CI: 1.02–3.35).

Subjects who had ever resided in such endemic goitre areas tended to report goitre or thyroid nodules twice as

TABLE 3 *Risk of thyroid cancer by history of residence in endemic goitre areas and sex. Northern Italy, 1986–87*

History of residence in endemic goitre areas	Males			Females			All
	Thyroid cancer	Controls	Relative risk* (95% CI)	Thyroid cancer	Controls	Relative risk* (95% CI)	Relative risk* (95% CI)
Never	56	101	1	149	263	1	1
<20 years	2	5	0.79 (0.14–4.44)	13	19	1.23 (0.58–2.61)	1.18 (0.60–2.33)
≥20 years	4	6	1.17 (0.28–4.89)	21	17	2.70 (1.31–5.55)	2.29 (1.23–4.29)
χ^2 (trend)			0.03			6.48 p = 0.01	6.09 p = 0.01
above age 25	2	6	0.66 (0.13–3.47)	10	16	1.05 (0.45–2.45)	1.03 (0.49–2.17)
below age 25	4	5	1.40 (0.32–6.06)	24	20	2.68 (1.36–5.28)	2.37 (1.30–4.30)
χ^2 (trend)			0.09			6.75 p = 0.01	6.55 p = 0.01

*Mantel-Haenszel estimates adjusted for age, geographical area and, when appropriate, sex.

TABLE 4 *Subjects who received heavy (>1000 rads) irradiation treatment to the head or neck by various characteristics. Northern Italy, 1986–87*

Sex	Age at diagnosis of thyroid cancer	Histological type	Age at radiation treatment	Indication
M	47	Follicular	27	Seminoma of the testis
F	57	Papillary	30	Tubercolosis
F	44	Follicular	10	Goitre
F	31	Papillary	26	Vegetant scar after benign thyroid nodule resection
F	23	Follicular	1	Angioma of the neck
F	26	Follicular	3	Enlarged thymus gland
F	56	Papillary	44	Thyroiditis

frequently compared with those who had not. Adjustment for history of benign thyroid disease reduced the RR estimate for having ever resided in endemic goitre areas in one's childhood or youth from 2.29 to 1.69 (95% CI: 0.93–3.06).

Radiation

Nine cases (3.7%) and six controls (1.5%) reported a history of radiation treatment to the head or neck (RR = 2.57, 95% CI: 0.94–7.07). Six control subjects but only two cases had radiation therapy as adults for degenerative arthritis of the neck which implies relatively low-dose irradiation of the anterior wall. Heavy (>1000 rad) radiation exposure of the thyroid gland was therefore restricted to seven cases, mostly (6/7) women, described in detail in Table 3 (lower confidence limit = 2.45). No excess of thyroid cancer was demonstrated in subjects receiving low doses of diagnostic radioiodine or x-rays to any part of the body.

Dietary habits

Table 5 provides results for 31 food items and six beverages included in the dietary questionnaire. Variables showing a significantly increased risk for thyroid cancer associated with high consumption were bread, polenta, potatoes, chicken and poultry, salami and sausages, cheese and butter. A significantly reduced risk was observed for high consumption of raw ham, fish, carrots, green vegetables, citrus fruit and all fresh fruit. Methylxanthine-containing and alcoholic beverages did not affect the probability of developing thyroid cancer significantly (Table 5). Carotenoids, but not preformed vitamin A and ascorbic acid, were negatively correlated with thyroid cancer risk, RR (for highest level of consumption) = 0.49, 95% CI: 0.32–0.75.

In Table 6 food items or groups of foods showing significant association with thyroid cancer were included in two series of multiple logistic regression equations. The risk estimates derived from multiple logistic regression were consistent with the age, sex and geographical area-adjusted ones, the trends being still significant for all but starchy foods and cheese. The models based on simultaneous inclusion of various foods are more difficult to interpret, because of problems of collinearity and hence increased standard errors. The apparent influence of various levels of consumption of butter, carrots and fresh fruit was substantially reduced whereas significant trends persisted for chicken and poultry, salami and sausages, (direct), and raw ham, fish and green vegetables (inverse) (Table 6).

Other factors

Thyroid cancer cases and controls did not differ as regards education (RR for >8 years of education versus ≤5 = 1.05, 95% CI: 0.65–1.67) and no association with any occupational group was detected. No trend of increasing risk with increasing weight was found in either males or females (average body mass index,—Kg/m^2—in cases and controls respectively 25.05 and 25.30 in males and 24.24 and 24.30 in females). Past histories of skin allergies, hay fever, auto-immune diseases, high blood pressure, diabetes and, among females, benign breast disease, breast cancer, ovarian cysts and uterine fibroids were not linked to thyroid cancer risk. Fewer cases than controls, however, reported diagnosis of hyperlipidaemia (RR = 0.57, 95% CI: 0.29–1.12).

