British Journal of Nutrition (2013), **109**, 118–128
doi:10.1017/S0007114512000591

The effect of raw vegetable and fruit intake on thyroid cancer risk among women: a case–control study in South Korea

Su Kyoung Jung[1], Kirang Kim[1,2], Kyung Tae[3], Gu Kong[4] and Mi Kyung Kim[1]*

[1]*Department of Preventive Medicine, College of Medicine, Hanyang University, Medical School Building A-Room 512, 17 Haengdang Dong, Sungdong Gu, Seoul 133-791, Republic of Korea*
[2]*Division of Health and Nutrition Survey, Korea Centers for Disease Control and Prevention, Cheongwon 363-951, Republic of Korea*
[3]*Department of Otolaryngology, College of Medicine, Hanyang University, Seoul, Republic of Korea*
[4]*Department of Pathology, College of Medicine, Hanyang University, Seoul, Republic of Korea*

(Submitted 1 September 2011 – Final revision received 27 January 2012 – Accepted 27 January 2012 – First published online 28 March 2012)

Abstract

Thyroid cancer is the most common cancer among Korean women. However, there are few data on dietary factors related to thyroid cancer risk. The objective of the present study was to evaluate the association between raw vegetables and fruits intake and thyroid cancer in a case–control study. We included 111 histologically confirmed malignant thyroid cancer cases and 115 benign cases. Controls who did not have nodules in thyroid ultrasonography were matched to cases by age (±2 years). Food and nutrient intakes were estimated using a quantitative FFQ with 121 items. Conditional logistic regression analysis was used to obtain OR and corresponding 95 % CI. The intake of total vegetables was not associated with malignant thyroid cancer, but inversely associated with benign cases. High raw vegetable intake was inversely associated with thyroid cancer risk both in malignant and benign cases (*P* for trend=0·01 in both malignant and benign cases). Among fruits, persimmon intake had an inverse association with thyroid cancer risk in both malignant and benign cases (*P* for trend=0·06 in malignant cases; *P* for trend=0·01 in benign cases) and tangerine intake had an inverse association in malignant cases (*P* for trend=0·03). The frequency of consumption of raw vegetables and persimmon also had a consistent inverse association in both malignant and benign cases. These results suggest that high consumption of raw vegetables, persimmons and tangerines may decrease thyroid cancer risk and help prevent early-stage thyroid cancer.

Key words: Vegetables: Persimmons: Tangerines: Thyroid cancer: Case–control study

Thyroid cancer is the most common tumour type of the endocrine system[1]. Since the 1970s, thyroid cancer incidence rates have increased worldwide[1]. In contrast to Western countries, where breast cancer is the most common cancer type in women, thyroid cancer is the most common cancer type in adult Korean women[2,3]. The age-standardised incidence rate of thyroid cancer in Korean women (86·1/100 000) is higher than that of other countries and worldwide (22·3/100 000 for the USA, 11·5/100 000 for Europe, 8·3/100 000 for Japan, 3·0/100 000 for China and 6·6/100 000 worldwide)[2]. Furthermore, the incidence of this cancer type in Korean women has increased remarkably over time from 11·9/100 000 in 1999 to 80·2/100 000 in 2008[3].

The best-established risk factors for thyroid cancer are exposure to radiation[4] and a history of benign thyroid nodules or adenomas[5]. Exposure to radiation and benign thyroid nodules or adenomas may induce thyroid cancer through gene rearrangements[6] or mutations[7]. However, to our knowledge, only one cohort study reported some possible risk factors such as family history of cancer, BMI and hormonal factors for benign thyroid nodules[8], while little is known about lifestyle factors that may increase or decrease the risk of benign thyroid nodules or adenomas. Some dietary factors have also been reported to be related to thyroid cancer risk including fruit intake[9], vegetable intake[9–12], cruciferous vegetable intake[4,10–13], fish intake[12–16], glycaemic index, glycaemic load[17], micronutrients[18], iodine[13,15] and nitrate[19,20]. Among dietary factors, fruits and vegetables have been reported to have protective effects against many different cancers[21,22]. Some epidemiological studies have investigated the effect of fruit and vegetable intake on thyroid cancer risk.

Abbreviation: KNHANES, Korean National Health and Nutrition Survey.

* **Corresponding author:** M. K. Kim, fax +82 2 2293 0660, email kmkkim@hanyang.ac.kr

British Journal of Nutrition

However, those studies were conducted primarily in Western countries[4,9–11] and their findings were inconsistent[4].

Vegetables can be consumed raw, cooked or pickled; these latter two procedures may destroy the antioxidants present in raw vegetables[23–26]. Thus, the effect of raw vegetables on cancer risk might be masked if total vegetable consumption, including all raw, cooked and pickled vegetables, is examined. Nevertheless, previous studies have not determined the effect of raw vegetable consumption on cancer risk separately, except for a Greek study that reported an inverse association between raw vegetable dietary pattern and thyroid cancer[9].

Although the effects of fruit intake on thyroid cancer risk have been investigated in a few previous studies, inconsistent results were reported. This could be because different fruits have different effects on different cancer types. A Norwegian study reported an increased risk of thyroid cancer with citrus fruit consumption, but no association with apple intake[10]. A Greek study reported that fresh tomatoes and lemons may reduce thyroid cancer risk (P for trend=0·002 for tomatoes; P for trend=0·001 for lemons). Our objective in the present study was to investigate the association between total and raw vegetable intake and fruit intake on benign and malignant thyroid cancer risk in a Korean population.

Materials and methods

Cases and controls

From June 2008 to June 2010, cases and controls were recruited at Hanyang University Medical Center in Seoul, South Korea. All participants were women between the ages of 20 and 70 years. All potential subjects were examined by ultrasonography to confirm the presence of thyroid cancer.

Malignant cases were diagnosed by fine needle aspiration biopsy and ultrasonography. About 90 % of malignant cases were papillary carcinoma. Benign cases were subjects who had benign nodules or adenomas in ultrasonography and/or fine needle aspiration biopsy. We included 111 histologically confirmed malignant cases and 115 benign cases in this study.

Subjects were excluded from the study if they had any history of cancer (ten cases), or an estimated total energy intake $<$2093 kJ/d (500 kcal/d) or $>$16 744 kJ/d (4000 kcal/d) (eighteen cases and one control). Controls were patients who visited the otolaryngology or orthopaedic surgery departments of the same hospital. Patients with hormone-related diseases, abnormal thyroid hormone levels (thyroxine, thyroid-stimulating hormone) or thyroid nodules found by ultrasonography were excluded. Cases and controls were matched by their age (within 2 years) (111 pairs of malignant cases and controls and 115 pairs of benign cases and controls). All interviews were conducted in the hospital and the response rates for malignant and benign cases combined and controls were 70·4 and 41·0 %, respectively. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects were approved by the Institutional Review Board of Hanyang University Medical Center. Written informed consent was obtained from all participants.

Data collection

Cases and controls were interviewed using questionnaires to determine patients' general characteristics, menstrual and reproductive history, family history of thyroid cancer, smoking and drinking habits, intake of multivitamins and average time spent exercising.

