History of Thyroid Diseases and Subsequent Thyroid Cancer Risk[1]

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Abstract

A history of benign thyroid diseases has been associated with the risk of thyroid cancer. We have analyzed this issue using data from a case-control study conducted in northern Italy between 1986 and 1992 on 399 incident, histologically confirmed thyroid cancer cases and 617 controls admitted to the hospital for acute, nonneoplastic, non-hormone-related diseases. The overall multivariate relative risk (RR) estimates were 2.8 [95% confidence interval (CI), 0.6–12.4] for previous episodes of thyroiditis, 27.1 (95% CI, 6.5–111.9) for adenoma, 8.2 (95% CI, 3.5–19.1) for goiter, 3.8 (95% CI, 1.4–10.9) for hyperthyroidism, and 1.5 (95% CI, 0.4–5.1) for hypothyroidism when all histotypes were analyzed. The RR for any thyroid disease was 7.7 (95% CI, 4.6–12.8). A family history of thyroid disease was significantly related to thyroid cancer with an RR of 1.6. The RR for having resided in endemic goiter areas was 1.3 for <20 years of residence and 1.6 for 20 or more years. These associations were somewhat stronger when only papillary, follicular, and mixed papillary/follicular cancers were considered. Analyses of data in separate strata of sex and age suggested that several benign conditions play a more important role in females and in subjects younger than 50 years. Results were similar to the overall ones when papillary and follicular carcinomas were considered separately. The population-attributable risk for any previous thyroid disease was approximately 20% in this Italian population. These results confirm that history of thyroid disease is a relevant indicator of subsequent thyroid cancer risk also in areas at relatively low prevalence of goiter and other thyroid diseases.

Introduction

Together with ionizing radiation, a history of benign thyroid diseases has been associated with the risk of thyroid cancer (1–3), but only a few studies have assessed and quantified these associations, producing heterogeneous results. In most investigations, the relative risk estimates were between 12 and 33 for adenoma and between 6 and 10 for goiter (4–11). In a study from Switzerland (7) the risk estimate for thyroiditis was 4.4. No significant elevations of risk were reported for history of hyperthyroidism (6–8); for hypothyroidism risk, estimates below or around 1 were provided by a population-based case-control study from the United States (6), by another American study on women (4), and by a study from Hawaii (8).

It has also been suggested that the association with thyroid disease is quantitatively different for the two sexes and in various age groups. Some studies have considered only women, who tend to have higher frequency of both benign and malignant thyroid diseases. Among these studies, a large historical cohort of women from Massachussetts showed a significantly elevated risk in women only for adenoma (9). Risks of 16 for adenoma and of 7 for goiter were found in a study conducted in women below age 55 in Shanghai, China (11). A population-based case-control study from Hawaii (8) reported (nonsignificant) RR[3] of 2.4 for goiter and of 1.4 for benign thyroid disease in females but a higher risk for benign thyroid disease in males (RR = 12.3, with, however, a lower confidence limit of 1.2).

Besides sex, age may interact on the relationship between thyroid disease and thyroid cancer, since the incidence of the disease according to histological types varies substantially by age, and the prevalence of most benign diseases tends to level off or even decline from the sixth decade (3).

We therefore analyzed data from a case-control study conducted in northern Italy, separately analyzing sex, age groups, and histotype, in order to evaluate and better quantify the role of benign thyroid conditions on thyroid cancer risk in different subgroups.

Materials and Methods

A case-control study of thyroid cancer has been conducted in northern Italy since January 1986. Its general design has already been described (12). Briefly, trained interviewers identified and questioned subjects admitted for histologically confirmed thyroid cancer and controls in the major teaching hospitals from selected regions of northern Italy, including the Greater Milan area, Friuli-Venezia Giulia, and Veneto regions (in northeast Italy). The present analysis is based on data collected before December 1992.

Cases were subjects under age 75 admitted to the network of participating hospitals for incident and histologically confirmed thyroid cancer diagnosed within 2 years before the interview. A total of 399 subjects (108 males and

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[3] The abbreviations used are: RR, relative risk, CI, confidence interval.

291 females), ages 16–72 years (median age, 44 years), were interviewed. Of these, 274 subjects had papillary carcinomas or mixed papillary/follicular, 69 follicular, 18 medullary, 8 anaplastic, 4 oxyphil cell neoplasms, and 26 undefined histological type. The pathological criteria used to differentiate papillary from follicular carcinomas were presence of ground-glass nuclei, well formed papillae, and psammona bodies.

