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Use of dietary vitamin supplements and risk of thyroid cancer: a population-based case-control study in Connecticut

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Abstract

Introduction—Certain dietary supplements have been reported to increase the risk of some cancers. Over half of the US population regularly uses dietary supplements. Thyroid cancer incidence has increased over the past several decades. However, few studies have investigated the association between dietary supplements and thyroid cancer. Thus, it is essential to clarify any association between dietary supplements and risk of thyroid cancer.

Materials and Methods—A population-based case-control study in Connecticut was conducted during 2010–2011 among 462 histologically confirmed incident thyroid cancer cases and 498 population-based controls. Dietary supplement intake was ascertained through in-person interviews and food frequency questionnaire. Multivariate unconditional logistic regression models were used to estimate the risk of thyroid cancer and dietary supplement use.

Results—Overall, no statistically significant associations were observed between dietary supplementation and thyroid cancer risk. Stratified analyses revealed a suggestive protective effect on risk of papillary microcarcinoma among long-term (>10 years) use of multivitamins (OR=0.59, 95% CI: 0.33, 1.04) and calcium supplementation (OR=0.45, 95% CI: 0.22, 0.93). An increased risk of large papillary thyroid cancers (tumor size >1cm) was observed among short-term (<5 years) users of calcium supplements (OR=2.24, 95% CI: 1.30, 3.88).

Discussion—No significant associations were observed between supplementation and overall thyroid cancer risk. The different associations between calcium supplements and risk of papillary thyroid cancer by tumor size warrants further investigation.

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Keywords

Thyroid cancer; vitamins; supplements; Connecticut

Introduction

The age-adjusted incidence rate of thyroid cancer has grown substantially over the past several decades across the world [1]. In the United States, the largest incidence in thyroid cancers were thyroid microcarcinomas (≤ 10 mm). While the increase has been attributed to advancements in diagnostic procedures, environmental and lifestyle factors might also play a role [2, 3]. Although most thyroid cancers have an excellent prognosis, particularly papillary and follicular thyroid cancers which account for more than 90% of cases, patients with thyroid cancer have an increased risk of secondary cancers (i.e., the cancers of the breast, skin, prostate, kidney, brain, and salivary gland, as well as lymphoma, myeloma, and leukemia) [4] and a reduced quality of life after treatment compared to the general population [5]. Prevention of thyroid cancer could reduce future treatment-related morbidity.

The safety, efficacy, and effectiveness of dietary supplementation has been hotly debated, but Americans have spent \$28 billion buying supplements [6]. Currently, the US Preventative Services Task Force recommends limited supplementation for the general population and recommends supplementation only for specific vulnerable populations (e.g. pregnant women) [7]. Despite these recommendations, general use continues to grow in the United States. Dietary supplements are now regularly used by more than half of the US population [8]. Currently, vitamin and mineral deficiency in the US is minimal [9] with the exception of vitamin D deficiency [10], but many Americans take supplements in hopes of reducing morbidity. Some supplements such as beta-carotene and α -tocopherol have actually increased the risk of developing cancer [9]. However, most supplements by themselves are unlikely to have much effect on overall health [11, 12].

A recent review suggested that supplementation and risk of thyroid cancer is inconclusive and further studies are necessary [13]. Among the population-based studies assessed, multivitamin [14, 15] and vitamins A, C, E [14] were associated with increased risk of thyroid cancer. Conversely, multivitamin with iron [14], vitamin C and E [16, 17] were associated with reduced risk of thyroid cancer. However, all these studies lacked adequate adjustment for dietary sources of vitamins from fruits and vegetables and lifestyle choices such as exercise. Based on these inconsistent reports, we evaluated the association of vitamin supplementation and risk of thyroid cancer in a population-based case-control study, with a focus on duration of use and the most common histologic subtype of thyroid cancer, papillary.

Materials and Methods

Study Population

This study population is described in Figure 1 and in full detail previously [18]. Cases were histologically confirmed, incident thyroid cancer patients (ICD-O-3: 8021 (anaplastic);

8050, 8052, 8130, 8260, 8340–8344, 8450, 8452 (papillary); 8290, 8330–8332, 8335 (follicular); and 8345, 8346, 8510 (medullary)) in Connecticut diagnosed between 2010 and 2011. Eligible subjects were 21 to 84 years old at diagnosis, had no previous diagnosis of cancer, with the exception of non-melanoma skin cancer, and were alive at the time of interview. A total of 701 eligible incident thyroid cancer cases were identified during the study period and 462 (65.9%) completed in-person interviews. Population-based controls with Connecticut addresses were recruited by random digit dialing. A total of 498 control subjects participated in the study, a participation rate of 61.5%. Cases and controls were frequency matched by age (5 years). Distributions of age and gender were similar between the participants and non-participants for both cases and controls (Table 1).

