Selected Micronutrient Intake and Thyroid Carcinoma Risk

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BACKGROUND. Protection from thyroid carcinoma due to certain dietary factors was suggested by several studies, but the findings were relatively inconsistent. The role of micronutrients has not yet been systematically analyzed. To investigate the relationship between micronutrient intake and thyroid carcinoma risk, the authors used data from a case-control study conducted in northern Italy between 1986 and 1992.

METHODS. The study included 399 incident, histologically confirmed thyroid carcinoma cases and 617 controls admitted to the hospital for acute, nonneoplastic, nonhormone-related diseases.

RESULTS. Retinol intake showed a direct association with thyroid carcinoma risk, with odds ratios (ORs) of 1.39 (95% confidence interval [CI], 0.9–2.0) in the third quartile of consumption and 1.52 (95% CI, 1.0–2.3) in the highest quartile, whereas beta-carotene had an inverse relationship, with ORs of 0.63 (95% CI, 0.4–0.9) in the third quartile of consumption and 0.58 (95% CI, 0.4–0.9) in the highest quartile compared with the lowest quartile. Some protection was observed for measures of vitamin C intake (with an OR of 0.72) and vitamin E (with an OR of 0.67) for the highest quartile of consumption, although the estimates were not statistically significant, and were reduced after adjustment for beta-carotene intake. No clear pattern in risk appeared for vitamin D, folate, calcium, thiamin, or riboflavin. The inverse relationship between beta-carotene and thyroid carcinoma was observed in both papillary and follicular carcinomas.

CONCLUSIONS. In this study, a significant inverse association between beta-carotene and thyroid carcinoma was observed, and some protection against thyroid carcinoma from vitamins C and E was also suggested. *Cancer* **1997;79:2186–92.**

KEYWORDS: thyroid carcinoma, histologic type, micronutrients, case–control study.

The possible relationship between thyroid carcinoma and diet has been investigated in only a few studies.[1–6] Protection from vegetable consumption was consistently observed in four studies,[1–3,5] and fish consumption was directly related to the development of thyroid carcinoma in some studies,[1,2] but inversely in others.[3,5] Starchy foods, possible indicators of a poor diet, were related to thyroid carcinoma risk in a study conducted in northern Italy and Switzerland,[3] but not in another study from Connecticut.[1] Two studies were able to estimate the role of selected nutrients and micronutrients in thyroid carcinogenesis.[2,4] In a prospective study conducted in Norway, Glattre et al.[4] found direct associations between thyroid carcinoma and indices of vitamin D and retinoids. In a Hawaiian study, Kolonel et al.[2] observed higher carbohydrate and iodine intake in patient cases, mostly females, but did not find significant differences between cases and controls according to intake of fats, proteins, and beta-carotene.

TABLE 1
Distribution of 399 Thyroid Carcinoma Cases and 617 Controls According to Sociodemographic Variables, History of Benign Thyroid Diseases, and Estimated Calorie Intake (Italy, 1986–1992)

	Cases		Controls	
	No.	(%)	No.	(%)
Gender				
Males	108	(27.1)	190	(30.8)
Females	291	(72.9)	427	(69.2)
Age (yrs)				
< 40	152	(38.1)	231	(37.4)
40–49	88	(22.1)	131	(21.2)
50–59	87	(21.8)	129	(20.9)
60–74	72	(18.0)	126	(20.4)
Center				
Milan	208	(52.1)	257	(41.7)
Veneto	132	(33.1)	221	(35.8)
Friuli-Venezia Giulia	59	(14.8)	139	(22.5)
Benign thyroid diseases				
No	312	(78.2)	596	(96.6)
Yes	87	(21.8)	21	(3.4)
Calorie intake				
< 1716	82	(20.6)	154	(25.0)
1716–2092	108	(27.1)	154	(25.0)
2093–2536	108	(27.1)	154	(25.0)
≥ 2537	101	(25.3)	155	(25.1)

To further investigate the issue, the authors considered the relationship between selected micronutrient intake and thyroid carcinoma using data from a case–control study conducted in northern Italy, previously analyzed with reference to intake of various foods.[3] That analysis showed direct associations with several starchy foods, various types of meat, cheese, butter, and oil, whereas fish and several types of vegetables and fruits were protective. Therefore, the question arises of whether there is an effect of specific micronutrients on thyroid carcinogenesis.

