British Journal of Nutrition (2010), **103**, 1345–1353 doi:10.1017/S0007114509993242

British Journal of Nutrition

A case–control study on seaweed consumption and the risk of breast cancer

Yoon Jung Yang[1], Seok-Jin Nam[2], Gu Kong[3] 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, South Korea*

[2]*Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul 135-710, South Korea*

[3]*Department of Pathology, College of Medicine, Hanyang University, Seoul 133-791, South Korea*

(Received 17 April 2009 – Revised 2 November 2009 – Accepted 4 November 2009 – First published online 8 December 2009)

Gim (*Porphyra* sp.) and miyeok (*Undaria pinnatifida*) are the seaweeds most consumed by Koreans. We investigated the association between the intake of gim and miyeok and the risk of breast cancer in a case–control study. Cases were 362 women aged 30–65 years old, who were histologically confirmed to have breast cancer. Controls visiting the same hospital were matched to cases according to their age (SD 2 years) and menopausal status. Food intake was estimated by the quantitative FFQ with 121 items, including gim and miyeok. Conditional logistic regression analysis was used to obtain the OR and corresponding 95 % CI. The average intake and consumption frequency of gim in cases were lower than in controls. The daily intake of gim was inversely associated with the risk of breast cancer (5th *v.* 1st quintile, OR, 0·48; 95 % CI, 0·27, 0·86; *P* for trend, 0·026) after adjustment for potential confounders. After stratification analysis was performed according to menopausal status, premenopausal women (5th *v.* 1st quintile, OR, 0·44; 95 % CI, 0·24, 0·80; *P* for trend, 0·007) and postmenopausal women (5th *v.* 1st quintile, OR, 0·32; 95 % CI, 0·13, 0·80; *P* for trend, 0·06) showed similar inverse associations between gim intake and the risk of breast cancer after an adjustment for potential confounders except dietary factors. Miyeok consumption did not have any significant associations with breast cancer. These results suggest that high intake of gim may decrease the risk of breast cancer.

Seaweed: Gim: Miyeok: Breast cancer: Case–control studies

Seaweeds have been featured in the diets of Asian culture since ancient times[1]. The nutritional and physiological effects of seaweeds have received much attention during the past decades. Seaweeds are rich in polysaccharides, minerals, vitamins and dietary fibre[2–5]. Antioxidant and antimutagenic effects of dietary seaweeds have been reported *in vitro*[6–8] and *in vivo* studies[9–11]. Polysaccharides[6,9,12,13], proteins[14], antioxidants (e.g. ascorbate, glutathione and carotenoids)[15,16], polyphenols[7] and extracts[7,17] of seaweeds have been reported to have antioxidant, antitumour and chemoprotective activities.

In particular, the potential benefits of seaweed consumption for breast cancer treatment have been traced back to the ancient Egyptian 'Ebers Papyrus', which mentioned that seaweed was used to treat breast cancer[18]. The putative protective effect of seaweed on breast cancer is in accord with the relatively low breast cancer rates in Japan[19], where seaweed-rich diets are consumed and with the increasing breast cancer rates in Japanese women who emigrate[20] or consume a Western style diet[21]. Animal studies[10,22,23] and *in vitro* studies[23–25] demonstrated the anticarcinogenic effects of seaweeds against mammary carcinogenesis. Iodine as well as other components of seaweeds have been suggested to act as antioxidants[26] and induce apoptosis in human breast cancer cell lines[23]. In an ecological study, the regions where iodine intake was low had higher breast cancer mortality rates[27]. However, few epidemiological studies have reported on the effects of seaweed consumption on breast cancer.