Dietary data were collected using a quantitative FFQ, modified from the validated FFQ[27], with visual aids such as food photographs and models to demonstrate item-specific units. Kim *et al.*[27] evaluated the validity and reproducibility of semiquantitative FFQ by administering it twice at an interval of 2 years and comparing it with four or five 24 h recalls collected at intervals of 3 months. The Pearson's correlation coefficients between energy-adjusted nutrient intakes averaged 0·44 on the first questionnaire *v.* 24 h recalls and 0·37 on the second questionnaire *v.* 24 h recalls for fourteen nutrients (protein, fat, carbohydrate, fibre, Ca, P, Fe, Na, K, vitamin A, thiamin, riboflavin, niacin and ascorbic acid). The reproducibility of this FFQ determined by the correlation of the nutrient intakes was greater than 0·5. Regarding reliability of the modified FFQ, using our data for controls, the Cronbach's α was 0·78 for food frequency and 0·87 for its portion size.

Subjects were asked by trained interviewers to recall their usual intake of 121 food items over a period of 12 months beginning from 3 years before the time of the interview[28]. Portion sizes were open-ended questions and standard units were used for all food items. All frequencies were standardised into 'times per d' by using the conversion factors 30·4 d/month and 4·3 d/week. Daily food intake was calculated using the standardised frequency per d and the amount of food per standard unit. Daily nutrient and energy intake were estimated using the daily food intake and recipe and nutrient database[29]. Nutrient intakes were adjusted for total energy intake by the residual method to avoid bias due to the simple relationship between nutrient intake and total energy intake[28]. Total vegetable intake was estimated by summing the daily consumption of pickled vegetables (cabbage kimchi, radish kimchi, watery radish kimchi, cucumber kimchi, sesame leaf kimchi and jangajji), raw vegetables (lettuce, Korean cabbage, cabbage, cucumber, pepper, carrot, sesame leaf, onion, radish, crown daisy, water dropwort, chicory, broccoli, celery and garlic), cooked vegetables (soyabean sprouts, mungbean sprouts, spinach, eggplant and bracken), mushrooms and seaweeds. Total fruit intake was estimated by totalling the daily intake of fourteen fruits (persimmon, tangerine, orange, kiwi, melon, grape, strawberry, watermelon, pear, apple, banana, peach, tomato and fruit juice).

Statistical analyses

Cases and controls were compared using the Wilcoxon signed rank test for continuous variables and the McNemar test for categorical variables. Data were analysed according to quartiles of daily intake (g/d) and average consumption frequency (times/week) of total vegetables, raw vegetables, total fruits and all single fruits. Among single fruits, only fruits significantly associated with malignant cancer or benign thyroid disease are presented in the tables. The OR and corresponding 95 % CI were obtained using conditional logistic regression analysis. The general linear model and Cochran–Mantel–Haenszel analysis were used to assess potential confounders among controls. Trend tests were conducted by treating the median values of each quartile of daily fruit and vegetable intake or the average consumption frequency of the specific fruit or vegetable as continuous values in each of the models. Variables that were significantly different between cases and controls and which showed significant linear trends across quartiles of daily intake of total vegetables, raw vegetables, total fruits, persimmons and tangerines were considered as potential confounders and adjusted in the analyses. Antioxidants such as vitamin C, β-carotene, and folate, which were highly correlated with fruit and vegetable intake ($r_p > 0{\cdot}40$), were not included in multiple logistic regression models as potential confounders. All multiple logistic regression models included parity (yes/no), energy (quartile) for malignant pair analyses and energy (quartile) for benign pair analyses. Additionally, Na (quartile) was added in the total vegetable model, whereas Na (quartile) and vitamin E (quartile) were added in the raw vegetable model, and age at menarche (years) was added in the persimmon model. Parity (yes/no) was added in the tangerine model. Statistical analyses were conducted using SAS (version 9.1) software.

Results

Table 1 shows the general characteristics of the cases and controls. The average ages of malignant cases and controls were 45·9 and 45·2 years, respectively, and those of benign cases and controls were 46·8 and 46·5 years, respectively. Parity was significantly higher in malignant cases than controls. Daily intake of raw vegetables was higher in controls than in malignant cases (34·1 g/d for malignant cases *v.* 47·7 g/d for controls). Daily intake of total vegetables and persimmons were higher in controls than benign cases (240·7 g/d for benign cases *v.* 268·9 g/d for controls in total vegetables

Table 1. General characteristics of the study subjects with and without thyroid cancer†
(Mean values and standard deviations or proportions)

	Malignant					Benign				
	Cases (*n* 111)		Controls (*n* 111)			Cases (*n* 115)		Controls (*n* 115)		
Characteristics	Mean	SD	Mean	SD	*P**	Mean	SD	Mean	SD	*P**
Age (years)	45·9	10·8	45·2	10·6	N/A	46·8	10·1	46·5	10·5	N/A
Education (years)	12·3	3·9	12·0	3·7	0·537	12·3	3·6	11·7	3·5	0·156
BMI (kg/m^2)	23·4	3·4	23·5	3·6	0·930	23·4	2·8	23·4	3·4	0·980
Children (*n*)	2·0	0·9	1·8	1·2	0·134	1·9	1·0	1·9	1·2	0·246
Age at menarche (years)	14·6	2·0	14·6	1·9	0·905	14·6	1·8	14·7	1·9	0·647
Age at first birth (years)	26·0	3·6	26·1	3·9	0·804	25·4	3·1	25·7	3·7	0·559
Age at menopause (years)	49·6	4·6	49·2	5·1	0·701	49·3	5·0	49·6	4·3	0·567
Dietary intake										
Energy (kJ/d)	8401·6	704·2	8567·7	681·1	0·772	8561·0	631·2	8332·1	651·2	0·391
Carbohydrate (g/d)	304·4	41·8	307·0	44·8	0·691	305·7	44·0	309·3	42·6	0·596
Fibre (g/d)	8·1	2·5	8·3	2·8	0·811	8·1	2·9	8·6	3·3	0·250
β-Carotene (μg/d)	3660·8	1492·6	4130·5	3048·5	0·685	4098·5	4168·2	4405·3	4276·8	0·457
Vitamin C (mg/d)	135·4	59·3	144·6	73·2	0·470	139·3	70·7	148·9	81·4	0·391
Folate (μg/d)	267·5	83·6	270·0	102·0	0·979	259·0	85·5	276·8	120·8	0·341
Vitamin E (mg/d)	9·2	3·2	9·0	3·7	0·344	9·6	3·6	9·1	3·8	0·196
Na (mg/d)	4146·7	1301·3	4048·7	1435·6	0·599	3907·8	1447·1	4053·7	1506·5	0·400
Total vegetables (g/d)	243·6	161·5	265·1	196·3	0·391	240·7	319·2	268·9	203·3	0·030
Raw vegetables (g/d)	34·1	43·0	47·7	59·5	0·015	45·0	79·9	53·2	71·8	0·316
Total fruits (g/d)	297·4	243·5	331·0	291·1	0·418	347·7	341·1	323·8	287·4	0·598
Persimmon (g/d)	14·1	34·0	18·2	37·7	0·063	14·2	40·6	19·3	37·8	0·036
Tangerine (g/d)	38·6	62·0	46·1	66·1	0·103	44·8	52·4	44·1	65·1	0·688
Menopause women (%)	46·0		40·5		0·109	47·0		46·1		0·835
Family history of thyroid cancer (%)	3·6		2·7		0·706	1·7		1·7		1·000
Current smoker (%)	0·9		4·5		0·103	4·4		4·4		1·000
Current alcohol drinker (%)	34·2		40·5		0·274	40·0		42·6		0·686
Regular exercise (>22·5 MET-h/week, %)	22·5		16·2		0·162	20·9		17·4		0·493
Multivitamin user (%)	14·4		21·6		0·182	21·7		21·7		1·000
Parity (%)	91·9		83·8		0·013	88·7		85·2		0·206
Oral contraceptive use (ever, %)	19·8		19·8		1·000	15·7		22·6		0·206
Breast-feeding (ever, %)	75·7		70·3		0·330	70·4		71·3		0·862
Used hormone compound (ever, %)	12·6		18·0		0·239	11·3		19·1		0·083

N/A, not applicable; MET, metabolic equivalent.
* Wilcoxon signed rank test for continuous variables and McNemar test for categorical variables.
† All nutrient intakes are total energy-adjusted values.

