Diabetes and Thyroid Cancer Risk in the National Institutes of Health-AARP Diet and Health Study

Briseis Aschebrook-Kilfoy,[1] Mona M. Sabra,[2] Alina Brenner,[3] Steven C. Moore,[4]
Elaine Ron,[3] Arthur Schatzkin,[4] Albert Hollenbeck,[5] and Mary H. Ward[1]

Background: We hypothesized that diabetes may play a role in thyroid cancer risk due to the parallel secular rise in diabetes prevalence and morbidity in the United States, the higher prevalence of thyroid disorders among diabetics compared with the general population, and the potential roles of metabolic syndrome, obesity, and diabetes as precipitating factors in cancer development.

Methods: We assessed the association between self-reported diabetes and the risk of differentiated thyroid cancer in the NIH-AARP Diet and Health Study, a prospective cohort of 200,556 women and 295,992 men, 50–71 years of age, in 1995–1996. Diabetes status and information on potential confounders was ascertained using a self-administered questionnaire. During an average of 10 years of follow-up, 585 thyroid cancer cases were identified. Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for thyroid cancer and thyroid cancer subtypes in men and women according to diabetes status.

Results: Nine percent of the total baseline cohort reported a history of diabetes (7% of women, 10% of men). A nonsignificant 25% increase in thyroid cancer risk (HR = 1.25; 95% CI: 0.95–1.64) was associated with diabetes. Among women, the risk was significantly increased (HR = 1.46, 95% CI: 1.01–2.10). The risk was not elevated among men (HR = 1.04, 95% CI: 0.69–1.58). In this cohort, diabetic women with differentiated thyroid cancer were at somewhat higher risk of follicular thyroid cancer (HR = 1.92; 95% CI: 0.86–4.27) than papillary thyroid cancer (HR = 1.25; 95% CI: 0.80–1.97).

Conclusion: This study lends support to the hypothesis that diabetes increases the risk of differentiated thyroid cancer.

Introduction

DURING THE PAST SEVERAL DECADES, an increasing incidence of thyroid cancer has been observed in several countries, including the United States (1,2), although the factors responsible for this rapid increase remain largely unknown (1). Certainly, increased prevalence of early-staged thyroid cancer can be partly attributed to enhanced detection and increased use of neck ultrasounds and ultrasound-guided fine needle aspiration biopsies in the management of thyroid nodules. Nevertheless, it cannot explain the rise in disease prevalence preceding the widespread use of ultrasounds in clinical settings (3) and increased prevalence of large thyroid tumors (>5 cm),

suggesting that other contributing factors may be involved (4). A parallel secular rise in diabetes prevalence and morbidity in the United States (5), a higher prevalence of thyroid disorders among diabetics compared with the general population (10.8% in diabetics compared with 6.6% in the U.S. population) (6), and the potential roles of metabolic syndrome, obesity, and diabetes as precipitating factors in cancer development suggest that diabetes may play a role in thyroid cancer risk (7–13).

Plausible biologic pathways linking diabetes to thyroid cancer risk include (i) chronic thyroid-stimulating hormone (TSH) stimulation, a known thyroid cancer risk factor, in diabetics who are susceptible to disruption in thyroid hormone homeostasis (14–20); (ii) elevated circulating

[1]Occupational and Environmental Epidemiology Branch, [3]Radiation Epidemiology Branch, and [4]Nutrition Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Rockville, Maryland.
[2]Endocrine Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, New York.
[5]Research and Strategic Analysis, AARP, Washington, District of Columbia.

insulin levels in type 2 diabetics (T2D) with insulin resistance (21); (iii) antidiabetic medication–mediated effect, either through chronic exposure of elevated circulating insulin levels or through inherent drug or drug class characteristics (e.g., Glargine [Lantus], GLP-1 agonists [Amylin (Byetta)], and Liraglutide [Victoza]) (22); (iv) concomitant increased body mass index (BMI) in the majority of diabetics, which has been associated with increased risk for malignancies in general, and thyroid cancer in particular (23–25); (v) chronic glucose and triglyceride exposure, linked recently to increased thyroid cancer risk in Metabolic Syndrome and Cancer Project (Me-Can) cohorts (8); (vi) elevated prevalence of vitamin D deficiency in diabetics, which, in epidemiological studies, is linked to increased cancer risk, although the mechanism is not yet elucidated (26,27).