Data Collection

All procedures were performed in accordance with a protocol approved by the Human

Investigations Committee at Yale University and the Connecticut Department of Public Health. After approval by the hospitals and by each subject's physician (cancer cases), or following selection through random sampling (control population), potential participants were contacted by letter and followed up with a phone call. Those who agreed to participate in the study were interviewed by trained study interviewers, either at the subject's home or at a convenient location. After obtaining written consent, a standardized, structured questionnaire [18] was used to obtain information on major known or suspected risk factors of thyroid cancer.

Information on dietary supplementation was ascertained through a food frequency questionnaire. Subjects were asked about their intake of fiber, multivitamins, beta-carotene, vitamins A, C, E, and calcium supplements outside of their normal diet (herbal supplements data were also collected but not considered for this study as the number of users of any type of herbal supplement was few (n=50)). For each supplement, the frequency (once a month, once a week, several times per week, daily) and duration (number of years) of use were collected. Subjects were considered ever users of a supplement if they took supplements at least once a month for a total of 6 months. Additionally, among ever users, total duration of use of each supplement was also calculated. Dietary intake was assessed by a food frequency questionnaire which asked participants to estimate the quantity (number eaten) and frequency (number per day, week, or year) of fruits (apples, pears, bananas, plums, melons, etc.) and vegetables (leafy greens, cabbage, carrot, broccoli, tomatoes, etc.) consumed over the past year. From this information, total servings per year of fruits and vegetables were estimated. Additional information on demographic, residential history, hobbies, and health-related conditions were also collected in a demographic questionnaire.

Statistical Analysis

Demographic variables between cases and controls were compared by the chi-squared test. Unconditional logistic regression models were used to generate odds ratios (OR) and 95% confidence intervals (95% CI) to estimate the association between dietary supplement use and risk of thyroid cancer. Ever and duration of dietary supplement use were the main predictors of interest (at least once a month for six months). Duration of use was not

stratified if less than 20 subjects were available (vitamin A, beta-carotene) or the distribution of duration was limited (fiber). Models treated never regular use of any dietary supplements as the reference group. All models were adjusted for age (continuous), race (white, other), gender (male, female), body mass index (BMI, continuous), family history of thyroid cancer (no, yes), family history of thyroid disease (no, yes), smoking status (ever, never), alcohol status (ever, never), thyroid disease history (ever, never), education (<college, college, >college, other), income (<\$15,000-\$34,999, \$35,000–\$69,999, \$70,000, refused), moderate and vigorous leisure time physical activity (hours per month), fruit intake (total servings per year), and vegetable intake (total servings per year). Additional stratified analysis by papillary thyroid cancer subtype, sex, and papillary tumor size were also adjusted for all covariates. P-trend was calculated by the modeling the duration variable continuously and the P-values were calculated using Wald chi-square statistic. With 498 controls and 462 cases, this study had 80% power to detect OR of 1.22 or greater or 0.82 or less. All statistical analyses were conducted in SAS 9.3 (SAS Institute).

Results

The demographics of the study population are presented in Table 1. There were no differences between cases and controls for race, smoking, and income level (P-values > 0.05). Cases tended to be more female, have a family history of thyroid cancer and other thyroid diseases, not drink alcohol, be less educated, be younger, have a higher BMI, exercise less, and eat fewer fruits and vegetables (P-values < 0.05).

Ever use of any supplements was not significantly associated with thyroid cancer risk (Table 2). Long-term use (>10 years) of multivitamins was significantly associated with reduced thyroid cancer risk (OR=0.63, 95%CI: 0.42, 0.95), however, the reduced risk became non-significant after adjusted for exercise, fruit consumption, and vegetable consumption (OR=0.70, 95%CI: 0.45, 1.08). A non-statistically significant reduced risk of thyroid cancer was suggested among long duration calcium users (OR=0.65, 95%CI: 0.39, 1.10). Among short-term (<5 years) users of calcium supplements, an increased risk of thyroid cancer was observed (OR: 1.72; 95% CI: 1.12–2.64). Similar associations were observed for analyses stratified by papillary thyroid cancer (Table 2) and sex (Table 3).