MATERIALS AND METHODS

Since 1986, a case–control study of thyroid carcinoma was conducted in the major teaching and university hospitals in three areas of northern Italy (the greater Milan area, the province of Pordenone in the Friuli-Venezia Giulia region, and the province of Padova in the Veneto region) through December 1992.

The study design has been previously described.[3] Trained interviewers identified thyroid carcinoma cases and controls admitted to hospitals in the same catchment areas, and administered a structured questionnaire to them that included questions on sociodemographic and anthropometric characteristics, lifestyle habits (including coffee and alcohol consumption), dietary habits, a problem-oriented medical history, family history of thyroid disease, history of residence in endemic goiter areas, use of diagnostic and therapeutic X-rays, and, for female subjects, gynecologic and reproductive history and use of exogenous hormones. The weekly frequency of consumption of 29 food items during the 2 years before the onset of symptoms that led to the diagnosis was also elicited, including the major sources of retinol, beta-carotene, vitamins C, D, and E, calcium, folate, thiamin, and riboflavin (Foods included in the questionnaire were: pasta or rice, bread, whole grain bread, polenta, pastries, veal meat and beef, poultry, fish, liver, raw ham, ham, cold cuts, canned meat, eggs, milk, cheese, potatoes, pulses, green vegetables, fresh fruit, cabbages and other cruciferae, carrots, spinach, tomatoes, peppers, lettuce, apples, citrus fruit, and watermelon).

Cases were 399 subjects younger than 75 years admitted to the hospital for histologically confirmed thyroid carcinoma diagnosed no more than 2 years before the interview. Of these, 291 were females and 108 were males, age 16–72 years (median age, 44 years). Papillary carcinomas and mixed papillary/follicular carcinomas accounted for 274 cases, follicular carcinomas for 69, medullary for 18, anaplastic for 8, and oxyphil cell type for 4. For 26 cases, documentation could not be found to define the histologic type. To differentiate papillary and mixed papillary/follicular carcinomas from follicular carcinomas the pathologic criteria included the presence of ground-glass nuclei, well formed papillae, and psammona bodies.

Control subjects were patients admitted to the same network of hospitals in which the cases were identified for acute nonneoplastic diseases not related to known or potential risk factors for thyroid carcinoma. Patients admitted for any hormone-related disease were explicitly excluded. A total of 617 subjects, including 427 females and 190 males, aged 16–74 years (median age, 46 years) were interviewed. The diagnostic categories of the controls were: traumas (15%), other nontraumatic orthopedic diseases (17%), acute surgical conditions (28%), and miscellaneous disorders, including acute infections or skin, ear, nose, and throat diseases (40%). Greater than 80% of the subjects (cases and controls) interviewed came from the 3 regions in which data collection was conducted, and >90% came from northern Italy. Cases and controls were not singularly matched, but were comparable in strata of gender and age. Less than 5% of the subjects identified (cases and controls) refused to participate.

Micronutrient intake was computed by multiplying the consumption frequency of each unit of food by the nutrient content of the standard average por-

TABLE 2
Correlation Matrix of the Nine Micronutrients Considered

	Retinol	Beta-carotene	Vitamin C	Vitamin D	Vitamin E	Folate	Calcium	Thiamin	Riboflavin
Retinol		0.09	0.15	0.17	0.16	0.43	0.15	0.28	0.47
Beta-carotene			0.39	0.07	0.74	0.57	0.20	0.33	0.28
Vitamin C				0.26	0.57	0.66	0.42	0.65	0.45
Vitamin D					0.22	0.34	0.80	0.67	0.80
Vitamin E						0.85	0.40	0.57	0.52
Folate							0.51	0.68	0.72
Calcium								0.70	0.89
Thiamin									0.80
Riboflavin									

tion using values from the Italian composition tables,[7] with the integration of other sources when necessary.[8] The questionnaire was limited to the frequency of consumption of 29 food items, with no quantitative indication of portion size. Therefore, the estimates of nutrient intake obtained are only approximations, and hence the related risks may be underestimations of the real associations.

