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Family history of benign thyroid disease and cancer and risk of thyroid cancer

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Abstract

In a population-based study of 313 case-control pairs in Kuwait, we evaluated whether a family history of benign thyroid disease (BTD) and thyroid or other cancers was associated with an increased risk of thyroid cancer, the second most common neoplasm among women in this and several other Arab countries in the Gulf region. Family history of BTD was reported by 78 (24.9%) cases and 40 (12.8%) controls in 132 and 57 relatives, respectively. There was an approximately 2-fold increased risk of thyroid cancer in individuals who had a mother (Odds Ratio (OR) = 2.3; 95% Confidence Intervals (95% CI): 1.1–5.1), sister(s) (OR = 2.6; 95% CI: 1.3–5.3) or aunt(s) (OR = 2.1; 95% CI: 0.9–5.3) with BTD; there was also a significant trend in increasing risk with an increasing number of affected female relatives ($P < 0.0001$). Stratification by age at diagnosis of the case showed that individuals aged $\leqslant 35$ years, who had an affected first- or second/third-degree relative(s), had an approximately 3-fold increased risk of the cancer. Family history of thyroid cancer was reported by 9 (2.9%) cases in 13 relatives (11 females, 2 males) and by 3 controls in 3 relatives (all females) (OR = 3.0; 95% CI: 0.8–11.1). The OR for all hormone-related cancers combined was 1.5 (95% CI: 0.8–2.6). There was no clear association with family history of breast or any other common cancer. Our data suggest that a family history of BTD is associated with an increased risk of thyroid cancer, and point to the role of familial susceptibility to BTD and thyroid cancer in the Kuwaiti population.

Keywords: Family history; Familial clustering; Benign thyroid disease; Thyroid cancer; Case-control study; Kuwait

1. Introduction

Thyroid cancer and the large majority of benign thyroid diseases (BTD) (e.g., nodule/adenoma, non-endemic goitre, hypo- and hyperthyroidism, Graves disease, thyroiditis) occur 3–5 times more frequently among women, and this female predominance, greatest during reproductive ages, is observed in all geographical areas and ethnic groups. Evidence from epidemiological and laboratory studies suggest that reproductive factors and patterns may influence, or contribute to, the risk of BTD and thyroid cancer in women [1,2]. Exposure to high-dose ionising radiation, particularly in childhood and adolescence, and previous hyperplastic thyroid disease (i.e. nodule/adenoma, goitre) are the two well-established risk factors for thyroid cancer [3–5].

Among the four primary histological types of thyroid cancer (papillary, follicular, anaplastic, and medullary) approximately 25% of medullary cancer is of a familial form that is inherited in an autosomal dominant pattern; which can occur alone or as part of a multiple endocrine neoplasia (MEN) syndrome [6]. Although there are reports of familial clustering of thyroid cancer and some evidence from case–control studies of an elevated risk associated with a family history of BTD or cancer, no clear pattern of genetic predisposition has been demonstrated for the most common papillary cancer (including mixed papillary/follicular variant),

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which accounts for between 50–80% of cases, or for sporadic medullary cancer.

Thyroid cancer is a relatively rare neoplasm; in most populations, it accounts for approximately 1–6% of all cancers in females and <2% in males; the age-standardised incidence rates (per 100 000) vary from approximately 2–10 in females and 1–4 in males [7]. Since the late 1970s, thyroid cancer has consistently been the second most commonly recorded neoplasm (after breast) among Kuwaiti women. During the period of 1997–2001, it accounted for 9.0% of all cancers among Kuwaiti and 6.5% among non-Kuwaiti (expatriate) women. The average annual age-standardised incidence rate (per 100 000) was 8.3 in Kuwaiti and 4.7 in non-Kuwaiti women. Similarly high relative frequency and rates of thyroid cancer among women have also been reported from other Arab countries in the Gulf region (Oman, Qatar, Saudi Arabia, United Arab Emirates) [5].

We conducted a population-based case-control study to examine the major aetiological hypotheses for thyroid cancer. In this report, we present an analysis of the association between family history of BTD and thyroid or other cancers and risk of thyroid cancer.