In stratified analyses by tumor size for papillary thyroid cancer (Table 4), long-term (>10 years) calcium supplementation was associated with a reduced risk of papillary microcarcinoma (OR=0.45, 95%CI: 0.22, 0.93, P-trend: 0.045), while short-term (<5 years) use was associated with an increased risk of large papillary thyroid cancer (tumor size >1cm) (OR=2.24, 95%CI: 1.30, 3.88). A suggestive protective effect on risk of papillary microcarcinoma was observed for long-term (>10 years) use of multivitamins (OR=0.59, 95%CI: 0.33, 1.04). No significant associations were observed for use of fiber, beta-carotene, vitamin A, C, and E.

Similar results were observed when we limited our study population to white or non-Hispanic white (data not shown).

Discussion

Overall, no significant association was observed between dietary supplements and risk of thyroid cancer in this study. Short term use of calcium was associated with increased risk of large papillary thyroid cancer (tumor size > 1cm), while long-term use of calcium (>10 years) was associated with a reduced risk of papillary microcarcinoma.

Only a few studies have investigated the association between dietary supplementation and risk of thyroid cancer, and those studies have been inconsistent [14–17]. Only one study assessed duration of use and risk, and found that longer duration of dietary supplements was associated with increased risk, particularly with the papillary subtype [15]; a finding that is the opposite of our study. An important consideration is that none of these earlier studies adjusted for physical activity, fruit and vegetable intake [14–17]. Supplementation was moderately correlated with increased exercise and dietary intake of vegetables and fruits ($r>0.21$, $P\text{-value} < 0.0001$) in our study. After adjusting for these variables, some of the significant results were diminished. While we controlled for these variables in our models, it is possible that there may be other lifestyle choices not accounted for in this analysis. As such, the associations observed could be due to residual confounding [19].

We also found that short-term calcium supplementation was associated with an increased risk of papillary thyroid cancer larger than 1 cm and long-term supplementation was associated with a reduced risk of papillary microcarcinoma. The conflicting directions of association by tumor size may be spurious chance findings, but it is possible that thyroid cancers with larger tumor size and thyroid microcarcinomas are distinct with different etiology. It is also possible that long term supplement users are more health conscious, are more likely to seek medical attention and thereby have their disease diagnosed earlier[20]. Only one published study has investigated calcium supplements and risk of thyroid cancer and found no association [21], which is consistent with our study. However, this published study did not examine the association by duration of supplementation or tumor size. While calcium intake is important in maintaining health of individuals with thyroid diseases such as Hashimoto's Disease [22], there is limited evidence of dietary calcium affecting thyroid cancer development in *in vitro* or *in vivo* studies.

Additionally, long-term supplementation is more common among individuals who believe and attempt to live a healthier lifestyle [23]. Being proactive about one's health has been found to boost immune system function and overall health [24]. Thus, the effect of vitamins may not necessarily be a causal factor in the reduction of thyroid cancer, but rather, a reflection of lifestyle choices. In this study, over 50% of the subjects used multivitamins and 38% used vitamin C regularly. The high percentage of users resembles the general US population, suggesting these results are representative of the US population [24]. Previous studies of dietary intake of fruits and vegetables that are rich in vitamins and minerals have generally found inverse associations with thyroid cancer risk [25–28].

The primary strength of this study is the comprehensive collection of potential factors that may be associated with thyroid cancer. The food frequency questionnaire collected wide-ranging supplementation use and quantity of vegetable and fruit intake. Unlike many

previous studies, vegetable and fruit intake was adjusted for in this study. Additionally, the recentness of our study reflects the recent changing landscape of thyroid cancer diagnoses that includes many more papillary microcarcinomas. The primary limitation of the study is the case-control design which may reflect recall bias inherent to retrospective studies in comparison to prospective cohort study designs. However, as dietary supplements commonly have the perception of a health promoting behavior, all people, regardless of case status, are likely to over report their usage [29]. Thus, there should be limited overall effect on the association of supplement use and thyroid cancer risk. Because supplement use is considered healthy, it is also possible that controls would over report their supplement use while cases would not, leading to the bias towards the null. For some sub-analyses with smaller sample size, the results should be interpreted with caution.

In conclusion, no statistically significant association was observed between supplementation and thyroid cancer risk. The different associations between calcium supplements and risk of thyroid cancer by tumor size warrants further investigation. Supplementation is likely reflective of people trying to live a healthier lifestyle which can improve overall health. Replication of these results in future research should focus on supplementation use tightly controlled for other health promoting choices.