Controls were subjects admitted to the same network of hospitals during the same calendar period as cases for acute nonneoplastic diseases, not related to known or potential risk factors for thyroid cancer. Further, explicitly excluded were patients admitted for any hormone-related disease, whenever such diseases were the index admission diagnoses. No exclusion was made for subjects with a history of hormone-related conditions unrelated to the index admission. A total of 617 controls (190 males and 427 females), ages 16–74 years (median age, 46 years), coming from comparable catchment areas were interviewed. Of these, 15% were admitted for traumatic conditions, 17% had other nontraumatic orthopedic diseases (such as disk disorders and low back pain), 28% had acute surgical conditions, and 40% were admitted for miscellaneous disorders, such as acute infections or skin, ear, nose, and throat diseases. The participation rate was over 95% for both cases and controls.

A structured questionnaire was administered by trained interviewers, including sociodemographic and anthropometric characteristics; lifestyle habits such as smoking, consumption of alcohol, coffee, and other methylxanthine-containing beverages; frequency of intake of a few indicator foods; a problem-oriented medical history; family history of thyroid diseases; residence in endemic goiter areas; history of use of diagnostic and therapeutic X-rays; gynecological and obstetric history; and use of oral contraceptives and female hormones for other indications. Information was specifically elicited on previous episodes (and corresponding date of onset) of thyroiditis, benign nodules (adenoma), goiter, hyperthyroidism, hypothyroidism, and other unspecified thyroid diseases. Information on medical history collected at interview was systematically checked for reliability and consistency with medical records, and any possible inconsistency was investigated further.

Data Analysis. Odds ratios as estimators of RR and the corresponding 95% CIs of thyroid cancer were computed according to history of selected diseases, family history of thyroid diseases, and duration of residence in endemic goiter areas, by means of unconditional multiple logistic regression equations, including terms for sex, age in quinquennia, and area of current residence (13). In order to account simultaneously for the potential confounding effects of other factors, logistic regression models were fitted (14), including also terms for body mass index (computed as kg/m^2), smoking habits (never, ex-, current smokers), family history of thyroid diseases (yes, no), residence in an endemic goiter area (never, <20 years, 20 or more years), and exposure to ionizing radiations for therapeutic reasons (ever, never).

Risk estimates were computed for all histological type cancers and for papillary, follicular, and mixed papillary/follicular cancers only, and subsequently in strata of sex and age (below age 50 and ages 50 or older), and for papillary and follicular thyroid carcinomas separately.

Table 1 Distribution of 399 thyroid cancer cases and 617 controls according to sociodemographic and anthropometric variables (Italy, 1986–1992)

	Cases		Controls	
	No.	(%)	No.	(%)
Sex				
Males	108	(27.1)	190	(30.8)
Females	291	(72.9)	427	(69.2)
Age (yr)				
<40	152	(38.1)	231	(37.5)
40–49	88	(22.1)	131	(21.2)
50–59	87	(21.8)	129	(20.9)
60–74	72	(18.0)	126	(20.5)
Education (yr)				
<7	178	(44.6)	297	(48.1)
7–11	111	(27.8)	196	(31.8)
≥12	110	(27.6)	124	(20.1)
Center				
Milan	208	(52.1)	257	(41.7)
Veneto	132	(33.1)	221	(35.8)
Friuli-Venezia Giulia	59	(14.8)	139	(22.5)
Body mass index (kg/m^2)				
<25	248	(62.2)	348	(56.4)
25–30	123	(30.8)	203	(32.9)
>30	28	(7.0)	66	(10.7)

Using the distribution of the risk factors in the cases and the relative risk estimates, population attributable risks were computed with the use of the method described by Bruzzi *et al.* (15) Assuming that the cases are representative of all thyroid cancers in the target population, this method can be applied to data from hospital-based case-control studies because it requires knowledge of the RR estimates and of the joint distribution of the risk factors in the population of cases only.

Results

The distribution of thyroid cancer cases and controls according to age, sex, and selected sociodemographic characteristics is presented in Table 1. About 60% of cases were younger than 50 years. No difference between cases and controls emerged with respect to education, but cases tended to be less frequently overweight or obese. The difference, however, was not significant.