2. Patients and methods

The study population and methods are described in detail elsewhere [2]. In brief, the study was conducted at the Kuwait Cancer Control Centre (KCCC), which is the only specialised cancer treatment and follow-up hospital in the country. A thyroid cancer clinic is held once a week at the centre for current and newly diagnosed patients for regular follow-up and consultation. A population-based cancer registry (Kuwait Cancer Registry) has been established at the centre since 1979. Thyroid cancer patients were identified through a systematic review of the records of the registry, thyroid clinic, and the KCCC. Patients were included in the study if thyroid cancer had occurred as the first primary cancer and if they were alive, aged ⩽70 years, and resident in Kuwait during the data collection period (1 May 1998–30 June 1999). The district of residence was determined for each thyroid cancer patient and the local primary health care clinic was visited to select a suitable matched control subject. Kuwait has a distinctive network of primary care clinics in terms of its accessibility and the wide range of services offered at these clinics; and all residents in the district have an equal opportunity to visit the local clinic [2]. One control subject was individually matched to each thyroid cancer patient, based on the year of birth (within 3 years), gender, nationality, and district of residence. Subjects were considered eligible to serve as controls if they were visiting the primary care clinic for minor complaints, or accompanying such persons, or visiting for any other purpose. The study finally included 313 patients with thyroid cancer and a similar number of individually matched control subjects.

2.1. Assessment of exposure and analysis

All cases and controls included in the study were initially contacted and interviewed in-person during the period of 1 May 1998–30 June 1999. The study protocol was approved by the relevant committees of Kuwait University and Kuwait Foundation for the Advancement of Sciences. Informed consent was obtained from all participants. A bilingual female interviewer, proficient in Arabic and English languages, and not aware of the epidemiology of thyroid cancer, obtained information from all the participants. The data were collected using a structured questionnaire which included information on: (i) sociodemographic characteristics; (ii) gynaecological and reproductive history; (iii) personal medical history (including BTD); (iv) family history (parental consanguinity, history of BTD, thyroid and other cancers); (v) habitual diet (frequency of consumption of 13 dietary items); and (vi) clinical and histopathological information (abstracted from the records of the cancer registry and KCCC).

Family history of BTD was recorded if any of the participant's first- and/or second/third-degree relative(s) had been diagnosed with a hyperplastic (nodule/adenoma, goitre) and/or functional (hypo-, hyperthyroidism, thyroiditis) thyroid disorder. The participant was then specifically requested to provide such information about each of the first-degree (parents, siblings, offspring) and second/third-degree (grandparents, aunt/uncle, niece/nephew, cousins) relatives. The questionnaire was appropriately structured to assist in the recall and recording of these disorders in female and male relatives separately. The same method was used for obtaining and recording family history of thyroid and other cancers.

We used conditional logistic regression method [8] for the estimation of Odds Ratios (OR) and corresponding 95% Confidence Intervals (95% CI) of thyroid cancer according to the family history of BTD and cancer in different types of relatives. We also examined the trends in ORs according to the increasing number of relatives with BTD. A sub-analysis was conducted to determine whether the risk associated with family history of BTD differed according to the age at diagnosis of the case. The risk of thyroid cancer according to family history of thyroid and other types of cancer was also assessed. Where applicable, cancers were grouped into broad categories (such as hormone-related, gastrointestinal etc.). The 95% CI shown are based on the likelihood ratio test procedure; and the *P*-values (two-sided) for the trend in ORs are based on a χ^2 test for trend. All

data management and analyses were performed using the Statistical Package for the Social Sciences (SPSS) and STATA statistical software.

3. Results

Table 1 shows the distribution of 313 thyroid cancer patients (238 females, 75 males; gender ratio: 3.2:1) according to selected variables; 172 (55%) were Kuwaiti citizens and 141 (45%) were non-Kuwaitis. Among the latter, 70% were from Arab countries and 26% were from Southeast Asia. Most cases (74%) were diagnosed at a relatively young age (15–44 years). The average age at diagnosis (standard deviation (S.D.)) was 34.7 (11) years (range 10–65 years) in women and 39 (13.4) years (range 6–69 years) in men. There was no difference in the average age at diagnosis between Kuwaiti and non-Kuwaiti patients. Papillary carcinoma (including mixed papillary/follicular variant) was the most common histopathological type accounting for approximately 83% of all cases.