Table 2. Potential confounders according to quartile of intake of total vegetables and raw vegetables among controls†‡

	Quartiles of daily total vegetable intake					Quartiles of daily raw vegetable intake				
	1st	2nd	3rd	4th	*P* for trend*	1st	2nd	3rd	4th	*P* for trend*
Median (g)	73·3	152·4	246·5	450·1		4·7	18·1	34·8	79·2	
Age (years)	41·8	43·9	48·3	46·3	0·158	40·5	43·9	48·8	45·3	0·250
Menopause women (%)	41·0	44·3	40·2	41·6	0·829	45·9	36·1	49·2	37·5	0·699
Education (years)	11·5	12·1	12·1	12·4	0·241	11·2	11·9	12·3	12·4	0·184
BMI (kg/m^2)	21·9	24·3	23·0	23·8	0·189	22·8	23·6	23·6	23·1	0·877
Family history of thyroid cancer (%)	10·5	4·7	0·0	0·0	0·064	2·3	4·2	0·0	1·7	0·510
Current smoker (%)	4·5	4·1	0·0	4·6	0·831	0·0	2·8	8·2	1·7	0·488
Current alcohol drinker (%)	35·5	39·1	49·1	40·1	0·817	31·9	42·0	37·8	47·0	0·464
Regular exercise (>22·5 MET-h/week, %)	20·1	13·8	12·4	16·2	0·717	16·6	11·2	19·3	12·9	0·914
Multivitamin user (%)	27·7	26·1	11·9	19·2	0·287	24·0	27·2	13·5	26·4	0·725
Parity (%)	80·6	82·5	90·7	81·6	0·796	84·3	78·6	76·1	90·7	0·286
Children (*n*)	1·8	1·9	2·0	1·7	0·645	1·9	1·8	1·7	1·9	0·485
Oral contraceptive use (ever, %)	9·9	17·4	37·8	21·6	0·356	15·2	16·0	18·3	25·5	0·360
Breast-feeding (ever, %)	75·0	49·4	83·1	72·4	0·317	69·9	64·1	69·2	76·1	0·399
Used hormone compound (ever, %)	25·2	21·8	10·3	18·6	0·272	33·7	18·4	15·5	16·9	0·356
Age at menarche (years)	15·1	14·0	15·0	14·2	0·161	14·4	14·8	14·5	14·4	0·624
Age at first birth (years)	24·9	26·4	26·1	26·1	0·482	25·9	25·5	26·1	26·1	0·631
Age at menopause (years)	47·9	48·4	49·2	50·5	0·074	47·9	47·4	50·2	49·7	0·293
Energy intake (kJ/d)	7499·2	8262·6	7724·3	9776·1	0·002	8068·0	7969·2	8474·8	9015·6	0·177
β-Carotene (μg/d)	2459·7	3503·8	4151·4	6644·8	<0·0001	2438·2	3267·7	3281·1	7452·3	<0·0001
Vitamin C intake (mg/d)	98·1	128·9	152·6	191·7	<0·0001	100·5	124·0	141·0	197·4	<0·0001
Folate intake (μg/d)	185·9	235·8	285·9	360·1	<0·0001	200·0	239·3	254·4	365·5	<0·0001
Vitamin E intake (mg/d)	8·3	8·6	9·6	9·8	0·090	6·7	8·4	8·8	11·3	<0·0001
Na intake (mg/d)	2587·7	3427·5	4385·1	5391·9	<0·0001	3226·5	4026·8	3925·6	4775·3	<0·0001

MET, metabolic equivalent.
* *P*-values for trends were determined by the general linear model for continuous variables and by the Cochran–Mantel–Haenszel test for categorical variables.
† All results except median and age were adjusted for age, and all nutrient intakes are total energy-adjusted values.
‡ Values are expressed as mean or percentage according to quartile of fruit and vegetable intake.

intake; 14·2 g/d for benign cases *v.* 19·3 g/d for controls in persimmon intake). Daily intake of energy, carbohydrates, fibre, β-carotene, vitamin C, folate, vitamin E, Na, total fruits and tangerines did not differ between cases and controls for either malignant pairs or benign pairs.

Potential confounding factors determined by using the quartiles of daily total vegetable and raw vegetable intake are shown in Table 2. Dietary intake of β-carotene, vitamin C, folate and Na increased across quartiles of total vegetable intake and quartiles of raw vegetable intake.

Potential confounding factors determined by using the quartiles of daily total fruit, persimmon and tangerine intake are shown in Table 3. Average age and age at menarche increased across quartiles of daily persimmon intake. Vitamin C increased across quartiles of total fruit intake, persimmon intake and tangerine intake. Daily intake of β-carotene and folate increased across quartiles of total fruit intake.

The association between vegetable and fruit intake and thyroid cancer risk is shown in Table 4. Total vegetable intake was inversely associated with benign thyroid cancer risk (OR 0·42; 95 % CI 0·19, 0·91; *P* for trend=0·028 in benign cases). After adjusting for potential confounders (energy intake and Na intake), the significant inverse association remained (OR 0·11; 95 % CI 0·03, 0·47; *P* for trend=0·003 in benign cases). A significant inverse association between raw vegetable intake and thyroid cancer risk was found (OR 0·31; 95 % CI 0·12, 0·79; *P* for trend=0·036 in malignant cases and OR 0·56; 95 % CI 0·27, 1·15; *P* for trend=0·085 in benign cases). The inverse association between raw vegetable intake and thyroid cancer risk remained (OR 0·20; 95 % CI 0·07, 0·62; *P* for trend=0·007 in malignant cases and OR 0·28; 95 % CI 0·10, 0·76; *P* for trend=0·007 in benign cases) after adjusting for potential confounders (parity, energy intake, vitamin E intake and Na intake). An inverse association between thyroid cancer risk and persimmon intake was found in both malignant and benign cases (OR 0·39; 95 % CI 0·17, 0·88 for the highest quartile; *P* for trend=0·037 in malignant cases and OR 0·35; 95 % CI 0·15, 0·82 for the highest quartile; *P* for trend=0·016 in benign cases). After adjusting for potential confounders, the significant inverse associations remained (OR 0·41; 95 % CI 0·17, 0·96 for the highest quartile; *P* for trend=0·061 in malignant cases and OR 0·35; 95 % CI 0·15, 0·83 for the highest quartile; *P* for trend=0·014 in benign cases). An inverse association between tangerine intake and malignant thyroid cancer risk was found after adjusting for potential confounders, but there was no significant association between daily tangerine intake and benign thyroid cancer risk (OR 0·34; 95 % CI 0·13, 0·86 for the highest quartile; *P* for trend=0·027 in malignant cases). There were no associations between thyroid cancer risk and daily intake of total vegetables or total fruits in the present study.