History of selected diseases and residence in endemic goiter areas are considered in Table 2 for all histological types and for papillary, follicular, and mixed papillary/follicular types only. The relative risks were similar when all thyroid cancers were considered or when only papillary, follicular, and mixed papillary/follicular neoplasms were considered, although most estimates were somewhat higher in this subgroup. This is attributable to the less strong relationship of other types with thyroid conditions (RR for any thyroid disease in other histological types, 3.4). In papillary, follicular, and mixed papillary/follicular cancers, the overall multivariate RR estimates were 3.7 (95% CI, 0.8–16.3) for previous episodes of thyroiditis, 31.6 (95% CI, 7.6–131.3) for thyroid adenoma, 7.9 (95% CI, 3.3–18.6) for goiter, 4.0 (95% CI, 1.4–11.7) for hyperthyroidism, and 1.5 (95% CI, 0.4–5.4) for hypothyroidism. The RR associated with any thyroid disease was 8.7 (95% CI, 5.1–14.8). Subjects reporting a history of thyroid disease in first-degree

Table 2 Relative risks (and 95% CIs)[a] of thyroid cancer in all cancers and papillary, follicular and mixed papillary/follicular cancers according to selected benign thyroid diseases (Italy, 1986–1992)

	Cases		Controls	Relative risks (95% CI)	
	All	Papillary, follicular, mixed		All	Papillary/follicular
Thyroiditis					
No	394	338	614	1[b]	1[b]
Yes	5	5	3	2.8 (0.6–2.4)	3.7 (0.8–16.3)
Adenoma					
No	365	309	615	1[b]	1[b]
Yes	34	34	2	27.1 (6.5–111.9)	31.6 (7.6–131.3)
Goiter					
No	366	314	610	1[b]	1[b]
Yes	33	29	7	8.2 (3.5–19.1)	7.9 (3.3–18.6)
Hyperthyroidism					
No	383	328	612	1[b]	1[b]
Yes	16	15	5	3.8 (1.4–10.9)	4.0 (1.4–11.7)
Hypothyroidism					
No	393	338	612	1[b]	1[b]
Yes	6	5	5	1.5 (0.4–5.1)	1.5 (0.4–5.4)
Other thyroid diseases					
No	396	340	615	1[b]	1[b]
Yes	3	3	2	2.6 (0.4–16.3)	3.1 (0.5–20.4)
Any thyroid disease					
No	312	262	596	1[b]	1[b]
Yes	87	81	21	7.7 (4.6–12.8)	8.7 (5.1–14.8)
Family history of thyroid disease					
No	336	286	558	1[b]	1[b]
Yes	63	57	59	1.6 (1.1–2.4)	1.7 (1.1–2.5)
Residence in endemic goiter areas					
Never	345	293	555	1[b]	1[b]
<20 yr	22	21	28	1.3 (0.7–2.4)	1.4 (0.7–2.6)
≥20 yr	32	29	34	1.6 (1.0–2.8)	1.8 (1.0–3.1)
χ^2 trend[a]				3.71[c]	5.15[c]

[a] Estimates from multiple logistic regression equations including terms for age, sex, years of education, smoking habits, body mass index, family history of benign thyroid disease, residence in endemic goiter area, and exposure to ionizing radiation.
[b] Reference category.
[c] $P < 0.05$.

relatives had a RR of thyroid cancer of 1.7 (95% CI, 1.1–2.5). The RR for having resided in endemic goiter areas for <20 years was 1.4, and 1.8 for 20 or more years. The trend in risk with duration was significant.

Table 3 shows the same variables in separate strata of sex only in papillary, follicular, and mixed papillary/follicular hystological types. Women more frequently reported a history of adenoma and goiter. Among males, however, only one control reported previous episodes of any thyroid disease. Percentages for any thyroid disease in men and women were 18.6 and 35.4% among cases and 0.5 and 4.7% among controls, respectively. Since among males only cases but no controls reported previous episodes of goiter, hyperthyroidism, hypothyroidism, and other unspecified thyroid diseases, the corresponding RR was not estimated. The RR for thyroiditis was 5.7 in males and 3.9 in females; the RR for adenoma was 18.3 in males and 49.2 in females. For goiter the RR was 6.1 in females. The risk estimates for any thyroid disease were 74.0 in males (based on 13 cases and only 1 control) and 6.7 in females. In males no significant association emerged for having resided in an endemic goiter area, but a direct trend in risk was apparent in females, with a RR of 1.6 for a period of <20 years and of 2.2 for a period of 20 or more years.