3.1. Family history of benign thyroid disease

A total of 78 (24.9%) cases and 40 (12.8%) controls reported a family history of BTD in 132 and 57 relatives, respectively. Table 2 shows the association between family history of BTD according to the type of relative and risk of thyroid cancer. There was an approximately 2-fold increased risk of thyroid cancer in individuals who had a mother (OR = 2.3; 95% CI: 1.1–5.1) or sister(s) with BTD (OR = 2.6; 95% CI: 1.3–5.3). An increased risk of similar magnitude was also observed for a history of BTD in aunt(s) (OR = 2.1; 95% CI: 0.9–5.3). For the combined categories of first- and second/third-degree female relatives, the ORs were 2.3 (95% CI: 1.3–3.8) and 2.0 (95% CI: 1.0–4.1), respectively. Overall, the OR for history of BTD in female relatives was 2.3 (95% CI: 1.5–3.7). The ORs for all types of male relatives were also raised above unity, but none reached statistical significance. There was a significant increasing trend in risk with increasing number of affected first- and second/third-degree female relatives and all relatives combined (Table 3).

When the risk associated with a family history of BTD (none, only second/third-degree relative(s) affected, first-degree relative(s) affected) was examined in relation to the age at diagnosis of the case, a statistically significant higher risk (OR of approximately 3) was found in those aged $\leqslant$35 years (Table 4). There was no association between parental consanguinity and risk of thyroid cancer (data not shown).

3.2. Family history of thyroid and other types of cancer

A total of 86 (27.5%) cases and 69 (22.0%) controls reported a family history of cancer (other than thyroid)

Table 1
Characteristics of 313 thyroid cancer patients in Kuwait

Characteristic	*n* (%)
Gender	
Female	238 (76.0)
Male	75 (24.0)
Nationality	
Kuwaiti	172 (55.0)
Non-Kuwaiti (expatriates)	141 (45.0)
Arabs[a]	71 (50.4)
Southeast Asian	37 (26.2)
Bedouin[b]	28 (19.9)
Other	5 (3.5)
Age at diagnosis (years)	
5–14	6 (1.9)
15–24	51 (16.3)
25–34	88 (28.1)
35–44	93 (29.7)
45–54	53 (16.9)
55–64	19 (6.1)
65–70	3 (1.0)
Histology	
Papillary	186 (59.4)
Papillary/follicular variant	75 (24.0)
Follicular	27 (8.6)
Medullary	3 (1.0)
Other	4 (1.3)
Unknown	18 (5.8)

[a] Arabs from Middle East and North Africa.
[b] "Stateless" Arabs resident in Kuwait.

Table 2
Risk of thyroid cancer associated with family history of benign thyroid disease[a]

Type of relative	Case/control[b]	OR (95% CI)
All relatives	78/40	2.4 (1.5–3.7)
Female relatives	72/36	2.3 (1.5–3.7)
Male relatives	14/9	1.6 (0.7–3.6)
First-degree[c]	53/27	2.1 (1.3–3.4)
First-degree female	48/23	2.3 (1.3–3.8)
Mother	24/12	2.3 (1.1–5.1)
Sister	29/11	2.6 (1.3–5.3)
Daughter	5/2	2.5 (0.5–12.9)
First-degree male	10/7	1.4 (0.5–3.8)
Father	5/1	5.0 (0.6–42.8)
Brother	7/6	1.2 (0.4–3.5)
Second/third-degree only[d]	25/13	1.9 (1.0–3.8)
Second/third-degree female only	22/11	2.0 (1.0–4.1)

[a] Based on conditional logistic regression analysis. Reference group in each analysis is subjects with no history of benign thyroid disease in that relative(s).
[b] Number of cases and controls reporting relative(s) with benign thyroid disease.
[c] Includes parents, siblings and offspring.
[d] Includes grandparents, uncle/aunt, niece/nephew and cousin.

in 111 and 94 relatives, respectively. Family history of thyroid cancer was reported by 9 (2.9%) cases in 13 relatives [mother (4) daughter (1) aunt (1) niece (4) female cousin (1) father (1) uncle (1)] and 3 controls in 3 relatives [mother (2) female cousin (1)]. The association between family history of different type of cancer and risk of thyroid cancer is shown in Table 5. A positive, but statistically non-significant, association was found with a family history of thyroid (OR = 3.0; 95% CI: 0.8–11.1) and lung cancer (OR = 2.8; 95% CI: 0.9–8.6). The ORs for other common cancers, including those of the breast, gastrointestinal and hepatobiliary system, and lymphoid/haematopoietic tissue, were close to unity; the OR for all hormone-related cancers combined was 1.5 (95% CI: 0.8–2.6). Overall, for all cancers combined, there was a modest increase in risk with a family history of cancer (OR = 1.4; 95% CI: 1.0–2.0). Table 6 shows the association between family history of cancer (other than thyroid) according to the type of relative and risk of thyroid cancer. There was no difference among cases and controls with regard to history of cancer in female relatives (OR = 0.9; 95% CI: 0.6–1.5). There was an approximately 2-fold increased risk with history of cancer in first-degree male relatives (OR = 2.3; 95% CI: 1.1–4.4) which was essentially due to an excess of lung cancer.