Breast cancer is the most common cancer in Korean women, with an age-standardised incidence rate of 31·1 per 100 000 persons in 2002[28]. Even though the incidence rate of breast cancer is lower than in Western countries[19], this rate has been increasing in Korea[29]. Seaweed is frequently consumed on a daily basis in a traditional Korean diet. According to the third Korean National Health and Nutrition Survey (2005)[30], the daily intake of seaweed was 8·5 g/d (fresh + dry mass). Gim (*Porphyra* sp.), miyeok (*Undaria pinnatifida*; 'wakame' in Japan) and dashima (*Laminaria* sp.; 'konbu' in Japan) are common seaweeds, which constitute over 95 % of seaweed consumption in Korea[30]. However, dashima (*Laminaria* sp.) is usually used for making broth (i.e. soaked in boiling water then removed), so that the actual intake is not substantial. Gim is a Korean style edible seaweed in the genus *Porphyra*. Gim (*Porphyra* sp.) looks like 'nori' in Japan, but sheets of gim are thinner than nori sheets. Seasoned roasted gim prepared with sesame oil and salts is the most common type of gim and it is consumed as a side dish. Gim is also used as wrappings, seasonings and

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

condiments. Miyeok (*U. pinnatifida*) is the second most commonly consumed seaweed in Korea and is usually consumed as the form of soup or a side dish.

Despite high consumption of seaweeds in Asian countries, the association between seaweed consumption and breast cancer risk has been determined in limited epidemiological studies[31]. Thus, the aim of the present study was to investigate the association between the consumption of seaweed, specifically gim (*Porphyra* sp.) and miyeok (*U. pinnatifida*), and the risk of breast cancer in a case–control study among Korean women.

Material and methods

Cases and controls

Cases and controls were recruited from October 2004 to June 2006 at Samsung Hospital of Sungkyunkwan University in Seoul, South Korea. All participants aged 30–65 years were examined by mammography to detect any possibility of breast cancer. Cases had histologically confirmed breast cancer. Subjects having any history of cancer (five cases) or having an estimated total energy intake < 2092 kJ/d (< 500 kcal/d) or > 16 736 kJ/d (> 4000 kcal/d; sixteen cases and thirteen controls) were excluded from the study. Controls were patients visiting one of the dentistry, orthopedic surgery, general surgery, ophthalmology, dermatology, rehabilitation, obstetrics and gynecology or family medicine clinics within the same hospital. Cases and controls were matched by their age (within 2 years) and menopausal status (362 pairs). The present study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving the human subjects were approved by the Institutional Review Board of the Samsung Hospital of Sungkyunkwan University. Written informed consent was obtained from all the subjects.

Data collection

Cases and controls were interviewed by trained interviewers with a questionnaire addressing patients' general characteristics, menstrual and reproductive history, family history of breast cancer, smoking and drinking habits, intake of multivitamins and the average time spent on exercising. Dietary data were collected by the quantitative FFQ, which were modified from the validated FFQ[32], with visual aids such as food photographs and models for item-specific units. The FFQ was composed of 121 food items which included roasted gim (*Porphyra* sp.) and miyeok soup (*U. pinnatifida*). The gim used as wrappings, seasonings and condiments was not asked in the questionnaire. The amounts of foods consumed were asked in open-ended questions with standard units such as cup, bowl and piece etc. Subjects were asked by trained interviewers to recall their usual intake of the 121 food items over a period of 12 months beginning from 3 years before the time of the interview[33]. All frequencies were standardised into 'times/day' by using the conversion factors 4·3 weeks/month and 30·4 d/month. Daily food intake was calculated with standardised frequency per day and the amount of food consumed. Detailed information on data collection has been presented in previous publications elsewhere[34,35].

The intake of gim and miyeok was calculated using standardised frequency per day and one portion per unit. One sheet of dried, roasted gim was 2 g in dry mass and one portion of miyeok soup was composed of 36 g of miyeok in fresh mass. Nutrient intakes adjusted for total energy intake by the residual method were used in all the analyses to avoid bias due to the simple relationship of nutrient intake with total energy intake.