The association between thyroid cancer risk and the average frequency of vegetable and fruit intake is shown in Table 5. There was a trend for an inverse association between thyroid cancer risk and the average frequency of raw vegetable intake in malignant and benign cases after adjusting for potential confounders. The frequency of raw vegetable intake was inversely associated with thyroid cancer risk (OR 0·28; 95 % CI 0·10, 0·78 for the highest quartile; *P* for trend=0·009 in malignant cases and OR 0·38; 95 % CI 0·16, 0·91 for the highest quartile; *P* for trend=0·043 in benign cases). A high frequency of persimmon intake was inversely associated with thyroid cancer risk (OR 0·44; 95 % CI 0·20, 0·94 for the highest quartile; *P* for trend=0·040 in malignant cases and OR 0·35; 95 % CI 0·15, 0·81 for the highest quartile; *P* for trend=0·017 in benign cases). The inverse association between the average frequency of persimmon intake and thyroid cancer risk remained after adjusting for potential confounders (OR 0·44; 95 % CI 0·20, 0·99 for the highest quartile; *P* for trend=0·060 in malignant cases and OR 0·33; 95 % CI 0·14, 0·79 for the highest quartile; *P* for trend=0·014 in benign cases). We did not find a significant association between thyroid cancer risk and the frequency of total vegetable intake, total fruit intake or tangerine intake. The additional adjustments for the risk factors reported in previous studies (education, family history of thyroid cancer, BMI, current smoker and current alcohol drinker) did not substantially change the results (data not shown).

Discussion

Given that the effects of vegetable and fruit intake on thyroid cancer risk have not been well characterised, we aimed to examine the association between vegetable and fruit intake and the risk of thyroid cancer. We found that consumption of raw vegetables, persimmons and tangerines had a significant protective effect against thyroid cancer. Raw vegetable and persimmon intake had a dose–response effect on both malignant cases and benign cases in terms of both frequency of consumption as well as amount consumed. The amount of tangerines consumed showed a dose–response association with malignant cases.

According to the fourth Korean National Health and Nutrition Survey (KNHANES 2007–9), the average intake of total vegetables and fruits by Korean women is 293·8 g/d and 209·6 g/d, respectively. In the present study, the consumption of total vegetables by malignant cases and benign cases (243·6 g/d for malignant cases, 240·7 g/d for benign cases and 270·5 g/d for controls) was lower than that reported by KNHANES (293·8 g/d). The total fruit intake of cases and controls (297·4 g/d for malignant cases, 347·7 g/d for benign cases and 325·4 g/d for controls) was higher than that reported by KNHANES (209·6 g/d). With regard to persimmon intake, cases and controls had a lower intake than that reported by KNHANES (14·1 g/d for malignant cases, 14·2 g/d for benign cases, 17·8 g/d for controls, *v.* 27·7 g/d for KNHANES). However, cases and controls had a higher tangerine intake than that reported by KNHANES (38·6 g/d for malignant cases, 44·8 g/d for benign cases, 45·1 g/d for controls, *v.* 28·2 g/d for KNHANES). The level of vegetable consumption by Korean adults has been reported to be relatively high[30,31]. The amount of vegetables consumed per person per year in Korea in 2005 was relatively high at 695 g for Korea, almost twice that of the USA (344 g) but lower than that of Greece (807 g)[32]. When the intake of fruits and vegetables was

Table 3. Potential confounders according to quartile of intake of fruit, persimmons and tangerines among controls†‡

	Quartiles of daily total fruit intake					Quartiles of daily persimmon intake					Quartiles of daily tangerine intake				
	1st	2nd	3rd	4th	*P* for trend*	1st	2nd	3rd	4th	*P* for trend*	1st	2nd	3rd	4th	*P* for trend*
Median (g)	66·4	176·1	299·5	599·2		0·0	3·4	7·9	31·5		3·3	20·0	40·0	76·8	
Age (years)	48·1	44·9	43·9	44·9	0·452	41·7	45·3	43·2	48·5	0·014	45·3	46·7	44·4	44·3	0·461
Menopause women (%)	37·0	54·3	39·4	38·0	0·372	40·3	45·7	42·9	38·2	0·809	40·3	47·5	41·7	38·0	0·436
Education (years)	11·2	11·6	12·8	12·3	0·143	12·4	11·7	12·4	12·0	0·835	11·0	11·9	13·3	11·9	0·424
BMI (kg/m^2)	24·2	23·1	22·9	23·4	0·726	23·6	23·8	22·9	23·1	0·527	22·9	23·3	23·6	23·4	0·602
Family history of thyroid cancer (%)	4·7	0·0	0·0	5·8	0·598	0·0	5·1	0·0	1·6	0·865	5·6	0·0	4·2	2·3	0·946
Current smoker (%)	1·1	0·0	0·0	5·5	0·305	3·2	6·4	0·0	4·4	0·881	11·2	2·8	0·0	2·5	0·072
Current alcohol drinker (%)	50·3	46·6	38·3	34·3	0·134	45·7	43·2	56·3	33·0	0·174	61·3	41·6	27·8	42·6	0·208
Regular exercise (>22·5 MET-h/week, %)	11·2	12·6	21·4	21·8	0·266	10·3	17·0	20·9	15·2	0·904	16·4	13·5	15·4	16·1	0·800
Multivitamin user (%)	38·1	15·6	13·1	26·9	0·615	32·1	20·4	19·1	18·0	0·280	31·9	26·3	18·0	14·0	0·056
Parity (%)	79·5	77·2	83·5	88·0	0·111	80·3	77·9	87·0	86·3	0·189	75·7	82·3	84·7	88·2	0·044
Children (*n*)	1·5	1·9	1·9	2·0	0·122	1·9	1·6	2·0	1·9	0·441	1·7	1·8	1·9	1·9	0·367
Oral contraceptive use (ever, %)	21·3	26·5	16·0	16·2	0·482	21·6	17·0	24·4	20·9	0·955	21·4	16·6	25·7	20·5	0·767
Breast-feeding (ever, %)	60·8	70·7	68·5	74·5	0·207	58·5	66·0	70·1	74·6	0·088	72·0	65·2	74·9	70·4	0·540
Used hormone compound (ever, %)	22·3	22·1	16·4	18·9	0·399	37·3	20·7	17·2	13·7	0·067	24·7	23·6	12·8	19·9	0·648
Age at menarche (years)	13·9	14·9	14·8	14·3	0·943	14·3	13·9	14·9	14·9	0·027	14·7	14·4	14·3	14·6	0·843
Age at first birth (years)	26·0	25·5	25·7	26·4	0·431	26·2	25·9	26·0	25·8	0·762	25·2	25·7	26·9	25·9	0·627
Age at menopause (years)	47·7	50·2	49·7	48·8	0·999	51·9	47·3	50·2	49·6	0·677	50·3	48·8	49·8	49·1	0·811
Energy intake (kJ/d)	7060·1	7567·4	8757·3	9971·1	<.0001	8538·0	7690·0	8070·5	9273·0	0·135	6756·7	8615·9	8632·6	9195·1	0·004
β-Carotene (μg/d)	3019·9	3805·3	4924·8	5523·1	0·021	4352·7	3197·7	5820·6	4649·7	0·479	3387·3	4894·1	4402·5	4619·9	0·566
Vitamin C intake (mg/d)	88·6	122·7	155·8	206·0	<.0001	121·0	114·7	168·6	178·1	0·000	103·9	126·6	153·5	192·3	0·039
Folate intake (μg/d)	221·2	258·9	285·6	323·6	0·001	252·9	248·0	326·2	283·3	0·345	244·7	280·3	273·2	294·3	0·191
Vitamin E intake (mg/d)	8·0	9·9	8·5	10·0	0·145	9·4	8·1	10·1	9·2	0·729	9·0	9·2	8·9	9·4	0·657
Na intake (mg/d)	3790·9	4151·8	4058·5	4323·2	0·247	3706·1	4018·2	4569·0	4108·4	0·641	3897·6	4350·5	3789·8	4198·1	0·802

MET, metabolic equivalent.
* *P*-values for trends were determined by the general linear model for continuous variables and by the Cochran–Mantel–Haenszel test for categorical variables.
† All results except median and age were adjusted for age, and all nutrient intakes are total energy-adjusted values.
‡ Values are expressed as mean or percentage according to quartile of fruit and vegetable intake.