Corresponding analyses in separate strata of age are given in Table 4. For all diseases considered, there was a systematic tendency for the associations to be stronger at younger age. Thus, the RRs for history of adenoma were 42.2 below age 50 and 27.2 at age 50 or over, those for goiter were 30.6 and 3.8, and those for hyperthyroidism were 16.1 and 1.3, respectively. Consequently, the risk estimates for any thyroid disease were 10.2 in subjects below age 50 and 7.1 in those aged 50 years or older. Likewise, the association with residence in endemic goiter areas was somewhat stronger in subjects below 50 years, with an RR of 2.5 for a period of 20 or more years, whereas the corresponding RR was 1.1 in subjects aged 50 or more.

The RRs for previous benign thyroid diseases in relation to the two most frequent histotypes (papillary and follicular carcinomas) separately are shown in Table 5. The RR associated to history of adenoma was 26.8 for papillary and 74.4 for follicular carcinoma. For history of goiter the estimates were 8.5 for papillary and 7.6 for follicular, respectively, and for any thyroid disease, 8.5 and 12.9, respectively. Residence in an area of goiter endemicity for 20 or more years was associated to a RR of 1.7 for papillary carcinoma and 1.9 for follicular carcinoma.

Table 3 RRs and 95% CIs[a] of thyroid cancer[b] according to history of selected benign thyroid diseases in separate strata of sex (Italy, 1986–1992)

	Males				Females			
	Cases	Controls	RR	(95% CI)	Cases	Controls	RR	(95% CI)
Thyroiditis								
No	82	189		1[c]	256	425		1[c]
Yes	1	1	5.7	(0.3–115.1)	4	2	3.9	(0.7–23.1)
Adenoma								
No	79	189		1[c]	230	426		1[c]
Yes	4	1	18.3	(1.5–230.1)	30	1	49.2	(7.6–318.7).
Goiter								
No	78	190		1[c]	236	420		1[c]
Yes	5				24	7	6.1	(2.4–15.1)
Hyperthyroidism								
No	81	190		1[c]	247	422		1[c]
Yes	2				13	5	2.8	(0.9–8.3)
Hypothyroidism								
No	83	190		1[c]	255	422		1[c]
Yes					5	5	1.5	(0.4–5.5)
Other thyroid diseases								
No	82	190		1[c]	258	425		1[c]
Yes	1				2	2	1.4	(0.2–11.1)
Any thyroid disease								
No	70	189		1[c]	192	408		1[c]
Yes	13	1	74.0	(8.1–675.6)	68	19	6.7	(3.8–11.8)
Residence in endemic goiter areas								
Never	76	173		1[c]	217	382		1[c]
<20 years	2	5	0.9	(0.1–5.2)	19	23	1.6	(0.8–3.2)
≥20 years	5	12	1.1	(0.3–3.8)	24	22	2.2	(1.2–4.3)
χ^2 trend[a]				0.02				7.33[d]

[a] Estimates from multiple logistic regression equations including terms for age, sex, years of education, smoking habits, body mass index, family history of benign thyroid disease, residence in endemic goiter area, and exposure to ionizing radiation.
[b] Papillary, follicular, and mixed papillary/follcular cancers only.
[c] Reference category.
[d] $P < 0.05$.

An analysis of the time interval between the diagnosis of the benign condition and the tumor is shown in Table 6 for goiter, hyperthyroidism, and for any thyroid disease. The risk was somewhat higher for a previous benign condition diagnosed <10 years in the past, compared to 10 or more years, for goiter and any thyroid disease, but not for hyperthyroidism. Still, the RR were 5.9 for goiter, 4.3 for hyperthyroidism, and 6.4 for any thyroid disease diagnosed since 10 years or more.

Discussion

This study confirms and further quantifies the presence of a consistent association between previous episodes of various benign thyroid diseases, including thyroiditis, thyroid adenoma, goiter, hyperthyroidism, hypothyroidism, and other unspecified benign thyroid diseases, and the risk of thyroid cancer. The associations were stronger for adenoma and goiter than for other diseases. An association of borderline significance also emerged for residence in endemic goiter areas. In this data set, hypothyroidism was not significantly associated to an increased risk of thyroid cancer. Family history of thyroid disease was also an indicator of subsequent thyroid cancer risk. There was a suggestion that some risk factors play a more important role in females and in individuals younger than 50 years.