Statistical analysis

All statistical analyses were performed using the SAS software (version 9.1; SAS Institute, Inc., Cary, NC, USA). Cases and their matched controls were compared by a paired *t* test for continuous variables and by the McNemar test for categorical variables. The quintiles of daily gim intake, consumption frequency of gim and daily miyeok intake were applied to the analyses. Since the variation of miyeok consumption frequency was not large, it could not be classified into quintile groups, thus, the quartiles of miyeok consumption frequency were applied to the analyses. In addition, the menopausal status-specific quintiles were used in the subgroup analysis of menopausal status. The general linear model and the Cochran–Mantel–Haenzel analysis were used to determine potential confounders among the controls. Conditional logistic regression analysis was applied to obtain the OR and corresponding 95 % CI. Three different models were applied to examine the associations of seaweed intake with the risk of breast cancer. Any variable was not adjusted in the first model. Variables which were significantly different between the cases and controls and showed significant linear trends across quintiles or quartiles of seaweed intake except dietary variables were adjusted in the second model. Dietary variables were additionally adjusted in the third model. The trend tests were conducted by treating the median values of each quintile as continuous variables in a multivariate model after inputting the median value of the controls into each dietary intake group. Daily intakes of gim and miyeok and the average consumption frequencies of gim and miyeok were also introduced as continuous variables, and the units were expressed in increments of 1 g/d and once per week, respectively.

Results

The characteristics of the breast cancer cases and the matched controls are presented in Table 1. Compared with the controls, the cases had lower proportions of multivitamin users and breast feeding and had fewer children. The cases consumed lower amounts of soya protein, mushrooms and gim (*Porphyra* sp.) than the controls. The frequency of gim intake was also lower in the cases than in the controls. However, the intake of miyeok and the average consumption frequency of miyeok did not differ between the cases and the controls.

To determine any potential confounding factors, the distributions of selected characteristics of the control subjects were examined by using the quintiles of gim intake, frequency of gim intake and miyeok intake, as well as the quartiles of frequency of miyeok intake (Table 2). Education, physical activity and oral contraceptive use increased across the quintiles of gim intake in the controls. The proportion with a family history of breast cancer decreased across the quintiles

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

Characteristics	Case (*n* 362) Mean	Case (*n* 362) SD	Control (*n* 362) Mean	Control (*n* 362) SD	*P**
Age (years)	46·1	8·5	46·0	8·6	NA
Education (years)	12·7	3·6	12·4	3·5	0·307
BMI (kg/m^2)	23·6	3·2	23·4	3·0	0·410
Alcohol intake (g/d)	1·9	6·2	2·4	8·1	0·295
Number of children	1·9	1·0	2·1	1·0	0·010
Age at menarche (years)	14·5	1·7	14·5	1·7	0·407
Age at first birth (years)	26·0	3·5	25·8	3·4	0·836
Age at menopause (years)	48·0	5·4	48·4	5·2	0·110
Dietary intake					
Energy (kJ/d)	8136·2	2389·1	8474·7	2753·9	0·305
β-Carotene† (μg/d)	4381·1	7289·5	4160·3	2367·6	0·584
Vitamin C† (mg/d)	151·7	91·7	146·9	79·1	0·440
Folate† (μg/d)	283·8	100·4	296·9	99·9	0·067
Vitamin E† (mg/d)	10·6	4·1	11·2	4·3	0·088
Fiber† (g/d)	10·1	4·5	10·1	4·1	0·964
Soya protein (g/d)	7·4	4·5	8·5	4·6	0·001
Mushroom (g/d)	7·8	10·0	11·4	21·2	0·005
Gim (g: dry mass/d)	0·86	0·93	1·17	1·43	<0·001
Gim (frequency/week)	3·01	2·85	3·76	3·72	0·002
Miyeok (g: fresh mass/d)	5·12	5·57	5·45	5·80	0·426
Miyeok (frequency/week)	1·10	1·10	1·15	1·13	0·499
Menopausal women (%)	35		35		NA
Family history of breast cancer (%)	8		12		0·099
Current smoker (%)	2		4		0·127
Regular exercise (≥22·5 MET-h/week) (%)	17		22		0·110
Multivitamin user (%)	9		14		0·030
Parity (%)	89		92		0·131
Oral contraceptive use (ever) (%)	15		14		0·831
Breast feeding (ever) (%)	64		77		<0·001
Used hormone compound (ever) (%)	14		14		0·821