Although the relationship between thyroid cancer and diabetes has been described in both case–control and cohort studies (28–39), small case numbers may have resulted in limited statistical power to detect an effect. To our knowledge, a limited number of studies have reported a statistically significant association between differentiated thyroid cancer risk and diabetes, though there have been reports of both nonsignificant positive and negative associations. In addition, previous analyses have not been stratified by histological type, which may be important as some evidence suggests that etiologic risk factors differ for papillary and follicular thyroid cancer, the two main types (40). The present study examines self-reported history of diabetes in relation to thyroid cancer risk and its variation by histologic type and gender, in the National Institutes of Health (NIH)-AARP Diet and Health Study, a large prospective cohort of men and women.

Methods

Study population

The NIH-AARP Diet and Health Study was initiated in 1995–1996 when a baseline questionnaire was mailed to 3.5 million AARP members, aged 50–71 years, residing in six U.S. states (California, Florida, Pennsylvania, New Jersey, North Carolina, and Louisiana) and two U.S. metropolitan areas (Atlanta, Georgia, and Detroit, Michigan) (41). The baseline questionnaire elicited information on usual dietary intake over the past 12 months, use of individual and multivitamin supplements, smoking history, alcohol intake, height and weight at baseline, other diet and lifestyle factors, and history of several personal and family medical conditions. A total of 617,119 persons (17.6%) returned the questionnaire, and 567,169 questionnaires were determined to have been satisfactorily completed.

We excluded those with duplicate questionnaires, those who had died or moved out of the study area before baseline, those who withdrew from the study, those who had questionnaires completed by proxy respondents, and those who had been previously found to have cancer except for non-melanoma skin cancer. After these exclusions, data for 496,548, including 295,992 men and 200,556 women, were available for the analysis.

The NIH-AARP Diet and Health Study was approved by the Special Studies Institutional Review Board of the National Cancer Institute.

Cancer ascertainment

Incident, first primary thyroid cancer cases (*International Classification of Diseases for Oncology*, Third Edition [ICD-O-3]) (42), topography code C73 were identified through December 31, 2006, via linkage of the cohort database to cancer registries of the eight original plus three additional states (Texas, Nevada, and Arizona). Thyroid cancers were classified as papillary (ICD-O-3 morphology codes 8050, 8660, 8340, 8341, 8343, 8344, and 8350) or follicular (ICD-O-3 morphology codes 8290, 8330, 8331, 8332, and 8335) type. The state cancer registries are certified by the North American Association of Central Cancer Registries as meeting the highest standard of quality (43).

Diabetes status

The medical history section of the baseline questionnaire asked about whether the study participant had ever been told by a doctor that he/she has diabetes. The question did not distinguish between type I diabetes (T1D) and T2D, and information about intake of diabetes medication was not collected. Among those included in our analysis, there were a total of 44,693 diabetics (14,766 women and 29,925 men). We did not have biochemical panels on self-reported diabetic subjects, including glucose, insulin, lipid, and HbA1c levels. Thus, in this study, we could not correlate thyroid cancer risk in diabetics with glucose control.

Statistical analysis

Person-years of follow-up for each participant accrued from the date of return of the baseline questionnaire to the date of thyroid cancer diagnosis, the date of moving out of the cancer registry ascertainment area, death, or the end of the follow-up period, December 31, 2006. Cox proportional hazards models with person-years as the underlying time metric were used to estimate hazard ratios (HR) and 95% confidence intervals (CI). The proportional hazards assumption was tested and upheld in all analyses. We present HR estimates adjusted for age and sex, as well as those from the full model with and without BMI adjustment. The full model included attained age, smoking status (never, current, former), self-reported race/ethnicity (White, Black, other), family history of any cancer (yes, no), education, and BMI, which we divided into 10 categories (16.0–18.4, 18.5–20.9, 21.0–23.4, 23.5–24.9, 25.0–26.4, 26.5–27.9, 28.0–29.9, 30.0–34.9, 35.0–39.9, and 40.0 or more, kg/m^2). The inclusion of vitamin D in the model did not result in a change and information on TSH was not available in this cohort.