The prevalence of benign thyroid diseases in males was too low in this data set to compute reliable estimates. More definite comparison with the pattern in females is hence prevented. Still, the apparently higher risk estimates for adenoma in females can be explained by possible differences in the hormonal correlates of thyroid carcinogenesis in the two sexes (16). The different pattern of the disease between subjects ages <50 years and 50 or older can offer some explanation in the different pathological profile of the disease in older subjects.

Problems of bias and misclassification have to be considered in these results. While selection bias is unlikely to have affected recruitment of cases and controls in this study, more concern may arise about information bias, as some differential recall bias between cases and controls is plausible. The presence of some recall bias is also indirectly supported by the observation of an association for a number of distinct thyroid conditions. Furthermore, in women, who may tend to be more health conscious than men and are more frequently affected by thyroid disorders and other hormone-related conditions, this bias may have been even larger and hence explain at least part of the difference between sexes.

A diagnostic ascertainment bias may have been present particularly in younger subjects because of a more intensive search for thyroid nodules than was done in older subjects. This may stem both from age *per se* (more active medical surveillance on younger individuals), and from a

Table 4 RR and 95% CI[a] of thyroid cancer[b] according to history of selected benign thyroid disease in separate strata of age (Italy, 1986–1992)

	<50 yr				≥50 yr			
	Cases	Controls	RR	(95% CI)	Cases	Controls	RR	(95% CI)
Thyroiditis								
No	208	359		1[c]	130	255		1[c]
Yes	4	3	2.8	(0.6–13.9)	1			
Adenoma								
No	191	361		1[c]	118	254		1[c]
Yes	21	1	42.2	(5.9–302.1)	13	1	27.2	(3.3–223.6)
Goiter								
No	195	361		1[c]	119	249		1[c]
Yes	17	1	30.6	(4.1–228.4)	12	6	3.8	(1.3–11.1)
Hyperthyroidism								
No	201	361		1[c]	127	251		1[c]
Yes	11	1	16.1	(2.2–116.1)	4	4	1.3	(0.3–6.0)
Hypothyroidism								
No	209	357		1[c]	129	255		1[c]
Yes	3	5	0.8	(0.2–3.4)	2			
Other thyroid diseases								
No	210	361		1[c]	130	254		1[c]
Yes	2	1	2.8	(0.2–35.8)	1	1	3.3	(0.2–65.2)
Any thyroid disease								
No	160	351		1[c]	102	246		1[c]
Yes	52	11	10.2	(5.0–20.8)	29	9	7.1	(3.1–16.4)
Residence in endemic goiter areas								
Never	179	328		1[c]	114	227		1[c]
<20 years	16	21	1.3	(0.6–2.7)	5	7	1.1	(0.3–3.9)
≥20 years	17	13	2.5	(1.1–5.4)	12	21	1.1	(0.4–2.6)
χ^2 trend[a]				5.32[d]				0.11

[a] Estimates from multiple logistic regression equations including terms for age, sex, years of education, smoking habits, body mass index, family history of benign thyroid disease, residence in endemic goiter area, and exposure to ionizing radiation.
[b] Papillary, follicular, and mixed papillary/follicular cancers only.
[c] Reference category.
[d] $P < 0.05$.

period effect (improvement of diagnostic procedures in the more recent years). Likewise, thyroid nodules and other thyroid conditions may have called for closer medical surveillance in subjects affected, increasing their likelihood to have a thyroid cancer diagnosed. Thus, accuracy in search and diagnosis of early thyroid neoplasms may be influenced by prior thyroid disease events. The incidental finding of a thyroid carcinoma during operation for benign thyroid disease is unlikely to have influenced the associations observed because screening or intensive search for thyroid cancer is not performed in Italy, at least not in the areas where the study was conducted. Therefore, thyroid carcinomas for which hospitalization and surgery are required are, in general, at relatively more advanced stages than in the United States or in Northern Europe, and goiter remains an unusual indication for thyroid surgery.

An association with family history of thyroid disease was observed. Results from most other works on family history of thyroid diseases and thyroid cancer indicate an excess risk (7, 8, 11), although the results are not totally consistent (10). It is possible that also for this variable, some recall bias explains part of the association observed.