NA, not applicable; MET, metabolic equivalent.
* Two-sided; paired *t* test for continuous variables and McNemar test for categorical variables.
† All nutrients were total energy-adjusted by a residual method after log transformation.

of the frequency of gim intake, miyeok intake and the frequency of miyeok intake. The proportion of exercise increased across the quintiles of the gim intake frequency. The intakes of energy, β-carotene, vitamin C, folate and vitamin E increased across the quintiles of gim intake, the frequency of gim intake, miyeok intake and the frequency of miyeok intake. The intake of soya protein increased across the quintiles of gim intake and the frequency of gim intake. The variables showing significant trends according to the consumptions of gim and miyeok in Table 2 are adjusted as potential confounding factors in Tables 3 and 4.

The associations between seaweed and the risk of breast cancer are given in Table 3. A significant inverse association was found between the breast cancer risk and gim intake (OR, 0·47; 95 % CI, 0·29, 0·75 for the last quintile in comparison with the lowest quintile; *P* for trend, 0·003). The inverse association between breast cancer risk and gim intake was significant after adjusting for potential confounders such as multivitamin supplement, number of children, breast feeding, education, exercise and oral contraceptive use (OR, 0·43; 95 % CI, 0·26, 0·70 for the last quintile; *P* for trend, 0·002). After an additional adjustment for the dietary potential confounders (quintiles of energy as well as consumption of β-carotene, vitamin C, folate, vitamin E, soya protein and mushrooms), the inverse association between breast cancer risk and gim intake remained (OR, 0·48; 95 % CI, 0·27, 0·86 for the last quintile; *P* for trend, 0·026). In the analyses with continuous data, gim intake showed inverse associations with breast cancer risk in the three models. A consumption frequency of gim was also inversely associated with breast cancer risk (OR, 0·52; 95 % CI, 0·32, 0·84 for the last quintile; *P* for trend=0·009). The inverse association of the consumption frequency of gim with the breast cancer risk remained after adjusting for potential confounders including a multivitamin supplement use, number of children, breast feeding, a family history of breast cancer and exercise (OR, 0·51; 95 % CI, 0·30, 0·84 for the last quintile; *P* for trend, 0·018). However, after the additional adjustment for dietary potential confounders (quintiles of energy as well as intake of β-carotene, vitamin C, folate, vitamin E, soya protein and mushrooms), the inverse association between breast cancer risk and consumption frequency of gim was no longer significant (OR, 0·58; 95 % CI, 0·32, 1·04 for the last quintile; *P* for trend, 0·144). In the analyses with the continuous data, the significant inverse associations between breast cancer risk and the consumption frequency of gim were found in the crude OR (OR, 0·93; 95 % CI, 0·88, 0·98) and in the multivariate model 1 (OR, 0·93; 95 % CI, 0·88, 0·98). Miyeok intake and the frequency of miyeok intake did not show any significant associations with the risk of breast cancer.

Table 2. Selected characteristics of control subjects according to the quintiles of gim intake and miyeok intake