We also conducted interaction analyses between diabetes and gender, median age, BMI, and educational level. We assessed multiplicative interaction by adding the relevant cross-product term to main-effects models. For all comparisons, *p*-values were two-sided and an alpha level of <0.05 indicated statistical significance.

Results

Of the 496,548 participants in our baseline analysis, 7.4% of female participants and 10.1% of male participants reported that a doctor had told them they had diabetes (Table 1). This is commensurate with CDC age-corrected diabetes prevalence in the general U.S. population (5). In this study population,

TABLE 1. MEANS AND PROPORTIONS FOR BASELINE CHARACTERISTICS OF THE NATIONAL INSTITUTES
OF HEALTH-AARP DIET AND HEALTH STUDY BASELINE COHORT BY DIABETES STATUS

Parameter	No diabetes	Diabetes	p-Values
Total (N = 496,548)	451,885	44,693	
Age (mean)	61.9	62.9	<0.01
Race (%)			
White	91.6	85.7	
Black	3.6	7.5	
Other	3.4	5.1	<0.01
Never smoker (%)	35.5	30.8	<0.01
Education, college graduate or post graduate (%)	39.2	30.8	<0.01
Vigorous physical activity, >five times per week (%)	19.5	16.0	<0.01
Energy (kcal/d)	1869 (990)	1883 (1017)	
BMI [Mean (SD)]	26.8 (4.9)	29.9 (6.0)	<0.01
Family history of cancer (%yes)	46.1	47.6	<0.01
Women (N = 200,556)	185,790	14,766	
Age (mean)	61.8	62.7	<0.01
Race (%)			
White	89.8	80.6	
Black	5.2	12.4	
Other	3.4	4.7	<0.01
Never smoker (%)	44.0	44.5	0.35
Education, college graduate or post graduate (%)	30.4	20.4	<0.01
Vigorous physical activity, >five times per week (%)	16.5	11.7	<0.01
Energy (kcal/d)	1599 (840)	1660 (975)	<0.01
BMI [Mean (SD)]	26.5 (5.8)	31.3 (7.1)	<0.01
Family history of cancer (%yes)	51.2	49.6	<0.01
Men (N = 295,992)	266,065	29,927	
Age (mean)	62.0	63.0	<0.01
Race (%)			
White	92.8	88.2	
Black	2.5	5.0	
Other	3.5	5.2	<0.01
Never smoker (%)	29.7	24.0	<0.01
Education, college graduate or post graduate (%)	45.3	35.9	<0.01
Vigorous physical activity, >five times per week (%)	21.6	18.2	<0.01
Energy (kcal/d)	2057 (1042)	1993 (1020)	<0.01
BMI [Mean (SD)]	27.1 (4.2)	29.2 (5.2)	<0.01
Family history of cancer (%yes)	47.1	45.1	<0.01

BMI, body mass index; SD, standard deviation.

the absolute risk of thyroid cancer in female diabetics was 24.5/100,000 woman-years and in male diabetics was 9.7/100,000 man-years. In non-diabetics, the absolute risk of thyroid cancer in females was 16.0/100,000 woman-years and in males was 8.8/100,000 man-years. A higher proportion of blacks and other race/ethnicity groups (Hispanic, Asian, Pacific Islander, and American Indian/Alaskan Native) were diabetic. In addition, diabetics reported lower levels of educational attainment, less vigorous physical activity, and a higher BMI. Also, diabetic men but not women tended to have a lower proportion of never smokers.