Table 4. Thyroid cancer according to quartiles of vegetable and fruit intake in multiple logistic regression models
(Odds ratios and 95 % confidence intervals)

Daily intake	Median	Min, max	No. of cases/no. of controls	Crude OR	95 % CI	Adjusted OR	95 % CI*
Malignant cases			111/111				
Total vegetables (g/d)							
Q1	83·3	8·2, 136·2	25/30	1·00	Referent	1·00	Referent
Q2	168·6	136·8, 211·9	31/25	1·53	0·69, 3·38	1·20	0·47, 3·09
Q3	254·3	213·1, 335·7	31/25	1·44	0·69, 3·04	0·90	0·34, 2·42
Q4	454·0	335·8, 1185·4	24/31	0·92	0·43, 1·94	0·51	0·15, 1·78
P for trend				0·603		0·202	
Raw vegetables (g/d)							
Q1	4·5	0·0, 10·7	30/17	1·00	Referent	1·00	Referent
Q2	17·9	11·4, 24·3	32/28	0·53	0·23, 1·22	0·64	0·25, 1·62
Q3	34·6	24·3, 50·5	25/34	0·32	0·13, 0·78	0·23	0·08, 0·70
Q4	72·5	50·5, 359·5	24/32	0·31	0·12, 0·79	0·20	0·07, 0·62
P for trend				0·036		0·007	
Total fruits (g/d)							
Q1	81·7	0·0, 128·0	30/24	1·00	Referent	1·00	Referent
Q2	176·4	129·4, 230·4	26/25	0·77	0·34, 1·78	0·84	0·34, 2·07
Q3	285·2	232·1, 381·0	29/30	0·74	0·35, 1·59	0·78	0·35, 1·76
Q4	606·1	385·8, 1873·2	26/32	0·62	0·28, 1·38	0·59	0·23, 1·52
P for trend				0·283		0·250	
Persimmons (g/d)							
Q1	0	0·0, 0·5	33/21	1·00	Referent	1·00	Referent
Q2	3·1	0·7, 5·3	31/30	0·64	0·29, 1·39	0·63	0·27, 1·47
Q3	10·5	6·8, 13·5	21/22	0·61	0·27, 1·37	0·61	0·25, 1·46
Q4	29·3	15·8, 330·8	26/38	0·39	0·17, 0·88	0·41	0·17, 0·96
P for trend				0·037		0·061	
Tangerines (g/d)							
Q1	4·1	0·0, 10·5	30/20	1·00	Referent	1·00	Referent
Q2	20·0	10·7, 26·7	28/32	0·60	0·28, 1·27	0·64	0·29, 1·39
Q3	40·0	30·0, 50·0	30/26	0·72	0·33, 1·54	0·61	0·27, 1·39
Q4	79·3	52·4, 600·0	23/33	0·45	0·20, 1·03	0·34	0·13, 0·86
P for trend				0·086		0·027	
Benign cases			115/115				
Total vegetables (g/d)							
Q1	80·8	13·9, 116·7	34/23	1·00	Referent	1·00	Referent
Q2	153·0	117·3, 201·0	30/28	0·75	0·35, 1·60	0·48	0·19, 1·23
Q3	237·9	201·2, 311·4	29/29	0·69	0·33, 1·43	0·32	0·11, 0·95
Q4	422·2	311·5, 3137·1	22/35	0·42	0·19, 0·91	0·11	0·03, 0·47
P for trend				0·028		0·003	
Raw vegetables (g/d)							
Q1	6·0	0·0, 10·8	28/19	1·00	Referent	1·00	Referent
Q2	18·6	11·8, 24·3	30/24	0·84	0·38, 1·89	0·68	0·27, 1·72
Q3	35·7	24·8, 49·2	31/36	0·61	0·28, 1·34	0·42	0·17, 1·06
Q4	77·3	52·0, 591·9	26/36	0·56	0·27, 1·15	0·28	0·10, 0·76
P for trend				0·085		0·007	
Total fruits (g/d)							
Q1	67·0	0·0, 127·7	23/26	1·00	Referent	1·00	Referent
Q2	176·1	131·9, 230·4	30/27	1·25	0·59, 2·64	1·26	0·59, 2·71
Q3	290·3	231·0, 380·3	31/31	1·12	0·53, 2·36	1·10	0·50, 2·44
Q4	643·8	382·3, 1873·2	31/31	1·12	0·53, 2·40	1·05	0·46, 2·37
P for trend				0·924		0·910	
Persimmons (g/d)							
Q1	0·0	0·0, 0·5	28/21	1·00	Referent	1·00	Referent
Q2	3·1	0·7, 5·6	26/30	0·69	0·33, 1·47	0·70	0·33, 1·51
Q3	6·8	6·2, 13·5	36/22	1·30	0·61, 2·77	1·36	0·62, 2·98
Q4	24·8	15·5, 346·5	25/42	0·35	0·15, 0·82	0·35	0·15, 0·83
P for trend				0·016		0·014	
Tangerines (g/d)							
Q1	3·3	0·0, 10·5	30/23	1·00	Referent	1·00	Referent
Q2	20·0	10·7, 26·7	24/35	0·54	0·25, 1·17	0·53	0·24, 1·16
Q3	40·0	30·0, 50·0	29/25	0·83	0·35, 1·96	0·79	0·32, 1·93
Q4	79·3	51·4, 600·0	32/32	0·73	0·32, 1·65	0·71	0·30, 1·67
P for trend				0·937		0·912	

Min, minimum; max, maximum.

* All adjusted OR models included parity (yes/no), energy (quartile) in the malignant cancer model. Energy (quartile) was adjusted for in the benign cancer model. The model for total vegetables was additionally adjusted by Na intake (quartile). The model for raw vegetables was additionally adjusted for Na intake (quartile) and vitamin E intake (quartile). The model for persimmons was additionally adjusted for age at menarche (years). The model for tangerines was additionally adjusted for parity (yes/no).