DISCUSSION

In the present investigation the risk of developing thyroid cancer was strongly related to history of prior thyroid disease. This was true for all histological types and for both sexes, although women tended to report positive history of thyroid disease more often than men. Benign thyroid conditions were differently classified in previous case-control studies, thus making comparisons difficult.[11-13] In agreement with this study, thyroid nodules (adenomas) were usually associated with the highest RR estimates in Ron *et al* (33.3)[13] and McTiernan *et al* (12.0).[11] The approximately six-fold

TABLE 5 *Risk of thyroid cancer by consumption of various food items, methylxanthine-containing alcoholic beverages. Northern Italy, 1986–87*

Food item*	Frequency of consumption (N. of cases: N. of controls) Low	Intermediate	High	Relative risk estimates† 1	2	3	χ^2 (trend)
Pasta or rice	70:142	114:176	61: 93	1	1.26	1.49	2.12
Bread	79:178	112:149	54: 84	1	1.83	1.61	6.66§
Whole-grain bread and pasta	183:312	37: 48	25: 51	1	1.21	0.71	0.70
Polenta	56:127	112:178	73:104	1	1.38	1.89	7.84§
Potatoes	78:159	116:199	51: 52	1	1.16	2.19	8.63§
Pastry	83:170	95:133	67:108	1	1.38	1.31	2.52
Beef	91:182	102:142	52: 87	1	1.30	1.04	0.40
Chicken and poultry	72:180	90:115	83:116	1	1.80	1.98	10.80§
Fish	105:151	94:148	46:111	1	0.84	0.55	6.07‡
Liver	105:208	100:128	35: 69	1	1.48	1.05	0.93
Raw ham	124:167	51:111	67:132	1	0.56	0.65	6.59‡
Cooked ham	107:197	62:113	74: 99	1	0.91	1.29	3.19
Salami and sausages	121:235	45: 78	77: 96	1	1.17	1.68	7.08§
Canned meat	170:274	60: 99	13: 36	1	0.93	0.52	2.61
Eggs	108:217	78: 96	52: 80	1	1.65	1.15	0.87
Milk	87:168	59: 70	99:173	1	1.33	1.15	0.49
Cheese	119:238	77: 89	49: 84	1	1.67	1.50	4.44‡
Butter	126:254	84:128	35: 29	1	1.35	2.68	12.80§
Margarine	217:365	28: 46	—	1	1.06	—	0.05
Olive oil	91:153	130:221	24: 37	1	0.88	1.03	0.47
Other oils	90:169	132:220	20: 22	1	1.28	1.39	3.39
Pulses	71:138	84:132	90:141	1	1.22	1.46	2.01
Carrots	128:172	86:160	30: 78	1	0.73	0.53	6.02‡
Cabbage and other cruciferae	105:158	111:190	29: 63	1	0.84	0.70	1.96
Tomatoes	107:186	81:118	57:107	1	1.31	1.05	0.26
Pepper	132:215	91:157	22: 39	1	0.86	0.87	0.54
All green vegetables	107:153	102:160	35: 98	1	1.01	0.50	5.56‡
Apples	92:140	79:126	74:144	1	0.92	0.74	0.94
Citrus fruit	99:139	85:134	61:138	1	0.89	0.63	4.03‡
Melon	90:137	91:149	63:125	1	0.95	0.77	1.72
All fresh fruit	98:148	115:176	32: 87	1	0.96	0.49	4.38‡
Coffee	78:128	82:109	85:173	1	1.30	0.80	1.37
Tea	208:333	36: 77	—	1	0.70	—	2.58
Cola-containing beverages	233:393	12: 18	—	1	0.97	—	0.01
Wine	119:203	65: 90	61:117	1	1.40	0.94	0.04
Beer	207:320	16: 37	22: 50	1	0.66	0.72	1.65
Spirits	189:319	56: 91	—	1	1.32	—	3.49

*Some figures do not add up to the total because of a few missing values.
†Mantel-Haenszel estimates adjusted for age, sex and geographical area.
‡$p<0.05$.
§$p<0.01$.

increase of thyroid cancer risk following goitre is also consistent with estimates from these studies.[11,13] Our overall RR of 9.61 for positive history of any thyroid disease is compatible with that reported by Preston-Martin *et al* for women only (14.5).[12] Less marked, non-significant elevation of risk was seen for positive history of hyperthyroidism and family history of goitre.

Subjects who had ever resided in endemic goitre areas, particularly those who had lived there longer and/or in their childhood or youth, seemed to have an increased probability of developing cancer of the thyroid. This suggests that subclinical iodine deficiency, documented in some areas of Italy,[4] may enhance risk of thyroid cancer. Hypothyroidism or goitrous state, induced by dietary iodine deficiency, partial thyroidectomy or administration of chemical goitrogens have been shown to cause excessive thyroid stimulating hormone (TSH) production and, in the long run, thyroid neoplasms in experimental animals.[28] In previous work[29] the geographical correlation between goitre endemicity and incidence of thyroid cancers was difficult to assess conclusively because of wide differences

TABLE 6 *Food items significantly related to thyroid cancer risk. Northern Italy, 1986–87*