In the analysis cohort, there were 585 thyroid cancers (336 in females and 252 in males), including 412 papillary and 113 follicular type tumors. Overall, we observed no significant association for men and women combined (Table 2). However, when we evaluated thyroid cancer risk separately for men and women, we found different HR although the interaction by gender was not significant (p for heterogeneity = 0.35). Among women with diabetes, risk of thyroid cancer was 1.46 times higher (95% CI: 1.01–2.10) than that of women without diabetes, whereas the respective risk among

men was close to one (HR = 1.04; 95% CI: 0.69–1.58). Thyroid cancer risk was increased for both the papillary (HR = 1.23; 95% CI: 0.88–1.71) and follicular histologic types (HR = 1.36; 0.75–2.46), though not significantly so. The differences in risk by gender for the papillary (p for heterogeneity = 0.40) and follicular (p for heterogeneity = 0.89) types were not significant. Among women, we found a HR of 1.25 for the papillary type (95% CI: 0.80–1.97) and a HR of 1.92 for the follicular type (95% CI: 0.86–4.27).

The risk of thyroid cancer associated with diabetes was similar among those at or above/below the median age of 62.6 years, at or above/below median BMI of 27 kg/m^2, and by education (high school or fewer years of education; some college or greater years of education) in the combined study population and women and men separately (not shown).

Discussion

In this large prospective cohort of AARP members, history of self-reported diabetes was associated with a 25% increase in thyroid cancer risk. This appeared to be primarily due to a

Table 2. Self-Reported History of Diabetes and Risk of Thyroid Cancer by Histologic Type and Gender in the National Institutes of Health-AARP Diet and Health Study Baseline Cohort

	Diabetes status and risk of thyroid cancer					
	Total thyroid cancer		Papillary		Follicular	
	No	Yes	No	Yes	No	Yes
Overall						
Number of cases	525	60	371	41	100	13
Multivariate HR[a]	1.00	1.32	1.00	1.31	1.00	1.42
95% CI	(ref)	1.01–1.73		0.95–1.81		0.80–2.54
Multivariate HR[b]	1.00	1.25	1.00	1.23	1.00	1.36
95% CI	(ref)	0.95–1.64		0.88–1.71		0.75–2.46
Women						
Number of cases	302	34	226	22	49	7
Multivariate HR[a]	1.00	1.54	1.00	1.35	1.00	1.93
95% CI	(ref)	1.08–2.20		0.87–2.10		0.85–4.71
Multivariate HR[b]	1.00	1.46	1.00	1.25	1.00	1.92
95% CI	(ref)	1.01–2.10		0.80–1.97		0.86–4.27
Men						
Number of cases	226	26	145	19	51	6
Multivariate HR[a]	1.00	1.11	1.00	1.26	1.00	1.08
95% CI	(ref)	0.74–1.66		0.78–2.03		0.46–2.52
Multivariate HR[b]	1.00	1.04	1.00	1.18	1.00	1.01
95% CI	(ref)	0.69–1.58		0.73–1.93		0.43–2.39

[a]Adjusted for entry age and sex (overall).
[b]Adjusted for age, sex (overall), smoking status, race/ethnicity, family history of cancer, BMI, and education.
HR, hazard ratios; CI, confidence interval.

46% significantly increased risk of thyroid cancer among women, with only a slight change in risk observed among men. The finding of an elevated risk was observed for both papillary and follicular histologic types of thyroid cancer.

Although thyroid cancer typically occurs about three times more frequently in women than in men in the United States, rates of diabetes in men and women in the United States are similar (1,5). Nonsignificant increases in risk in women have been observed in previous epidemiologic investigations of the association between thyroid cancer and diabetes (31,36,37) as well as in men (28,32,36,38), although the association between thyroid cancer and diabetes in general has been inconsistent. A study conducted by Meinhold *et al.* of U.S. Radiologic Technologists (24) reported a relative risk of 1.34 (95% CI: 0.49–3.77) among women and no association among men (although only about 25% of the cohort are men). Similarly, Chodick *et al.* recently reported an increased risk of thyroid cancer in women (HR = 1.61; 95% CI: 0.96–2.69) but not men (HR = 0.72; 95% CI: 0.25–2.04) with T2D in an Israeli cohort (39).