Subjects were classified in quartiles based on the distribution of controls for estimated calorie and selected micronutrient intake. It has been shown that the distribution of quartiles in cases, controls, and cases and controls combined leads to similar results and statistical power.[9] The distribution of quartiles on controls only may nonetheless improve data readibility because each quartile included approximately 155 controls. Odds ratios (OR), as estimators of relative risks, and the corresponding 95% confidence intervals of thyroid carcinoma were computed by unconditional multiple logistic regression equations,[10] including terms for gender, age in quinquennia, and study center (Model 1), plus previous benign thyroid diseases (ever/never), and estimated calorie intake (in quartiles) (Model 2). ORs were computed on the overall sample, papillary and mixed papillary/follicular and follicular carcinomas, and females and males separately, using gender specific cutpoints. For multiple levels of exposure, the significance of the linear trend in risk was assessed by comparing the difference between the deviances of the models with and without the term of interest to the chi-square distribution with one degree of freedom.[10]

RESULTS

Table 1 presents the distribution of thyroid carcinoma cases and controls according to age, gender, history of benign thyroid diseases, and quartiles of calorie intake. Patient cases more often reported a history of previous benign thyroid diseases and higher calorie intake than controls. Therefore, allowance for these variables (in addition to age, gender, and study center) was made in all subsequent analyses.

The correlation coefficients between the nine micronutrients considered is given in Table 2. Coefficients of approximately 0.7 were observed between vitamin E, beta-carotene and folate, vitamin D, thiamin, riboflavin and calcium, and folate and thiamin.

Table 3 shows the distribution of cases and controls, and the corresponding ORs, according to consumption of the micronutrients considered. Cases reported a higher intake of retinol, whereas consumption of beta-carotene and vitamins C and E was higher among controls. Thus, retinol intake showed a direct association with thyroid carcinoma risk, with ORs of 1.39 in the third quartile of consumption and 1.52 in the highest quartile, and beta-carotene showed an inverse relationship, with ORs of 0.63 in the third quartile and 0.58 in the highest quartile of consumption; the trends in risk were significant for both these micronutrients. Some protection also was observed for measures of vitamin C intake, with an OR of 0.72, and vitamin E, with an OR of 0.67 for the highest quartile of consumption, respectively. No clear pattern in risk appeared for vitamin D, folate, calcium, thiamin, and riboflavin. When the terms for vitamin C and vitamin E intake were added to a single model including study center, age, gender, history of benign thyroid diseases, total calorie intake, and beta-carotene, the ORs for the subsequent quartiles of vitamin C intake were 1.02, 1.33, and 1.06, and they were 1.07, 1.33, and 1.37 for vitamin E relative to the lowest quartile, whereas the inverse association for beta-carotene was strengthened.

Papillary (also including mixed papillary/follicular histologies) and follicular carcinomas were analyzed separately in Table 4. Only the protection due to beta-carotene was apparent in both histologic types. There

TABLE 3
Distributions of 399 Cases of Thyroid Carcinoma and 617 Controls According to Quartiles of Selected Micronutrients, and Corresponding Odds Ratios and 95% Confidence Intervals (Italy, 1986–1992)[a]