	Quintiles of gim intake				Quintiles of frequency of gim				Quintiles of miyeok intake				Quartiles of the miyeok frequency				
	1st	3rd	5th	*P* for trend*	1st	3rd	5th	*P* for trend	1st	3rd	5th	*P* for trend	1st	2nd	3rd	4th	*P* for trend
Median (g/d per week)	0·05	0·79	2·24		0·21	3·01	7·00		0·72	2·88	15·48		0·21	0·56	0·98	3·01	
Age (years)	48·1	44·1	45·8	0·214	48·2	44·9	45·4	0·164	48·0	45·2	45·4	0·194	47·8	45·8	45·6	45·2	0·182
Education (years)	11·5†	12·4	12·7	0·037	11·3	13·0	12·3	0·352	11·8	12·3	12·6	0·372	11·7	12·5	12·8	12·7	0·188
BMI (kg/m^2)	23·7	23·5	23·1	0·170	23·8	23·8	23·1	0·380	23·6	23·2	23·2	0·580	23·5	23·4	23·5	23·3	0·534
Family history of breast cancer (%)	12·7	10·9	7·9	0·089	15·4	12·9	6·8	0·021	19·4	15·0	4·1	0·002	17·5	14·6	11·2	4·7	0·009
Current smoker (%)	1·7	6·1	4·4	0·361	1·7	4·2	6·2	0·092	1·7	4·2	8·2	0·118	1·7	4·3	1·9	7·0	0·179
Alcohol intake (g)	2·4	1·9	1·6	0·329	2·3	2·1	2·7	0·604	2·3	4·2	1·6	0·356	2·2	3·5	1·4	2·0	0·453
Physical activity (≥22·5 MET-h/week, %)	14·1	17·1	30·1	0·005	15·6	25·0	32·0	0·003	18·9	20·8	21·9	0·989	20·6	20·6	21·6	23·0	0·601
Multivitamin user (%)	5·5	17·2	19·8	0·106	7·8	17·2	12·0	0·776	17·5	11·6	17·2	0·495	19·3	11·7	11·3	16·6	0·672
Parity (%)	93·1	92·9	90·9	0·769	91·4	90·6	93·0	0·345	90·3	91·4	93·2	0·249	91·7	90·5	93·8	93·0	0·573
Number of children	2·3	2·1	2·1	0·389	2·3	2·0	2·2	0·789	2·1	2·0	2·1	0·914	2·1	2·0	2·1	2·1	0·742
Oral contraceptive use (ever, %)	3·0	14·6	16·0	0·037	2·9	15·0	15·3	0·051	14·9	19·5	10·9	0·546	14·7	17·5	10·1	12·0	0·336
Breast feeding (ever, %)	81·9	74·7	70·4	0·103	78·0	72·2	74·2	0·567	74·7	77·0	75·5	0·496	75·9	74·7	79·9	74·9	0·933
Age at menarche (years)	14·8	14·5	14·5	0·446	14·7	14·4	14·6	0·883	14·5	14·5	14·8	0·140	14·6	14·5	14·4	14·7	0·374
Age at first birth (years)	25·3	26·2	25·4	0·179	25·2	26·1	24·9	0·084	25·8	25·8	25·6	0·621	25·7	25·8	26·0	25·7	0·881
Age at menopause (years)	47·4	48·0	49·5	0·133	47·5	49·7	47·9	0·641	47·8	48·5	49·1	0·506	47·9	49·0	48·1	48·4	0·978
Menopause (%)	39·4	31·3	35·3	0·440	37·4	34·6	32·5	0·221	35·0	36·5	31·6	0·834	37·6	33·5	35·6	34·6	0·722
Energy intake (kJ/d)	7528·7	8398·5	9004·8	<0·001	7457·1	8607·7	8924·9	<0·001	7066·8	8845·0	9772·6	<0·001	7014·5	8560·1	8483·5	9655·8	<0·001
β-Carotene intake‡ (μg/d)	3743·5	4045·7	4995·1	<0·001	3606·9	4173·1	5075·7	<0·001	3489·3	4173·7	4941·2	<0·001	3492·0	3879·8	4532·4	4765·7	0·001
Vitamin C intake‡ (mg/d)	145·4	144·4	173·6	<0·001	141·2	142·0	180·0	<0·001	139·5	140·7	165·5	0·019	141·1	132·9	156·8	161·7	0·026
Folate intake‡ (μg/d)	274·5	289·2	356·5	<0·001	272·8	291·4	352·8	<0·001	268·5	292·1	339·6	<0·001	267·5	279·7	313·4	330·4	<0·001
Vitamin E intake‡ (mg/d)	9·8	10·9	12·5	<0·001	9·8	11·1	12·2	<0·001	10·3	11·5	12·1	0·021	10·2	11·4	10·9	12·1	0·026
Soya protein (g/d)	7·1	8·8	9·7	0·001	7·7	8·4	9·9	<0·001	7·9	8·8	9·3	0·094	7·9	8·8	8·2	9·1	0·176
Mushroom (mg/d)	10·6	13·6	14·3	0·638	10·6	11·7	13·1	0·555	11·7	13·0	11·9	0·866	11·3	13·0	13·3	11·1	0·665