Table 5. Thyroid cancer according to quartiles of the average frequency of vegetable and fruit consumption in multiple logistic regression models (Odds ratios and 95 % confidence intervals)

Average frequency	Median	Min, max	No. of cases/no. of controls	Crude OR	95 % CI	Adjusted OR	95 % CI*
Malignant cases			111/111				
Total vegetables (times/week)							
Q1	17·5	3·8, 22·7	21/34	1·00	Referent	1·00	Referent
Q2	27·7	23·1, 31·8	37/19	2·75	1·30, 5·83	2·54	1·11, 5·80
Q3	37·4	32·2, 45·1	27/29	1·32	0·61, 2·86	1·19	0·49, 2·90
Q4	58·4	45·6, 92·0	26/29	1·30	0·59, 2·87	1·24	0·43, 3·59
P for trend				0·921		0·924	
Raw vegetables (times/week)							
Q1	0·8	0·0, 2·4	30/25	1·00	Referent	1·00	Referent
Q2	3·2	2·4, 3·9	31/25	0·94	0·44, 2·02	0·76	0·33, 1·79
Q3	5·2	3·9, 6·7	29/27	0·81	0·36, 1·84	0·66	0·25, 1·73
Q4	10·0	6·8, 28·4	21/34	0·48	0·21, 1·11	0·28	0·10, 0·78
P for trend				0·050		0·009	
Total fruits (times/week)							
Q1	2·7	0·0, 4·3	29/26	1·00	Referent	1·00	Referent
Q2	6·2	4·3, 7·7	31/25	1·13	0·50, 2·52	1·31	0·55, 3·10
Q3	9·7	7·7, 12·0	26/30	0·75	0·35, 1·65	0·80	0·35, 1·85
Q4	16·1	12·0, 44·9	25/30	0·75	0·35, 1·62	0·73	0·30, 1·78
P for trend				0·318		0·267	
Persimmons (times/week)							
Q1	0·0	0·0, 0·0	33/22	1·00	Referent	1·00	Referent
Q2	0·3	0·1, 0·3	30/29	0·71	0·34, 1·51	0·61	0·26, 1·39
Q3	0·4	0·3, 0·6	24/24	0·67	0·31, 1·45	0·76	0·33, 1·78
Q4	1·2	0·9, 5·3	24/36	0·44	0·20, 0·94	0·44	0·20, 0·99
P for trend				0·040		0·060	
Tangerines (times/week)							
Q1	0·3	0·0, 0·4	39/27	1·00	Referent	1·00	Referent
Q2	0·9	0·5, 0·9	22/20	0·77	0·33, 1·76	0·83	0·35, 1·97
Q3	1·2	0·9, 1·4	24/36	0·47	0·23, 0·96	0·41	0·19, 0·88
Q4	1·8	1·5, 5·3	26/28	0·60	0·27, 1·30	0·50	0·21, 1·19
P for trend				0·112		0·066	
Benign cases							
Total vegetables (times/week)							
Q1	14·7	3·2, 20·6	30/27	1·00	Referent	1·00	Referent
Q2	26·0	20·8, 31·3	23/35	1·81	0·83, 3·96	1·84	0·83, 4·06
Q3	36·2	31·7, 45·8	33/25	0·76	0·35, 1·69	0·71	0·28, 1·78
Q4	58·0	45·9, 101·4	29/28	1·03	0·45, 2·32	0·94	0·35, 2·52
P for trend				0·716		0·858	
Raw vegetables (times/week)							
Q1	1·4	0·0, 2·4	33/24	1·00	Referent	1·00	Referent
Q2	3·1	2·4, 3·9	29/29	0·72	0·33, 1·59	0·57	0·24, 1·36
Q3	5·6	4·0, 7·3	27/31	0·68	0·34, 1·37	0·45	0·19, 1·05
Q4	10·7	7·5, 29·5	26/31	0·67	0·34, 1·32	0·38	0·16, 0·91
P for trend				0·288		0·043	
Total fruits (times/week)							
Q1	3·0	0·0, 4·6	28/29	1·00	Referent	1·00	Referent
Q2	5·9	4·7, 7·3	32/26	1·27	0·59, 2·73	1·30	0·58, 2·89
Q3	9·7	7·3, 12·2	25/33	0·80	0·38, 1·71	0·82	0·38, 1·80
Q4	18·6	12·2, 44·9	30/27	1·14	0·53, 2·46	1·09	0·46, 2·59
P for trend				0·902		0·928	
Persimmons (times/week)							
Q1	0·0	0·0, 0·1	33/25	1·00	Referent	1·00	Referent
Q2	0·3	0·1, 0·3	26/29	0·67	0·33, 1·38	0·67	0·32, 1·37
Q3	0·4	0·4, 0·6	33/22	1·28	0·59, 2·74	1·31	0·59, 2·92
Q4	1·2	0·9, 5·3	23/39	0·35	0·15, 0·81	0·33	0·14, 0·79
P for trend				0·017		0·014	
Tangerines (times/week)							
Q1	0·3	0·0, 0·4	34/27	1·00	Referent	1·00	Referent
Q2	0·9	0·5, 0·9	21/20	0·50	0·22, 1·13	0·50	0·22, 1·14
Q3	1·2	1·2, 1·5	28/36	0·94	0·43, 2·08	0·91	0·40, 2·07
Q4	1·8	1·5, 7·0	32/28	0·95	0·43, 2·11	0·92	0·40, 2·12
P for trend				0·727		0·811	

Min, minimum; max, maximum.

* All adjusted OR models included parity (yes/no), energy (quartile) for the malignant cancer model. Energy (quartile) was adjusted for in the benign cancer model. The model for frequency of consumption of total vegetables was additionally adjusted for Na intake (quartile). The model for frequency of consumption of raw vegetables was additionally adjusted for Na intake (quartile) and vitamin E intake (quartile). The model for frequency of consumption of persimmons was additionally adjusted for age at menarche (years). The model for tangerines was additionally adjusted for parity (yes/no).

combined (503·4 g/d in the fourth KNHANES), the intake by Koreans based on national surveys was higher than that of Europeans[33,34].

Several meta-analyses of the association between fruit and vegetable intake and the risk of cancers including breast cancer[35], colon cancer[36], oral cancer[37] and gastric cancer[38] have found that vegetable intakes were inversely associated with the risk of breast cancer[35], oral cancer[37] and gastric cancer[38], but the site-specific associations of colon cancer were not consistent[36] and that the fruit intakes were significantly related to oral cancer[37] and gastric cancer risk[38]. Fruits and vegetables may exert their protective effects via antioxidant mechanisms, by serving as substrates for the formation of anti-neoplastic agents, by inhibiting nitrosamine formation, and/or by altering hormone metabolism, among other possible mechanisms[21,39]. Furthermore, multiple substances present in fruits and vegetables such as antioxidant vitamins (β-carotene, vitamin A, vitamin E, vitamin C), dietary fibres, micronutrients and other phytochemicals may protect against cancer[40]. Several studies have also investigated the association between thyroid cancer risk and consumption of vegetables, especially in western countries[4,9–12,16]. These studies reported an inverse association between thyroid cancer risk and raw vegetable consumption[4,10–12]. In the present study, we focused on the effect of raw vegetables to obtain additional information about the inverse, dose–response associations between the amount and frequency of raw vegetable intake and thyroid cancer risk (more than 24·3 g/d) in malignant and benign cases. However, unlike the intake of raw vegetables, the intake of total vegetables and the frequency of vegetable consumption were not associated with malignant thyroid cancer. More than 50 % of the total vegetables consumed in Korea are pickled or cooked based on the results of the third KNHANES in 2005; the consumption of pickled and cooked vegetables may attenuate the effects of raw vegetables, possibly due to the carcinogenic effect of salt in pickled vegetables[25] and/or the destruction of the anti-carcinogenic activity of raw vegetables by processing and storage under acidic and oxygen-rich conditions[41].