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Figure 1.
Study design and characteristics of study population in Connecticut from 2010–2011

Table 1
Demographic characteristics of thyroid cancer cases and controls in Connecticut, USA 2010–2011

	Cases (n=462)		Controls (n=498)		P-value*
	Number	%	Number	%	
Age (years)					
<50	201	43.5	187	37.6	0.0022
50–59	149	32.3	139	27.9	
>60	112	24.2	172	34.5	
Race					
White	415	89.8	450	90.4	0.39
Black	18	3.9	25	5.0	
Other	29	6.3	23	4.6	
Gender					
Male	87	18.8	154	30.9	<0.0001
Female	375	81.2	344	69.1	
Family history of thyroid cancer					
No	388	84.0	450	90.4	0.003
Yes	74	16.0	48	9.6	
Family history of thyroid disease					
No	347	75.1	422	84.7	0.0002
Yes	115	24.9	76	15.3	
History of benign thyroid disease					<0.0001
No	400	86.6	484	97.2	
Yes	62	13.4	14	2.8	
Ever smoker (>100 cigarettes)					
No	321	69.5	326	65.5	0.18
Yes	141	30.5	172	34.5	
Ever alcohol drinker (>6 drinks)					
No	274	59.3	231	46.4	<0.0001
Yes	188	40.7	267	53.6	
Education					

	Cases (n=462)		Controls (n=498)		P-value *
	Number	%	Number	%	
<College	160	34.6	113	22.7	0.0007
College	185	40.0	236	47.4	
>College	100	21.6	130	26.1	
Other/Unspecified	17	3.7	19	3.8	
Family income					
\$15,000–\$34,999	43	9.3	66	13.3	0.17
\$35,000–\$69,999	80	17.3	70	14.1	
>\$70,000	192	41.6	210	42.2	
Refused	147	31.8	152	30.5	
Body mass index (kg/m ²)					
Normal (<25)	150	32.5	212	42.6	<0.0001
Overweight (25–29.99)	146	31.6	168	33.7	
Obese (≥ 30)	166	35.9	118	23.7	
Leisuretime physical activity (Hours/month)					
None	156	33.8	135	27.1	0.0044
>0–19.99	136	29.4	128	25.7	
20	170	36.8	235	47.2	
Vegetable intake (Servings per year)					
<350	172	37.2	174	34.9	0.12
350–699	136	29.4	127	25.5	
700	154	33.3	197	39.6	
Fruits intake (Servings per year)					
<150	173	37.4	160	32.1	0.20
150–349	127	27.5	142	28.5	
350	162	35.1	196	39.4	

* Chi-squared test

Table 2

Vitamin supplementation use and risk of thyroid cancer overall and papillary thyroid cancer