There are a variety of possible biological mechanisms for the relationship between thyroid cancer and diabetes. Diabetics have a higher prevalence of thyroid disorders compared with the general population (10.81% vs. 6.6%) (6). Type 1 diabetics are prone to autoimmune thyroid disease, with up to 30% of women with T1D affected. As such, screening for thyroid dysfunction is recommended in this population (44). The association between T2D and subclinical hypothyroidism is also well recognized with reported prevalence in 2.2%–17% range (44). Although screening is not recommended, endocrinologists examining those patients are more prone to screen for thyroid dysfunction and nodularity than general practitioners, thus contributing to increased detection of thyroid cancer in this population. Furthermore, diabetics are more prone to mild, chronic TSH elevation, which, in recent studies, was demonstrated to be an independent risk factor for thyroid cancer development (15–20).

The association between thyroid cancer and diabetes risk may be due to variation in deiodinase expression in these disorders. Deiodinase enzymes regulate intracellular thyroid hormone levels, converting circulating prohormone T4 into its active form T3 (DIO1 or DIO2) or its inactive form rT3 (DIO3) (45,46). Specifically, type 2 deiodinase regulates intracellular T3 concentration in the pituitary, brain, and brown fat (47). It is also expressed in skeletal muscle, where it indirectly regulates GLUT4 expression (48). As such, inactivation of DIO2 results in decreased intracellular T3 levels in skeletal muscle, which, in turn, would decrease GLUT4 transcription in skeletal muscle and adipose tissue, further contributing to insulin resistance. Similarly, inactivation of DIO2 results in decreased intracellular T3 levels in pituitary cells, which in turn stimulates TSH release (45,46). DIO2 expression is modulated by a host of factors, including selenium and vitamin D3 levels, activation of Protein Kinase A, and Protein Kinase C pathways, and the presence of a DIO2 gene mutation (Thr92Ala variant). A recent metaanalysis of 11,033 participants found that subjects who had DIO2 Thr92Ala missense variation experienced increased T2D risk (49). Furthermore, DIO1 and DIO2 expression is reduced in papillary thyroid cancer (50,51), whereas DIO2 expression is reported to be significantly increased in widely metastatic follicular thyroid carcinoma (52–54). Although the role of DIO1 and DIO2 in carcinogenesis is not known, studies have suggested that they play a role in tumor differentiation as opposed to *de novo* neoplastic transformation. In contrast, reactivation of DIO3 expression in tumoral cells with its ensuing intracellular hypothyroidism (low T3, elevated rT3) results in inhibition

of thyroid hormone receptor-mediated suppression of ras-mediated transcription, proliferation, and transformation (55). This provides tumoral cells proliferation advantage as compared with neighboring normal cells.

In diabetics, chronic exposure to elevated circulating insulin levels is characteristic, from either endogenous (mediated by insulin resistance) or exogenous (chronic insulin therapy) sources. Insulin and insulin-like growth peptides share structural homology and affinity of its respective receptors (56). They are both important determinants of cell proliferation and apoptosis (56). Elevated circulating levels of insulin and insulin-like growth factor 1 are linked to increased risk of various cancers, including breast and colon (57–59). To date, there has been no association between insulin exposure and thyroid cancer in human studies. However, in laboratories, thyroid cancer cell lines are grown using a medium containing TSH, insulin, and cortisol, suggesting that insulin may play a role in thyroid carcinogenesis (60).