	Cases		Controls			
	No.	(%)	No.	(%)	OR1	OR2
Retinol (μg/day)						
< 274	84	21.1	155	25.1	1[b]	1[b]
274–1580	81	20.3	153	24.8	1.15 (0.8–1.7)	1.11 (0.7–1.7)
1581–1801	113	28.3	154	25.0	1.40 (1.0–2.0)	1.39 (0.9–2.0)
≥ 1802	121	30.3	155	25.1	1.64 (1.1–2.4)	1.52 (1.0–2.3)
χ^2 1trend					8.17[c]	5.05[c]
Beta-carotene (μg/day)						
< 3124	112	28.1	154	25.0	1[b]	1[b]
3124–4279	118	29.6	154	25.0	1.02 (0.7–1.4)	0.86 (0.6–1.2)
4280–5826	89	22.3	154	25.0	0.83 (0.6–1.2)	0.63 (0.4–0.9)
≥ 5827	80	20.1	155	25.1	0.77 (0.5–1.1)	0.58 (0.4–0.9)
χ^2 1trend					2.72	7.85[c]
Vitamin C (mg/day)						
< 113	102	25.6	154	25.0	1[b]	1[b]
113–155	101	25.3	155	25.1	0.97 (0.7–1.4)	0.93 (0.6–1.4)
156–224	117	29.3	153	24.8	1.19 (0.8–1.7)	1.04 (0.7–1.5)
≥ 225	79	19.8	155	25.1	0.89 (0.6–1.3)	0.72 (0.5–1.1)
χ^2 1trend					0.02	1.10
Vitamin D (mg/day)						
< 0.57	85	21.3	155	25.1	1[b]	2[b]
0.57–0.99	122	30.6	153	24.8	1.35 (0.9–1.9)	1.23 (0.8–1.8)
1.0–1.54	99	24.8	153	24.8	1.22 (0.8–1.8)	1.11 (0.7–1.7)
≥ 1.55	93	23.3	156	25.3	1.25 (0.9–1.8)	1.08 (0.7–1.6)
χ^2 1trend					0.88	0.04
Vitamin E (mg/day)						
< 9	90	22.6	154	25.0	1[b]	1[b]
9–11	118	29.6	154	25.0	1.33 (0.9–1.9)	1.11 (0.7–1.7)
12–14	109	27.3	154	25.0	1.32 (0.9–1.9)	0.93 (0.6–1.4)
≥ 15	82	20.6	155	25.1	1.08 (0.7–1.6)	0.67 (0.4–1.0)
χ^2 1trend					0.15	3.07
Folate (mg/day)						
< 189	88	22.1	154	25.0	1[b]	1[b]
189–242	97	24.3	154	25.0	1.13 (0.8–1.6)	0.89 (0.6–1.4)
243–302	125	31.3	154	25.0	1.63 (1.1–2.4)	1.22 (0.8–1.9)
≥ 303	89	22.3	155	25.1	1.29 (0.9–1.9)	0.86 (0.5–1.4)
χ^2 1trend					3.43	0.00
Calcium (mg/day)						
< 712	87	21.8	154	25.0	1[b]	1[b]
712–1016	107	26.8	154	25.0	1.23 (0.9–1.8)	1.07 (0.7–1.6)
1017–1431	118	29.6	154	25.0	1.45 (1.0–2.1)	1.24 (0.8–1.9)
≥ 1432	87	21.8	155	25.1	1.27 (0.8–1.9)	0.96 (0.6–1.5)
χ^2 1trend					2.25	0.02
Thiamin (mg/day)						
< 0.76	74	18.6	156	25.3	1[b]	1[b]
0.76–0.94	116	29.1	152	24.6	1.60 (1.1–2.3)	1.51 (1.0–2.3)
0.95–1.14	112	28.1	154	25.0	1.63 (1.1–2.4)	1.37 (0.8–2.2)
≥ 1.15	97	24.3	155	25.1	1.60 (1.1–2.4)	1.25 (0.7–2.2)
χ^2 1trend					5.00[c]	0.40
Riboflavin (mg/day)						
< 1.49	88	22.1	154	25.0	1[b]	1[b]
1.49–1.95	108	27.1	155	25.1	1.23 (0.8–1.9)	1.23 (0.8–1.9)
1.96–2.51	115	28.8	154	25.0	1.46 (1.0–2.1)	1.28 (0.8–2.0)
≥ 2.52	88	22.1	154	25.0	1.29 (0.9–1.9)	1.00 (0.6–1.7)
χ^2 1trend					2.36	0.001

OR: odds ratio; χ^2: chi-square test.

[a] Estimates from multiple logistic regression equations including terms for study center, age, gender in OR1 and the same variables plus history of benign thyroid diseases (yes/no) and total calorie intake in OR2.

[b] Reference category.

[c] $P < 0.05$.