Supplement	Overall				Papillary			
	Controls	Cases	OR* (95CI)	OR** (95CI)	Controls	Cases	OR* (95CI)	OR** (95CI)
Never any supplement	158	160	(ref)	(ref)	158	137	(ref)	(ref)
Ever any supplement	340	302	0.94(0.69–1.26)	0.99(0.72–1.36)	340	255	0.93(0.68–1.27)	0.96(0.68–1.34)
Multivitamin	267	217	0.81(0.59–1.12)	0.91(0.65–1.28)	267	184	0.81(0.58–1.13)	0.88(0.61–1.25)
<5 years	113	100	0.89(0.61–1.30)	0.98(0.66–1.46)	113	84	0.87(0.58–1.29)	0.94(0.62–1.42)
5–10 years	34	41	1.13(0.65–1.96)	1.24(0.71–2.18)	34	32	1.03(0.58–1.85)	1.10(0.60–2.00)
>10 years	120	76	0.63(0.42–0.95)	0.70(0.45–1.08)	120	68	0.67(0.43–1.02)	0.72(0.46–1.13)
<i>P-trend</i>			0.053	0.16			0.093	0.21
Vitamin A	15	9	0.73(0.29–1.87)	0.85(0.32–2.25)	15	7	0.73(0.27–2.01)	0.81(0.29–2.28)
Vitamin C	134	100	0.79(0.54–1.15)	0.82(0.54–1.25)	134	79	0.71(0.47–1.07)	0.72(0.46–1.12)
<5 years	58	56	0.95(0.59–1.52)	0.99(0.60–1.62)	58	46	0.86(0.52–1.42)	0.85(0.50–1.45)
5–10 years	17	10	0.58(0.24–1.39)	0.58(0.24–1.43)	17	7	0.45(0.17–1.21)	0.44(0.16–1.21)
>10 years	59	34	0.68(0.40–1.15)	0.71(0.40–1.25)	59	26	0.63(0.36–1.13)	0.65(0.35–1.19)
<i>P-trend</i>			0.1	0.17			0.063	0.091
Vitamin E	60	47	0.85(0.52–1.40)	1.08(0.62–1.88)	60	38	0.82(0.48–1.39)	0.97(0.54–1.74)
<5 years	29	22	0.83(0.43–1.63)	1.05(0.52–2.12)	29	17	0.76(0.37–1.57)	0.89(0.42–1.90)
5–10 years	10	7	0.70(0.24–2.06)	0.96(0.31–3.00)	10	5	0.58(0.18–1.89)	0.74(0.21–2.58)
>10 years	21	18	0.95(0.46–1.98)	1.18(0.55–2.54)	21	16	1.02(0.48–2.17)	1.18(0.54–2.60)
<i>P-trend</i>			0.67	0.71			0.71	0.83
Beta-Carotene	11	8	0.92(0.33–2.52)	1.11(0.39–3.17)	11	6	0.84(0.28–2.55)	0.97(0.31–3.05)
Calcium	184	199	1.13(0.81–1.59)	1.18(0.82–1.70)	184	166	1.11(0.78–1.59)	1.12(0.76–1.64)
<5 years	72	115	1.67(1.11–2.50)	1.72(1.12–2.64)	72	95	1.58(1.04–2.42)	1.58(1.01–2.47)
5–10 years	38	41	0.93(0.54–1.59)	0.95(0.55–1.65)	38	35	0.93(0.53–1.63)	0.93(0.53–1.66)
>10 years	74	43	0.63(0.39–1.03)	0.65(0.39–1.10)	74	36	0.65(0.39–1.11)	0.67(0.38–1.15)
<i>P-trend</i>			0.085	0.086			0.14	0.12
Fiber	63	43	0.67(0.40–1.12)	0.71(0.41–1.24)	63	36	0.66(0.38–1.13)	0.67(0.37–1.20)

* Adjusted for age, race, gender, BMI, family history of cancer, family history of disease, smoking, alcohol consumption, thyroid disease history, education, and income.

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Additional adjustment for vigorous physical activity, fruit intake, and vegetable intake.
**

Table 3

Vitamin supplementation use and risk of thyroid cancer overall by gender

Supplement	Males			Females		
	Controls	Cases	OR* (95CI)	Controls	Cases	OR* (95CI)
Never any supplement	63	39	(ref)	95	121	(ref)
Ever any supplement	91	48	0.95(0.52–1.70)	249	254	0.91(0.64–1.29)
Multivitamin	73	30	0.69(0.35–1.33)	194	187	0.83(0.57–1.19)
<5 years	31	12	0.68(0.30–1.58)	82	88	0.94(0.61–1.46)
5–10 years	9	6	1.18(0.32–4.39)	25	35	1.03(0.56–1.91)
>10 years	33	12	0.57(0.23–1.41)	87	64	0.62(0.38–0.99)
<i>P-trend</i>			0.27			0.065
Vitamin A	5	3	0.98(0.15–6.42)	10	6	0.66(0.20–2.19)
Vitamin C	35	19	0.98(0.46–2.12)	99	81	0.74(0.47–1.16)
<5 years	11	11	1.54(0.57–4.19)	47	45	0.82(0.48–1.42)
5–10 years	4	2	1.03(0.15–6.90)	13	8	0.50(0.18–1.38)
>10 years	20	6	0.59(0.20–1.76)	39	28	0.71(0.38–1.34)
<i>P-trend</i>			0.45			0.18
Vitamin E	17	5	0.75(0.22–2.57)	43	42	0.89(0.51–1.57)
<5 years	7	3	1.28(0.26–6.42)	22	19	0.81(0.38–1.72)
5–10 years	3	0	--	7	7	0.79(0.25–2.47)
>10 years	7	2	0.60(0.10–3.64)	14	16	1.08(0.47–2.52)
<i>P-trend</i>			0.47			0.95
Beta-Carotene	4	2	0.45(0.06–3.44)	7	6	1.13(0.33–3.90)
Calcium	33	24	1.51(0.72–3.17)	151	175	1.11(0.75–1.63)
<5 years	10	15	3.94(1.42–10.92)	62	100	1.51(0.96–2.38)
5–10 years	8	3	0.51(0.11–2.35)	30	38	1.02(0.56–1.85)
>10 years	15	6	0.71(0.22–2.31)	59	37	0.61(0.35–1.06)
<i>P-trend</i>			0.78			0.11
Fiber	17	9	0.93(0.31–2.80)	46	34	0.58(0.32–1.06)

* Adjusted for age, race, gender, BMI, family history of cancer, family history of disease, smoking, alcohol consumption, thyroid disease history, education, and income.