Table 3
Risk of thyroid cancer associated with number of relatives with benign thyroid disease[a]

No. of relatives	Case/control[b]	OR (95% CI)	P-trend[c]
All relatives			
0	235/273	1.0 –	<0.0001
1	49/32	1.9 (1.1–3.1)	
2	16/3	6.0 (1.7–20.8)	
⩾3	13/5	2.9 (1.0–8.3)	
Female relatives			
0	241/277	1.0 –	<0.0001
1	47/29	1.9 (1.2–3.2)	
2	16/4	4.5 (1.5–13.5)	
⩾3	9/3	3.4 (0.9–12.7)	
Male relatives			
0	299/304	1.0 –	0.23
1	11/8	1.4 (0.6–3.4)	
2	3/1	3.0 (0.3–28.8)	
First-degree[d]			
0	260/286	1.0 –	<0.01
1	38/22	1.8 (1.1–3.1)	
⩾2	15/5	3.3 (1.2–9.2)	
First-degree female			
0	265/290	1.0 –	<0.01
1	37/20	2.0 (1.1–3.5)	
⩾2	11/3	4.1 (1.1–14.9)	
Second/third-degree[e]			
0	281/296	1.0 –	<0.01
1	15/13	1.2 (0.6–2.6)	
⩾2	17/4	4.3 (1.4–12.8)	
Second/third-degree female			
0	283/297	1.0 –	<0.01
1	14/13	1.1 (0.5–2.4)	
⩾2	16/3	5.4 (1.6–18.4)	

[a] Based on conditional logistic regression analysis.
[b] Number of cases and controls reporting relative(s) with benign thyroid disease.
[c] Linear trend using categories as ordinal variables.
[d] Includes parents, siblings and offspring.
[e] Includes grandparents, uncle/aunt, niece/nephew and cousin.

4. Discussion

This population-based case-control study provides detailed information on the family history of BTD and confirms that there is an association between a family history of BTD and risk of thyroid cancer. The indication is that risk of thyroid cancer is increased (by approximately 2-fold) for persons with a mother, sister(s), or aunt(s) with a history of BTD, and there is a clear upward trend in risk with an increasing number of affected female relatives. Previous case–control studies (mostly from Europe and the United States of America (USA) and one from Asia) collected little information (usually as a single parameter/variable) on family history of BTD, but all have reported a positive association with thyroid cancer (Table 7). In the only study with prospectively collected information, including 196 incident cases of thyroid cancer, Iribarren and colleagues [19] reported an approximately 2-fold increased

Table 4
Risk of thyroid cancer (and 95% Confidence Interval) according to benign thyroid disease reported in first- and second/third-degree relatives by age of case or control[a]

Age of case/control[b] (year)	No family history of benign thyroid disease	Family history in second/third-degree relatives only	Family history in first-degree relatives
⩽35	1.0 (120, 146)[c]	3.0 (1.2–7.4) (17, 7)	2.9 (1.5–5.8) (31, 13)
>35	1.0 (115, 127)	1.6 (0.5–4.7) (8, 6)	1.8 (0.9–3.7) (22, 14)

[a] Based on unconditional logistic regression analysis, adjusted for age, gender and nationality. Reference group in each analysis is subjects with no family history of benign thyroid disease in that age group.
[b] Age at diagnosis of thyroid cancer (cases)/pseudo-diagnosis (controls).
[c] Numbers of cases and controls shown in parentheses.

risk with a family history of thyroid disease (Relative Risk (RR) = 2.2; 95% CI: 1.2–4.1).