No consistent association between fruit intake and thyroid cancer risk has been found in previous studies. Markaki *et al.*[9] reported that high fruit consumption had a protective effect on thyroid cancer risk (OR 0·68, P=0·01). In contrast, studies in Kuwait[12] and Northern Europe[10] showed no association between the amount of fruit consumed and thyroid cancer risk. We found no significant association between total fruit intake and thyroid cancer risk but among fruits, persimmon and tangerine intakes were inversely associated with thyroid cancer risk. *Diospyros kaki* Thunb. (Ebenaceae), more commonly known as persimmon, is widely distributed in East Asian countries such as Korea, Japan and China[42]. Persimmon contains many bioactive agents such as flavonoids, tannins, carotenoids, antioxidant vitamins and minerals[43,44] that may mediate anti-carcinogenic processes. Furthermore, the anti-oxidative activity of persimmon has been examined both *in vitro*[44–47] and *in vivo*[45]. Among the extracts of persimmon, tannins in particular may increase catalase and superoxide dismutase activity, thereby reducing oxidative damage to cells[45]. As another explanation for the anti-carcinogenic effects of persimmon, 24-hydroxyursolic acid from persimmon may inhibit cell proliferation by activating AMP-activated protein kinase signalling, resulting in growth inhibition and cell apoptosis[46]. However, there is very limited evidence available regarding the association between persimmon intake and cancer risk in epidemiological studies[48]. In the present study, both the amount of persimmon consumed (more than 15·8 g/d) and the frequency of consumption (approximately once per d) had a significant inverse relationship with thyroid cancer risk. These results are consistent with those reported by a case–control study in China; the authors of that study reported that persimmon intake significantly reduced breast cancer risk (OR 0·60; 95 % CI 0·42, 0·86; P for trend=0·006)[48]. Tangerine (*Citrus reticulate* Blanco) is a citrus fruit that is a good source of bioactive compounds such as flavonoids, vitamin C, carotenoids, limonene and citric acid[21]. Citrus flavonoids are known to have strong anti-proliferative activities in human cancer cells[49]. Citrus flavonoids may function as anticancer agents by inhibiting enzymes such as protein kinases involved in mitogenic signal transduction[50]. Epidemiological studies have been conducted in the past to determine if there is a relationship between citrus fruit intake, including tangerine intake, and thyroid cancer risk[10], colon, rectum cancer risk[51] and breast cancer risk[48,51]. However, no significant negative association was observed in any of these previous studies[48,51].

The present study had several limitations. First, it was a hospital-based case–control study, and thus, the results may not be generalisable to the general population[52]. Second, recall bias is one of the important potential biases in a case–control study. The differential recall between cases and controls may induce biased results[53]. However, in the present study, almost all cases were interviewed before diagnosis so that differential recall biases may not be substantial. Third, the sample size was not sufficient to draw definitive conclusions and we were not able to analyse the differences in risk factors according to the subtype of thyroid cancer (papillary, follicular, medullary, anaplastic). The number of pairs assuming $\alpha = 0{\cdot}05$, $\beta = 0{\cdot}10$ and an OR of 2·0 (or 0·5) was 281 pairs[54]. However, the final sample size was smaller than the calculated number. Therefore, a weak relationship (OR < 2·0 or 0·5 < OR < 1·0) may not have been detected in the present study. Fourth, although the semiquantitative FFQ has been validated in previous studies, we did not perform the additional validity–reliability study for the modified version and for food items. Fifth, among the non-dietary risk factors for thyroid cancer, the best-established cause of thyroid cancer is exposure to ionising radiation, particularly during early childhood[1,4]. We could not measure the extent of radiation exposure. In future studies, radiation in everyday life including medical radiation needs to be assessed and to be analysed for the association with thyroid cancer. Sixth, we could not examine the association between benign thyroid nodules or adenomas and malignant thyroid cancer risk in the present study, because we recruited controls who did not have thyroid nodules or thyroid hormone diseases. In the analyses, after excluding pairs with history of any thyroid disease in cases (twenty-nine pairs in malignant cancer and forty-three

https://doi.org/10.1017/S0007114512000591 Published online by Cambridge University Press

pairs in benign thyroid nodules or adenomas), the association between fruit and vegetable intake and thyroid cancer risk did not substantially change. To the best of our knowledge, ours is the first study to focus on benign thyroid cases and to use controls without any nodules in the thyroid gland.

The findings in the present study suggest that high consumption of raw vegetables, persimmons and tangerines may decrease thyroid cancer risk. In addition, consumption of raw vegetables and these fruits may help prevent thyroid cancer. However, our findings need to be confirmed in a large-scale cohort study.

Acknowledgements

The present study was supported by the Korean Ministry of Science and Technology (grant nos M10418020002-08N1802-00210 and M10418020002-09N1802-00210). The authors wish to thank all subjects for their dedication and commitment. M. K. K. designed and supervised the execution of the study. S. K. J. performed the data analyses and wrote the manuscript with K. K. In addition, K. T. and G. K. contributed to the data preparation. All authors participated in the interpretation of the results and the editing of the manuscript. None of the authors had a personal or financial conflict of interest.

References

1. DeLellis RA (2004) *Pathology and Genetics of Tumours of Endocrine Organs*, vol. 8. Geneva: World Health Organization.
2. Ferlay J, Shin H, Bray F, *et al.* (2010) *Globocan 2008, Cancer Incidence and Mortality Worldwide*. Lyon, France: International Agency for Research on Cancer.
3. The Korea Central Cancer Registry (2010) *Annual Report of Cancer Statistics in Korea in 2008: Ministry of Health and Welfare*. Seoul, South Korea: The Korea Central Cancer Registry.
4. Dal Maso L, Bosetti C, La Vecchia C, *et al.* (2009) Risk factors for thyroid cancer: an epidemiological review focused on nutritional factors. *Cancer Causes Control* **20**, 75–86.
5. Franceschi S, Preston-Martin S, Maso LD, *et al.* (1999) A pooled analysis of case–control studies of thyroid cancer. IV. Benign thyroid diseases. *Cancer Causes Control* **10**, 583–595.
6. Elisei R, Romei C, Vorontsova T, *et al.* (2001) RET/PTC rearrangements in thyroid nodules: studies in irradiated and not irradiated, malignant and benign thyroid lesions in children and adults. *J Clin Endocrinol Metab* **86**, 3211–3216.
7. Kondo T, Ezzat S & Asa SL (2006) Pathogenetic mechanisms in thyroid follicular-cell neoplasia. *Nat Rev Cancer* **6**, 292–306.
8. Wong FL, Ron E, Gieriowski T, *et al.* (1996) Benign thyroid tumors: general risk factors and their effects on radiation risk estimation. *Am J Epidemiol* **144**, 728–733.
9. Markaki I, Linos D & Linos A (2003) The influence of dietary patterns on the development of thyroid cancer. *Eur J Cancer* **39**, 1912–1919.
10. Galanti MR, Hansson L, Bergstrom R, *et al.* (1997) Diet and the risk of papillary and follicular thyroid carcinoma: a population-based case–control study in Sweden and Norway. *Cancer Causes Control* **8**, 205–214.
11. Bosetti C, Negri E, Kolonel L, *et al.* (2002) A pooled analysis of case–control studies of thyroid cancer. VII. Cruciferous and other vegetables (International). *Cancer Causes Control* **13**, 765–775.
12. Memon A, Varghese A & Suresh A (2002) Benign thyroid disease and dietary factors in thyroid cancer: a case–control study in Kuwait. *Br J Cancer* **86**, 1745–1750.
13. Truong T, Baron-Dubourdieu D, Rougier Y, *et al.* (2010) Role of dietary iodine and cruciferous vegetables in thyroid cancer: a countrywide case–control study in New Caledonia. *Cancer Causes Control* **21**, 1183–1192.
14. Bosetti C, Kolonel L, Negri E, *et al.* (2001) A pooled analysis of case–control studies of thyroid cancer. VI. Fish and shellfish consumption. *Cancer Causes Control* **12**, 375–382.
15. Horn-Ross PL, Morris JS, Lee M, *et al.* (2001) Iodine and thyroid cancer risk among women in a multiethnic population. *Cancer Epidemiol Biomarkers Prev* **10**, 979–985.
16. Mack WJ, Preston-Martin S, Bernstein L, *et al.* (2002) Lifestyle and other risk factors for thyroid cancer in Los Angeles County females. *Ann Epidemiol* **12**, 395–401.
17. Randi G, Ferraroni M, Talamini R, *et al.* (2008) Glycemic index, glycemic load and thyroid cancer risk. *Ann Oncol* **19**, 380–383.
18. D'Avanzo B, Ron E, Vecchia CL, *et al.* (1997) Selected micronutrient intake and thyroid carcinoma risk. *Cancer* **79**, 2186–2192.
19. Kilfoy B, Zhang Y, Park Y, *et al.* (2011) Dietary nitrate and nitrite and the risk of thyroid cancer in the NIH-AARP Diet and Health Study. *Int J cancer* **129**, 160–172.
20. Ward MH, Kilfoy BA, Weyer PJ, *et al.* (2010) Nitrate intake and the risk of thyroid cancer and thyroid disease. *Epidemiology* **21**, 389–395.
21. Vainio H & Bianchini F (2003) *IARC Handbooks of Cancer Prevention. Volume 8: Fruit and Vegetables*. Lyon, France: IARC Press, International Agency for Research on Cancer.
22. Marmot M, Atinmo T, Byers T, *et al.* (2007) *Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective*. Washington, DC: World Cancer Research Fund/American Institute for Cancer Research.
23. Kim HJ, Lim SY, Lee JS, *et al.* (2010) Fresh and pickled vegetable consumption and gastric cancer in Japanese and Korean populations: a meta analysis of observational studies. *Cancer Sci* **101**, 508–516.
24. Yu H, Hwang JY, Ro J, *et al.* (2010) Vegetables, but not pickled vegetables, are negatively associated with the risk of breast cancer. *Nutr Cancer* **62**, 443–453.
25. Ying WZ & Sanders PW (2002) Dietary salt intake activates MAP kinases in the rat kidney. *FASEB J* **16**, 1683–1684.
26. Kaur C & Kapoor H (2001) Antioxidants in fruits and vegetables – the millennium's health. *Int J Food Sci Technol* **36**, 703–725.
27. Kim M, Lee S & Ahn Y (1996) Reproducibility and validity of a self-administered semiquantitative food frequency questionnaire among middle-aged men in Seoul. *Korean J Community Nutr* **1**, 376–394.
28. Willett WC (1998) *Nutritional Epidemiology*. New York, NY: Oxford Universtiy Press.
29. The Korean Nutrition Society (2003) *Foods and Nutrients Database of Computer Aided Nutritional Analysis Program Version 2.0*. Seoul, South Korea: The Korean Nutrition Society.
30. Popkin B (2000) The nutrition transition in South Korea. *Am J Clin Nutr* **71**, 44–53.
31. Lee MJ, Popkin BM & Kim S (2002) The unique aspects of the nutrition transition in South Korea: the retention of