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Additional adjustment for vigorous physical activity, fruit intake, and vegetable intake. (ref) is the reference (comparison) category

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Table 4

Vitamin supplementation use and risk of papillary thyroid cancer by size of tumor

Supplement	Controls	Papillary 1cm			Papillary >1cm		
		Cases	OR* (95CI)	OR** (95CI)	Cases	OR* (95CI)	OR** (95CI)
Never any supplement	158	68	(ref)	(ref)	69	(ref)	(ref)
Ever any supplement	340	125	0.77(0.52–1.14)	0.76(0.50–1.16)	130	1.08(0.73–1.60)	1.16(0.76–1.77)
Multivitamin	267	86	0.66(0.44–1.01)	0.69(0.44–1.09)	98	0.97(0.64–1.47)	1.09(0.70–1.71)
<5 years	113	37	0.69(0.41–1.14)	0.71(0.42–1.21)	47	1.04(0.64–1.70)	1.16(0.69–1.95)
5–10 years	34	15	0.88(0.42–1.84)	0.91(0.43–1.91)	17	1.17(0.57–2.40)	1.32(0.63–2.75)
>10 years	120	34	0.57(0.33–0.97)	0.59(0.33–1.04)	34	0.81(0.47–1.38)	0.91(0.51–1.62)
<i>P-trend</i>			0.057	0.10		0.51	0.82
Vitamin A	15	2	0.38(0.08–1.80)	0.34(0.07–1.73)	5	1.14(0.35–3.75)	1.41(0.41–4.89)
Vitamin C	134	38	0.65(0.39–1.08)	0.57(0.32–1.00)	41	0.79(0.46–1.33)	0.89(0.51–1.58)
<5 years	58	21	0.74(0.39–1.39)	0.64(0.33–1.25)	25	1.00(0.53–1.87)	1.12(0.58–2.18)
5–10 years	17	5	0.58(0.19–1.77)	0.53(0.17–1.67)	2	0.27(0.06–1.29)	0.29(0.06–1.43)
>10 years	59	12	0.56(0.26–1.18)	0.49(0.22–1.09)	14	0.74(0.35–1.55)	0.85(0.39–1.89)
<i>P-trend</i>			0.084	0.057		0.23	0.45
Vitamin E	60	20	0.79(0.42–1.50)	0.86(0.42–1.75)	18	0.89(0.45–1.78)	1.24(0.58–2.66)
<5 years	29	10	0.84(0.36–1.98)	0.90(0.37–2.23)	7	0.71(0.27–1.86)	0.96(0.34–2.68)
5–10 years	10	3	0.65(0.16–2.59)	0.70(0.17–2.99)	2	0.58(0.11–3.08)	0.92(0.15–5.63)
>10 years	21	7	0.80(0.31–2.11)	0.88(0.32–2.41)	9	1.33(0.52–3.45)	1.74(0.64–4.71)
<i>P-trend</i>			0.51	0.70		0.84	0.34
Beta-Carotene	11	1	0.27(0.03–2.26)	0.26(0.03–2.32)	5	1.60(0.47–5.48)	2.30(0.62–8.60)
Calcium	184	81	0.89(0.57–1.40)	0.84(0.52–1.36)	85	1.34(0.86–2.10)	1.46(0.90–2.36)
<5 years	72	42	1.16(0.68–1.97)	1.09(0.62–1.89)	53	2.09(1.24–3.51)	2.24(1.30–3.88)
5–10 years	38	23	0.96(0.49–1.86)	0.90(0.46–1.77)	12	0.80(0.38–1.71)	0.86(0.39–1.85)
>10 years	74	16	0.49(0.25–0.97)	0.45(0.22–0.93)	20	0.83(0.43–1.61)	0.92(0.46–1.84)
<i>P-trend</i>			0.071	0.045		0.49	0.58
Fiber	63	20	0.69(0.36–1.33)	0.63(0.31–1.28)	16	0.63(0.30–1.34)	0.68(0.31–1.50)

* Adjusted for age, race, gender, BMI, family history of cancer, family history of disease, smoking, alcohol consumption, thyroid disease history, education, and income.

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Additional adjustment for vigorous physical activity, fruit intake, and vegetable intake.
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