Although the large majority of non-medullary forms of thyroid cancer (which account for approximately 97% of all cases) are thought to be sporadic, several studies have reported an approximate 4- to 9-fold increased risk associated with a positive family history of thyroid cancer; the proportion of thyroid cancer patients with at least one similarly affected relative has varied between 3–6% [14,17,20–29]. In an analysis of the national cancer database in the USA and other large studies, it was found that familial non-medullary thyroid cancer accounts for approximately 4–6% of patients with papillary thyroid cancer [29–31]. In the nationwide Swedish Family Cancer Database, thyroid cancer had the highest familial relative risk (FRR = 9.1; 95% CI: 5.7–13.0) than any other cancer and the risk was approximately twice as high for male as for female offspring [32]; a recent analysis of histopathology-specific cancers showed that papillary adenocarcinoma had one of the highest standardised incidence ratio (SIR = 4.2) [33]. Our results were marginally lower than previous studies, with a 3-fold increased risk of thyroid cancer associated with a family history of the disease; and approximately 3% of the cases had at least one affected relative.

Table 5
Risk of thyroid cancer associated with family history of cancer at different sites[a]

Type of cancer (ICD-10 code)	Case/Control[b]	OR (95% CI)
Thyroid (C73)	9/3	3.0 (0.8–11.1)
Lung (C34)	11/4	2.8 (0.9–8.6)
Bone (C40-41)	4/2	2.0 (0.4–10.9)
Uterus and ovary (C55-56)	4/2	2.0 (0.4–10.9)
Breast (C50)	19/16	1.2 (0.6–2.4)
Head and neck (C76.0)	6/5	1.2 (0.4–3.9)
Gastrointestinal (C15-18)	11/11	1.0 (0.4–2.3)
Hepatobiliary (C22-25)	8/8	1.0 (0.5–2.7)
Lymphoma/leukaemia (C81-85, C91-95)	15/16	0.9 (0.5–1.9)
Urinary tract (C64-68)	4/6	0.7 (0.2–2.4)
Other	7/11	0.6 (0.2–1.6)
Hormone-related cancers[c]	33/24	1.5 (0.8–2.6)
All sites except thyroid	86/69	1.4 (0.9–2.0)
All sites	91/72	1.4 (1.0–2.0)

ICD, International Classification of Diseases.

[a] Based on conditional logistic regression analysis. Reference group in each analysis is subjects with no family history of cancer at that site(s).

[b] Number of cases and controls reporting relative(s) with cancer.

[c] Includes cancer of the breast, endometrium, ovary, testis, prostate and thyroid.

Table 6
Risk of thyroid cancer associated with family history of cancer (other than thyroid)[a]

Type of relative	Case/control[b]	OR (95% CI)
All relatives	86/69	1.4 (0.9–2.0)
Female relatives	42/44	0.9 (0.6–1.5)
Male relatives	53/37	1.5 (1.0–2.3)
First-degree[c]	42/35	1.2 (0.8–2.0)
First-degree female	15/23	0.7 (0.3–1.3)
First-degree male	29/14	2.3 (1.1–4.4)
Second/third-degree[d]	51/38	1.4 (0.9–2.2)
Second/third-degree female	29/23	1.3 (0.7–2.3)
Second/third-degree male	26/24	1.1 (0.6–2.0)

[a] Based on conditional logistic regression analysis. Reference group in each analysis is subjects with no family history of cancer in that relative(s).

[b] Number of cases and controls reporting relative(s) with cancer.

[c] Includes parents, siblings and offspring.

[d] Includes grandparents, uncle/aunt, niece/nephew and cousin.

The high frequency of thyroid cancer (and possibly BTD) in the Kuwaiti population provides a unique opportunity to study the aetiology of this disease. Familial aggregation of thyroid cancer (as well as BTD) could be ascribed to several factors, such as incidence of the disease in the general population, prevalence of BTD, genetic predisposition, exposure, or increased susceptibility, to shared environmental factors, gene-environment interaction, and socioeconomic/cultural factors. The likelihood of identifying affected relatives depends on the study design, family size, the age distribution and survival of the relatives, and their degree of relationship with the index subject [34]. Clustering of BTD and thyroid cancer among women in a family may reflect exposure to similar reproductive risk factors and patterns rather than the presence of an inherited mutation. Conversely, absence of family history does not exclude genetic predisposition, and a number of genes, in particular *RET*, have been implicated in sporadic papillary thyroid cancer [35]. Kuwait and several other Arab countries in the Gulf region, with relatively high frequency and rates of thyroid cancer, also have high birth and total fertility rates (approximately 5–6 children per woman). For example, in 1998, the total fertility rates in Kuwait, Oman, Qatar, Saudi Arabia and the United Arab Emirates were 5.2, 6.5, 5.1, 5.0 and 4.9, respectively [36]. Other reproductive health patterns in these countries include high prevalence of consanguinity, young age at first marriage and childbearing, short birth intervals, and older ages at last birth [37]. It is plausible that this reproductive pattern and culture may, in part, account for the high frequency and familial aggregation of BTD and thyroid cancer among Kuwaiti women. Additional environmental causes of thyroid disease in these populations may include over-use of X-rays for diagnostic purposes, iodine levels and dietary habits [5].