healthful elements in their traditional diet. *Public Health Nutr* **5**, 197–204.

32. Korea Rural Economic Institute (2006) *Food Supply and Demand Table*. Seoul, South Korea: Korea Rural Economic Institute.
33. Department for Environment Rural Affairs (2007) *Family Food in 2005–06: [A Report on the 2005–06 Expenditure and Food Survey]*. London: The Stationery Office.
34. Joffe M & Robertson A (2001) The potential contribution of increased vegetable and fruit consumption to health gain in the European Union. *Public Health Nutr* **4**, 893–901.
35. Gandini S, Merzenich H, Robertson C, *et al.* (2000) Meta-analysis of studies on breast cancer risk and diet: the role of fruit and vegetable consumption and the intake of associated micronutrients. *Eur J Cancer* **36**, 636–646.
36. Koushik A, Hunter DJ, Spiegelman D, *et al.* (2007) Fruits, vegetables, and colon cancer risk in a pooled analysis of 14 cohort studies. *J Natl Cancer Inst* **99**, 1471–1483.
37. Pavia M, Pileggi C, Nobile CGA, *et al.* (2006) Association between fruit and vegetable consumption and oral cancer: a meta-analysis of observational studies. *Am J Clin Nutr* **83**, 1126–1134.
38. Lunet N, Valbuena C, Vieira AL, *et al.* (2007) Fruit and vegetable consumption and gastric cancer by location and histological type: case–control and meta-analysis. *Eur J Cancer Prev* **16**, 312–327.
39. Steinmetz KA & Potter JD (1991) Vegetables, fruit, and cancer. II. Mechanisms. *Cancer Causes Control* **2**, 427–442.
40. La Vecchia C, Altieri A & Tavani A (2001) Vegetables, fruit, antioxidants and cancer: a review of Italian studies. *Eur J Nutr* **40**, 261–267.
41. Kaur C & Kapoor HC (2001) Antioxidants in fruits and vegetables-the millennium's health. *Int J Food Sci Technol* **36**, 703–725.
42. Sakanaka S, Tachibana Y & Okada Y (2005) Preparation and antioxidant properties of extracts of Japanese persimmon leaf tea (kakinoha-cha). *Food Chem* **89**, 569–575.
43. Mallavadhani U, Panda AK & Rao Y (1998) Pharmacology and chemotaxonomy of *Diospyros*. *Phytochemistry* **49**, 901–951.
44. Kawase M, Motohashi N, Satoh K, *et al.* (2003) Biological activity of persimmon (*Diospyros kaki*) peel extracts. *Phytother Res* **17**, 495–500.
45. Ahn HS, Jeon TI, Lee JY, *et al.* (2002) Antioxidative activity of persimmon and grape seed extract: *in vitro* and *in vivo*. *Nutr Res* **22**, 1265–1273.
46. Khanal P, Oh WK, Thuong PT, *et al.* (2010) 24-Hydroxyursolic acid from the leaves of the *Diospyros kaki* (persimmon) induces apoptosis by activation of AMP-activated protein kinase. *Planta Med* **76**, 689–693.
47. Jang IC, Jo EK, Bae MS, *et al.* (2010) Antioxidant and antigenotoxic activities of different parts of persimmon (*Diospyros kaki* cv. Fuyu) fruit. *J Med Plant Res* **4**, 155–160.
48. Shannon J, Ray R, Wu C, *et al.* (2005) Food and botanical groupings and risk of breast cancer: a case–control study in Shanghai, China. *Cancer Epidemiol Biomarkers Prev* **14**, 81–90.
49. Manthey JA & Guthrie N (2002) Antiproliferative activities of citrus flavonoids against six human cancer cell lines. *J Agric Food Chem* **50**, 5837–5843.
50. Manthey JA, Guthrie N & Grohmann K (2001) Biological properties of citrus flavonoids pertaining to cancer and inflammation. *Curr Med Chem* **8**, 135–153.
51. Franceschi S, Parpinel M, La Vecchia C, *et al.* (1998) Role of different types of vegetables and fruit in the prevention of cancer of the colon, rectum, and breast. *Epidemiology* **9**, 338–341.
52. Breslow NE & Day NE (1980) *Statistical Methods in Cancer Research*, vol. 32. Lyon: IARC.
53. Gordis L (2004) *Epidemiology*, 3rd ed. Philadelphia, PA: WB Saunders.
54. Schlesselman JJ & Stolley PD (1982) *Case–control Studies: Design, Conduct, Analysis*. New York, NY: Oxford University Press.

British Journal of Nutrition