TABLE 4
Odds Radios and 95% Confidence Intervals[a] or Thyroid Carcinoma for Quartiles of Consumption of Various Micronutrients in Papillary and Follicular Thyroid Carcinomas Separately (Italy, 1986–1992)

	Papillary[b]				Follicular			
	Quartile[c]				Quartile[c]			
	2	3	4	χ^2 1trend	2	3	4	χ^2 1trend
Retinol	0.98 (0.6–1.6) [58:153][e]	1.24 (0.8–2.0) [71:154]	1.46 (0.9–2.3) [88:155]	3.88[d]	1.05 (0.4–2.5) [16:153]	1.10 (0.5–2.5) [19:154]	0.92 (0.4–2.2) [15:155]	0.03
Beta-carotene	0.88 (0.6–1.4) [81:154]	0.69 (0.4–1.1) [67:154]	0.59 (0.4–0.9) [56:155]	5.56[d]	0.80 (0.4–1.7) [19:154]	0.40 (0.2–0.9) [12:154]	0.53 (0.2–1.2) [17:155]	3.61
Vitamin C	1.20 (0.8–1.9) [71:155]	1.38 (0.9–2.2) [87:153]	0.81 (0.5–1.3) [57:155]	0.30	0.74 (0.3–1.6) [15:155]	0.75 (0.3–1.6) [18:153]	0.83 (0.4–1.9) [17:155]	0.19
Vitamin D	1.13 (0.7–1.8) [75:153]	1.13 (0.7–1.8) [73:153]	1.02 (0.6–1.6) [69:156]	0.01	1.69 (0.8–3.8) [23:153]	1.23 (0.5–2.9) [15:153]	1.47 (0.6–3.6) [19:156]	0.29
Vitamin E	1.12 (0.7–1.8) [78:154]	0.96 (0.6–1.6) [77:154]	0.65 (0.4–1.1) [61:155]	2.69	1.60 (0.7–3.7) [24:154]	0.97 (0.4–2.5) [17:154]	0.80 (0.3–2.3) [16:155]	0.93
Folate	1.04 (0.6–1.7) [69:154]	1.23 (0.7–2.0) [83:154]	0.99 (0.6–1.8) [69:155]	0.02	0.69 (0.3–1.7) [17:154]	0.88 (0.3–2.2) [19:154]	0.72 (0.3–2.1) [18:155]	0.12
Calcium	0.87 (0.6–1.4) [68:154]	0.99 (0.6–1.6) [76:154]	0.84 (0.5–1.4) [69:155]	0.19	1.32 (0.6–3.1) [18:154]	2.33 (1.0–5.6) [28:154]	0.75 (0.3–2.2) [12:155]	0.00
Thiamin	2.01 (1.2–3.3) [80:152]	1.90 (1.1–3.3) [84:154]	1.52 (0.8–2.9) [69:155]	0.92	0.98 (0.4–2.4) [17:152]	0.92 (0.3–2.5) [16:154]	1.14 (0.4–3.4) [21:155]	0.05
Riboflavin	1.11 (0.7–1.8) [72:155]	1.10 (0.7–1.8) [76:154]	0.88 (0.5–1.6) [67:154]	0.17	0.88 (0.4–2.1) [15:155]	1.23 (0.5–3.1) [22:154]	0.73 (0.2–2.2) [16:154]	0.12

[a] Estimates from multiple logistic regression equations including terms for study center, age, gender, history of benign thyroid diseases (yes/no), and total calorie intake.
[b] Papillary carcinomas also include mixed papillary/follicular carcinomas.
[c] Reference category is first quartile.
[d] $P < 0.05$.
[e] Numbers in brackets are those of cases and controls.

was an increasing risk of thyroid carcinoma at a higher consumption of retinol and lower consumption of vitamin E in papillary carcinomas, but not in follicular carcinomas.

When the data were analyzed for females and males separately, inverse relationships for beta-carotene, vitamin C, and vitamin E in females but not in males were observed. The ORs for subsequent quartiles of beta-carotene intake, compared with the lowest one, were 0.72, 0.59, and 0.40 in females, and 1.33, 0.87, and 1.15 in males. For vitamin C the ORs were 0.91, 0.99, and 0.72 in females and 1.25, 1.13, and 1.05 in males, and, for vitamin E, were 1.04, 0.83, and 0.53 in females and 1.48, 0.95, and 1.38 in males. However, estimates in males were based on small numbers and had wide confidence intervals. The interaction with gender was significant only for vitamin E.