Chronic exposure to certain hypoglycemic agents used to treat patients with diabetes may also play a role in the complex relationship between diabetes and thyroid cancer incidence (22). Patients receiving metformin therapy (decreases insulin resistance) have a decreased risk of cancer and cancer mortality compared with those on insulin or sulfonylureas (increases insulin secretion) (22). Among insulin users (which typically includes all patients with T1D and some with T2D), those on Glargine (an insulin analog) may have an increased risk of cancer compared with those on human insulin, as suggested by a recently published observational study (22). The effect is believed to be mediated by increased and prolonged binding to the insulin-like growth factor 1-receptor leading to increased mitotic activity. To date, thyroid cancer has not been specifically implicated with prolonged sulfonylurea or insulin therapy. More recently, GLP-1 agonist therapy was linked with C-cell hyperplasia in humans and increased incidence of C-cell hyperplasias and medullary thyroid carcinoma in rodents. GLP-1 agonist does not appear to modulate differentiated thyroid cancer risk (22). The PPAR gamma agonist, Rosiglitazone (Avandia), was shown to induce apoptosis in PPAR gamma-positive thyroid cancer cell lines and increases radioiodine uptake in dedifferentiated thyroid tumors (20).

Alternatively, increased thyroid cancer risk in diabetics may be accounted for by metabolic syndrome-related confounding variables, including abnormal glucose metabolism, triglyceride levels, and BMI. Obese subjects are at a 10-fold increased risk of developing diabetes (61), and obesity is also associated with increased risk of thyroid cancer including in this cohort (25). Obesity is thought to promote insulin resistance through the inappropriate inactivation of gluconeogenesis. In this study, detailed adjustment for BMI slightly reduces (<10%) the risk of thyroid cancer, but did not explain the association between diabetes and thyroid cancer in women.

Recently, researchers from the Metabolic Syndrome and Cancer project linked glucose and triglyceride, independent of BMI, with increased risk of cancer (8). Specifically, an increased risk for thyroid cancer was observed for both men and women (RR = 1.88; 95% CI: 1.16–3.07 and RR = 0.72; 95% CI: 0.47–1.10, respectively) with 1 mmol/L blood glucose increments, though nonsignificant in women (8). Similarly, men were more prone to thyroid carcinoma with elevated triglycerides levels in the top studied quintile compared with bottom quintile (8).

Finally, vitamin D deficiency is hypothesized to account for lower incidence of cancer and cancer-related death in individuals living in southern latitudes compared with northern latitudes (62,63). Vitamin D promotes differentiation and apoptosis of cancer cells in culture studies. Association of vitamin D therapy/sufficiency and risk of specific cancers (colon, breast, prostate, and pancreas) has yielded inconsistent results in observational studies (64,65). To date, vitamin D deficiency, detected in up to 70% of diabetics, has not been associated with thyroid cancer risk. Low vitamin D levels decrease DIO2 expression (66), thus potentially linking diabetes to increased thyroid cancer risk.

The strengths of this study include its prospective design, completeness of follow-up, and the relatively large number of thyroid cancer cases with morphological diagnoses allowing for stratification by gender and histologic type. Limitations include the fact that we were unable to discriminate between T1D and T2D, and had no information on diabetes control, confounding variables such as TSH, lipid, and vitamin D levels, or diabetes medication. However, it seems that the proportion of subjects with T1D is likely to be small. The high proportion of non-Hispanic whites in our study population did not allow us to evaluate the effect of diabetes on thyroid cancer by race/ethnicity. As thyroid dysfunction is known to occur in diabetic patients and can contribute to significant metabolic disturbances, screening for thyroid abnormalities is not that uncommon (5), increasing the opportunity for incidental findings in the diabetic population. Unfortunately, we did not have data on the frequency of thyroid examinations in our study population. In sum, in the largest prospective evaluation to date, we found that thyroid cancer was significantly associated with diabetes among women. This study is also the first to present findings suggesting elevated risks for both the papillary and follicular types of thyroid cancer. As thyroid cancer is the sixth most common cancer among American women and the most common cancer of the endocrine system (1,2), our findings warrant further evaluation.

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Address correspondence to:
Briseis Aschebrook-Kilfoy
Occupational and Environmental Epidemiology Branch
Division of Cancer Epidemiology and Genetics
National Cancer Institute
National Institutes of Health
Department of Health and Human Services
6120 Executive Blvd, EPS 8111
Bethesda, MD 20892

E-mail: kilfoyb@mail.nih.gov