An increased risk for residence in endemic goiter areas emerged in a study from Switzerland, where areas of goiter endemicity were highly prevalent in the past (7). Also in this data set there was an indication of some association, although it was less strong, and the risk estimates were reduced after allowance for history of benign thyroid disease. It is in any case not surprising that the association is moderate in areas where past goiter prevalence was relatively low.

Our results do not show important differences between the impact of thyroid diseases on the two most frequent histological types. Still, risk estimates of papillary thyroid cancer, apparently lower than those of follicular cancer, were found for adenoma.

Because of the small numbers of follicular thyroid cancers in most developed areas and the difficulties in histological classification, there are scant epidemiological data about the differences according to histological types. In a study on American women (4) the risk estimates for history of goiter were 6.9 for papillary and 17.0 for follicular carcinoma. Problems of classification have to be considered, since the criteria for diagnosis have varied across time periods, and substantial variation between observers has been documented (3). On the other hand, an absence of major differences in risk between the two histological types is conceivable, since the increased proportion of papillary carcinomas (*i.e.*, the earliest phase of thyroid carcinogenesis) during the last few decades is in part explainable in terms of diagnostic anticipation (3, 17).

Table 5 RRs and 95% CIs[a] of thyroid cancer for previous benign thyroid disease in papillary and follicular thyroid cancers, separately (Italy, 1986–1992)

	Papillary[b]			Follicular		
	Cases	RR	(95% CI)	Cases	RR	(95% CI)
Thyroiditis						
No	269		1[c]	69		1[b]
Yes	5	4.5	(1.0–20.0)			
Adenoma						
No	252		1[c]	57		1[b]
Yes	22	26.8	(6.7–107.5)	12	74.4	(15.2–363.4)
Goiter						
No	251		1[c]	63		1[b]
Yes	23	8.5	(3.5–20.7)	6	7.6	(2.3–24.9)
Hyperthyroidism						
No	262		1[c]	66		1[b]
Yes	12	4.7	(1.6–13.9)	3	4.9	(1.1–22.1)
Hypothyroidism						
No	269		1[c]	69		1[b]
Yes	5	2.3	(0.6–8.4)			
Other thyroid diseases						
No	271		1[c]	69		1[b]
Yes	3	4.4	(0.6–29.5)			
Any thyroid disease						
No	213		1[c]	49		1[b]
Yes	61	8.5	(4.9–14.8)	20	12.9	(6.1–27.2)
Residence in endemic goiter areas						
Never	237		1[c]	56		1[b]
<20 years	16	1.3	(0.7–2.5)	5	1.9	(0.6–6.1)
≥20 years	21	1.7	(1.0–3.1)	8	1.9	(0.7–5.3)
χ^2 trend[a]			3.52			2.34

[a] Estimates from multiple logistic regression equations including terms for age, sex, years of education, smoking habits, body mass index, family history of benign thyroid disease, residence in endemic goiter area, and exposure to ionizing radiation.
[b] Papillary cancers include also mixed papillary/follicular cancers.
[c] Reference category.

Table 6 Relative risks (and 95% CIs)[a] of thyroid cancer[b] according to time since diagnosis of selected benign conditions (Italy, 1986–1992)

Time since diagnosis for	Cases	Controls	RR	(95% CI)[b]
Goiter				
<10 yr	9	1	22.6	11(2.9–173.6)
≥10 yr	20	6	5.9	(2.3–15.3)
Hyperthyroidism				
<10 yr	10	3	4.2	(1.1–16.3)
≥10 yr	5	2	4.3	(0.8–22.9)
Any thyroid disease				
<10 yr	41	8	11.3	(5.1–25.0)
≥10 yr	40	13	6.6	(3.4–12.8)

[a] Estimates from multiple logistic regression equations including terms for age, sex, and years of education.
[b] Papillary, follicular, and mixed papillary/follicular cancers only.
[c] Reference category is no diagnosis of the disease.

Although the proportions of thyroid cancer cases attributable to most single thyroid disease are modest, the percentages are greater for adenoma and goiter, each of which is responsible for about 8% of thyroid cancer cases. The proportion attributable to any benign thyroid disease was approximately 20% in this Italian population. These estimates confirm that history of thyroid disease is a relevant indicator of subsequent thyroid cancer risk in areas at relatively low prevalence of goiter and other thyroid diseases.

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