Food item	Model	Relative risk estimates Frequency of consumption Low	Intermediate	High	χ^2 (trend)
Starchy foods	A*	1	1.45	1.53	3.76
	B†	1	1.15	1.15	0.34
Chicken and poultry	A*	1	1.94	1.93	10.50§
	B†	1	2.25	2.44	15.47§
Salami and sausages	A*	1	1.17	1.67	6.46‡
	B†	1	1.13	1.70	5.34‡
Cheese	A*	1	1.76	1.31	3.30
	B†	1	1.72	1.34	3.19
Butter	A*	1	1.29	2.47	9.80§
	B†	1	0.99	2.10	3.33
Raw ham	A*	1	0.57	0.61	6.54
	B†	1	0.62	0.57	7.14§
Fish	A*	1	0.90	0.57	5.80‡
	B†	1	0.78	0.56	5.70‡
Carrots	A*	1	0.70	0.52	8.30§
	B†	1	0.71	0.73	2.46
Green vegetables	A*	1	0.92	0.49	7.00§
	B†	1	0.87	0.44	7.58§
Fresh fruit	A*	1	0.92	0.53	5.10‡
	B†	1	1.08	0.60	1.96

*Model including terms of age, sex, geographical area, residence in endemic goitre areas, education and smoking habits.
†Model including the same non-dietary variables plus all the above listed food items.
‡$p<0.05$.
§$p<0.01$.

between countries in diagnostic standards and preventive measures (ie iodine supplementation). However, significant excesses of follicular carcinomas, but not of papillary carcinomas, were reported in endemic goitre areas.[1] In the present study residence in endemic goitre areas did not seem to affect the risk of thyroid carcimoma of papillary or follicular type in a substantially different way whereas sex did, with females influenced more heavily than males. If not due to chance, this may suggest a higher susceptibility of the thyroid gland to iodine deficiency in females. Part of the effect of residence in endemic goitre areas could be mediated by prior development of benign thyroid conditions, more frequently in females than males.

Although rare in the present series, radiation therapy of head and neck was confirmed as a strong risk factor for thyroid cancer. History of radiation exposure, particularly in childhood, is probably the best studied risk factor for thyroid cancer,[6-13] although uncertainties remain about the dose-response relationship.[1] The overall RR estimate (2.57) is close to the lowest reported by Ron *et al*,[13] but when only exposures involving heavy irradiation of the anterior wall of the neck (or received as children) were considered, much more substantial increase emerged.[11] Excess risk of thyroid cancer associated with radiation exposure did not vary with histological type but, in agreement with previous work,[6-13] was related to age (6/7 heavily irradiated patients who developed thyroid cancer were irradiated in the first three decades of life) and sex (6/7 were females).

From the dietary part of the present investigation there was a relationship between various indicator foods and risk of thyroid cancer. Among the apparently protective foods, green vegetables and fish may have a beneficial effect because they are important sources of dietary iodine.[30] Raw ham is lean pork meat, processed with large amounts of salt. Since it is expensive, it may simply emerge as an indicator of a particularly affluent and well planned diet. Among positively associated food items, the apparent role of starchy foods, cheese and butter was substantially diminished by taking into account their high degree of inverse collinearity with food items that turned out to be protective. By contrast, salami and sausages and chicken and poultry retained their significance. It is also noteworthy that all food items showing direct or inverse correlation with thyroid cancer risk tended to do so in both sexes, making an effect mediated by female hormones implausible.[12,13,31]

Protection conferred by high consumption of vegetables has already been reported.[13] Cabbage and other cruciferae are particularly interesting since they contain goitrogenous substances as well as potentially protective substances such as indole components, isothiocyanates and phenols.[32] At least in affluent countries, high consumption of cruciferous vegetables seems, if anything, protective.[13] A few discrepancies between the findings of a North-American case-control study[13] and the present investigation concern chicken, fish and, most of all, starchy foods. It is, however, clear that the influence of certain dietary factors may depend on the general dietary pattern of the population under study, thus producing apparently different results. In some of the mountaneous areas where patients were recruited for the present study diet tended to be rather poor till the 1950s[33] and largely consisted of starchy foods, especially polenta (a porridge made from maize). It is possible that plants such as cereals which contain less thiocyanate than cruciferous plants, but which are eaten in much larger amounts, may interfere more severely with thyroid gland function.

It seems unlikely that the present dietary results simply derive from the choice of hospital controls, since they were not restricted to any major control group (eg orthopaedic, skin diseases, etc) or from any socio-cultural imbalance between thyroid cancer cases and

controls. Cases of thyroid cancer and controls were comparable with regard to education, occupation, geographical area and lifestyle and, in addition, these variables were taken into account in the multiple logistic regression analysis.

In conclusion, the present case-control study confirms the importance of benign thyroid disease and radiation exposure in the aetiology of thyroid cancer and provides clues for further research on the way through which residence in endemic goitre areas and dietary habits affect the function and the malignant transformation of the thyroid gland.

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