A relationship between thyroid cancer and a family history of other neoplasms has not been clearly established. In an analysis of the Utah Population Database, Goldgar and colleagues [24] found an excess of breast

Table 7
Summary of findings of case–control studies of thyroid cancer: association with family history of benign thyroid disease

Study location [reference]	No. of cases	Variable	Type of relatives(s)	OR (95% CI)
Europe				
Switzerland [9]	86	Benign thyroid disease	First-degree	3.9 (2.1–7.1)
Italy [10]	399	Thyroid disease	First-degree	1.6 (1.1–2.4)
South-eastern Sweden [11]	93	Goitre	All relatives	2.0 (1.1–3.6)
Northern Sweden [12]	171	Goitre	Mother	1.5 (0.8–3.0)
			Sister/brother	2.4 (1.1–5.3)
Yugoslavia [13]	100	Goitre	Mother	8.0 (2.3–27.4)
USA				
California [14]	153	Thyroid hyperplasia	Mother	2.0 (0.9–4.2)
Hawaii [15]	140	Benign thyroid disease	All relatives	1.7 (1.0–3.0)
Washington [16]	410	Benign thyroid disease	First-degree female	1.8 (1.3–2.5)
			Second-degree female	2.8 (1.7–4.5)
California [17]	292	Thyroid disease	First-degree	2.0 (1.1–3.7)
Asia				
Shanghai, China [18]	207	Thyroid disease	Mother	3.0 (1.0–10.6)
			Sister	4.3 (1.4–17.4)
Kuwait [present study]	313	Benign thyroid disease	Mother	2.3 (1.1–5.1)
			Sister	2.6 (1.3–5.3)
			Aunt	2.1 (0.9–5.3)
			First-degree female	2.3 (1.3–3.8)
			Second/third-degree female only	2.0 (1.0–4.1)

USA, United States of America.

cancer in first-degree relatives of thyroid cancer patients (RR = 1.7; 95% CI: 1.3–2.2). Similar findings were also reported in a recent study from Canada Incidence rate ratio (IRR) = 1.7; 95% CI: 1.0–3.0) [28]. A case–control study from Serbia found excesses of cancers of the breast, uterus and stomach among first- and second-degree relatives of thyroid cancer patients [38]. However, other studies did not show any such association [15,17,18,21,25,39]. In our study, in which we obtained a more detailed family history by collecting information on cancer site and type of relative, there was an overall modest excess of cancer among relatives of thyroid cancer patients (due primarily to an excess of lung cancer in first-degree male relatives); there was no clear association with breast or any other common cancers.

Our study is subject to a number of limitations, particularly the potential for recall bias since family history data were based on self-reported information from the participants. There is also the possibility of information bias between cases and controls, as cases may have a better recollection and knowledge of their family history of BTD and cancer; and reports in first-degree relatives are generally considered to be more reliable than those in second/third-degree relatives, as accuracy may vary by site of cancer and by closeness of the relationship to the affected person [40,41]. Selection bias is unlikely to have affected our results as each case/control pair was appropriately matched and drawn from the same residential district and overall participation rates were high among cases and controls [2]. Our questionnaire was appropriately structured to assist in recall and recording of these events in each type of first- and second/third-degree relative. There was also little or no difference among cases and controls in the reporting of several apparently unrelated cancer sites. Although in this study we collected more detailed information on family history of thyroid disease than many previous studies, the lack of information on the number of non-affected relatives is a limitation in this and the previous studies.

In summary, our study of a Middle Eastern population with relatively high incidence of thyroid cancer (and possibly BTD) suggests that a family history of BTD is associated with an increased risk of thyroid cancer, with an increasing risk with increasing number of affected first-degree female relatives. Our results also indicate that a family history of thyroid cancer is associated with the risk of developing the disease. These findings highlight the importance of obtaining a family history of BTD and cancer from patients with thyroid cancer, as genetic factors may be important in a small proportion of these patients.

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