DISCUSSION

This study showed significant protection from beta-carotene consumption against thyroid carcinoma. The apparent protection of vitamins C and E diminished when their effect was controlled for by that of beta-carotene, and the association between beta-carotene itself with thyroid carcinoma risk was unchanged or even enhanced when observed in the same model with vitamins C or E. Retinol intake showed a direct association with thyroid carcinoma risk. No clear association emerged for vitamin D, folate, calcium, thiamin, and riboflavin. The protective effect of beta-carotene was noted in papillary and follicular carcinomas, but appeared to be restricted to females.

The protective effect of beta-carotene against thyroid carcinoma is in agreement with its antioxidant activity.[11] This micronutrient has been shown to exert some protective effects on various other cancer sites.[12,13]

Beta-carotene, vitamin C, and a portion of vitamin E are derived from fruits, and various vegetables, which are present in the Italian diet. In a previous analysis of foods based on a smaller dataset from this same study, the ORs for the highest tertile, relative to the lowest one, of green vegetable consumption was 0.50, and was 0.53 for carrots.[14] It is still unclear whether the protection conveyed by fruits and vegetables is due mainly to beta-carotene, other carotenoids, or by some other constituents.[15]

In this study, thyroid carcinoma risk increased with increasing intake of retinol. Although various biologic mechanisms have been considered to explain a possible carcinogenic effect of retinol, including its prooxidant activity,[16] it is conceivable that retinol is an indicator of other factors, such as high consumption of liver, dairy products, eggs, or other related food groups.

The nutrient risk pattern and, in particular, the protective effect of beta-carotene were very consistent in papillary and follicular carcinomas of the thyroid. The two most common types of differentiated thyroid carcinomas may have different prognoses and, according to some hypotheses, different etiology.[17] Dietary data, including the current data, do not support this possibility. No association was found for other micronutrients investigated.

When females and males were analyzed separately, the results showed some apparently different patterns of risk. This also was observed in a study from Hawaii.[2] It is possible that the more marked association for women and the inconsistencies with the pattern of risk in males are, at least to some extent, due to the more accurate recall of diet in women, or to the smaller number of males, and hence to the instability of the estimates. Alternatively, it is conceivable that the micronutrients considered have a greater role in thyroid carcinogenesis for females, who also frequently have better differentiated, papillary tumors. However, the data do not allow the distinction of a sex specific effect, independent from tumor characteristics, from a more complex interaction between gender (and, possibly, gender-related hormones), diet, and histologic features of thyroid cancer.

Some of the results observed could be partly explained by bias or misclassification. The questionnaire used included only a limited number of food items, and was not validated. Nevertheless, the comparison with the average daily level of nutrient intake for the Italian population[18,19] is reassuring in terms of the reliability of the information obtained, although these estimates were based on the consumption of only 29 food items. Recall and information bias, with a systematic overestimation of various dietary intakes by cases, is possible, but adjustment for calorie intake should have limited the effect of any such bias. Furthermore, selection bias is unlikely to have substantially influenced any of the results obtained, given the comparable catchment areas of cases and controls, and the practically complete response rate and surveillance of the areas under study. Adjustment for the potential confounding effect of major recognized risk factors for thyroid carcinoma did not materially modify any pattern of risk. However, there remains concern regarding the choice of hospital controls, who may represent a selected population, with diets different from those of the general population.

Various methods of energy adjustment have been proposed, leading to potentially different results and interpretations for macronutrients.[20-22] However, because only micronutrients were considered in the current study, the results are not materially affected by the type of model used for energy adjustment.

In conclusion, this study suggests a protective role of dietary beta-carotene, and, possibly, vitamins C and E in thyroid carcinoma risk. Whether these results reflect a real effect of these micronutrients or limitations of the data requires further investigation.

REFERENCES

1. Ron E, Kleinerman RA, Boice JD Jr., LiVolsi VA, Flannery JT, Fraumeni JF. A population-based case-control study of thyroid cancer. *J Natl Cancer Inst* 1987;79:1–12.
2. Kolonel LN, Hankin JH, Wilkens LR, Fukunaga FH, Hinds MW. An epidemiologic study of thyroid cancer in Hawaii. *Cancer Causes Control* 1990;1:223–4.
3. Franceschi S, Levi F, Negri E, Fassina A, La Vecchia C. Diet and thyroid cancer: a pooled analysis of four European case-control studies. *Int J Cancer* 1991;48:395–8.
4. Glattre E, Haldorsen T, Berg JP, Stensvold I, Solvoll K. Norwegian case-control study testing the hypothesis that seafood increases the risk of thyroid cancer. *Cancer Causes Control* 1993;4:11–6.
5. Wingren G, Hatschek T, Axelson O. Determinants of papillary cancer of the thyroid. *Am J Epidemiol* 1993;138:482–91.
6. Preston-Martin S, Jin F, Duda MJ, Mack WJ. A case-control study of thyroid cancer in women under age 55 in Shanghai (People's Republic of China). *Cancer Causes Control* 1993;4:431–40.
7. Fidanza F, Liguori G. Nutrizione umana. Napoli: Ed. Idelson, 1984.
8. Souci SW, Fachman W, Kraut H. Food composition and nutrition tables. Deutsche Forschunganstalt fur Lebensmittelchemie edition, Garching (Munchen). Milano: OEMF, 1989/1990.

9. Hsieh C, Maisonneuve P, Boyle P, Macfarlane GJ, Robertson C. Analysis of quantitative data by quantiles in epidemiologic studies: classification according to cases, noncases, or all subjects. *Epidemiology* 1991;2:137–40.
10. Breslow NE, Day NE. Statistical methods in cancer research. Volume I. The analysis of case-control studies. Lyon, IARC Scientific Publications, 1980:32.
11. Halliwell B. Free radicals, antioxidants, and human disease: curiosity, cause, or consequence? *Lancet* 1994;344:721–4.
12. Hennekens CH, Mayrent SL, Willett W. Vitamin A, carotenoids, and retinoids. *Cancer* 1986;58:1837–41.
13. Ziegler RG. Vegetables, fruits, and carotenoids and the risk of cancer. *Am J Clin Nutr* 1991;53:251S–9S.
14. Franceschi S, Fassina A, Talamini R, Mazzolini A, Vianello S, Bidoli E, et al. Risk factors for thyroid cancer in Northern Italy. *Int J Epidemiol* 1989;18:578–84.
15. Ziegler RG, Subar AF, Craft NE, Ursin G, Patterson BH, Graubard BI. Does beta-carotene explain why reduced cancer risk is associated with vegetable and fruit intake? *Cancer Res* 1992;52(Suppl):2060s–6s.
16. Mayne ST, Graham S, Zheng T. Dietary retinol: prevention or promotion of carcinogenesis in humans? *Cancer Causes Control* 1991;2:443–50.
17. Franceschi S, Boyle P, Maisonneuve P, La Vecchia C, Burt AD, Kerr DJ, et al. The epidemiology of thyroid carcinoma. *Crit Rev Oncog* 1993;4:25–52.
18. Carnovale E, Miuccio F. Tabelle di Composizione degli Alimenti. Roma: Istituto della Nutrizione, 1989.
19. Atlante Ragionato di Alimentazione. Milano: Istituto Scotti Bassani per la Ricerca e l'Informazione Scientifica e Nutrizionale, 1992.
20. Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. *Am J Epidemiol* 1986;142:17–27.
21. Wacholder S, Schatzkin A, Freedman LS, Kipnis V, Hartman A, Brown CC. Can energy adjustment separate the effects of energy from those of specific macronutrients? *Am J Epidemiol* 1994;10:848–55.
22. Decarli A, Favero A, La Vecchia C, Russo A, Ferraroni M, Negri E, et al. Macronutrients and breast cancer risk: implications from different models. *Epidemiology*. In press.