MET, metabolic equivalent.
* *P* values for the trends were determined by the general linear model for continuous variables and by the Cochran–Mantel–Haenszel test for categorical variables.
† All variables except median and age were adjusted for age and values are expressed as a least square mean or percent.
‡ All nutrient consumptions were adjusted for total energy intake.

https://doi.org/10.1017/S0007114509993242 Published online by Cambridge University Press

Table 3. Risk of breast cancer according to gim and miyeok consumption
(OR and 95 % CI; median, min and max values)

					Crude		Multivariate model 1		Multivariate model 2	
Daily intake	Median	Min	Max	No. of cases/ controls (362/362)	OR	95 % CI	OR	95 % CI*	OR	95 % CI†
Gim intake‡ (g: dry mass/d)										
Q1	0·06	0·00	0·16	90/61	1·00	Referent	1·00	Referent	1·00	Referent
Q2	0·29	0·16	0·47	75/66	0·79	0·50, 1·26	0·74	0·45, 1·21	0·72	0·42, 1·25
Q3	0·72	0·48	0·86	76/88	0·58	0·37, 0·92	0·57	0·35, 0·92	0·61	0·36, 1·05
Q4	1·32	0·92	1·58	60/59	0·70	0·44, 1·13	0·65	0·39, 1·08	0·64	0·36, 1·15
Q5	2·00	1·67	14·00	61/88	0·47	0·29, 0·75	0·43	0·26, 0·70	0·48	0·27, 0·86
P for trend					0·003		0·002		0·026	
Continuous (1 g/d)					0·78	0·67, 0·90	0·77	0·66, 0·90	0·79	0·66, 0·94
Gim: frequency§ (per week)										
Q1	0·21	0·00	0·75	83/63	1·00	Referent	1·00	Referent	1·00	Referent
Q2	0·98	0·82	2·51	78/65	0·95	0·59, 1·52	0·88	0·53, 1·45	0·82	0·47, 1·44
Q3	3·01	2·77	3·01	94/105	0·68	0·44, 1·05	0·66	0·41, 1·04	0·75	0·45, 1·27
Q4	5·53	3·23	5·53	49/46	0·83	0·49, 1·40	0·87	0·50, 1·51	0·89	0·47, 1·68
Q5	7·00	5·83	24·5	58/83	0·52	0·32, 0·84	0·51	0·30, 0·84	0·58	0·32, 1·04
P for trend					0·009		0·018		0·144	
Continuous, once per week					0·93	0·88, 0·98	0·93	0·88, 0·98	0·94	0·89, 1·00
Miyeok intake‖ (g: fresh mass/d)										
Q1	0·54	0·00	1·08	78/75	1·00	Referent	1·00	Referent	1·00	Referent
Q2	1·93	1·44	2·52	57/39	1·39	0·85, 2·28	1·53	0·92, 2·57	1·76	0·98, 3·18
Q3	2·88	2·88	4·32	82/91	0·86	0·56, 1·33	0·87	0·55, 1·37	0·99	0·60, 1·65
Q4	5·04	5·04	7·74	77/86	0·85	0·56, 1·29	0·89	0·58, 1·38	0·97	0·59, 1·59
Q5	15·48	10·08	46·44	68/71	0·90	0·57, 1·42	0·89	0·55, 1·44	1·09	0·62, 1·90
P for trend					0·558		0·481		0·949	
Continuous (1 g/d)					0·99	0·96, 1·02	0·99	0·96, 1·01	1·00	0·97, 1·03
Miyeok: frequency¶ (per week)										
≤1/month	0·21	0·00	0·21	76/73	1·00	Referent	1·00	Referent	1·00	Referent
≤ 2–3/month	0·56	0·56	0·56	107/119	0·84	0·56, 1·28	0·89	0·57, 1·37	0·96	0·59, 1·56
≤ 1/week	0·98	0·98	0·98	107/89	1·14	0·76, 1·72	1·21	0·79, 1·86	1·47	0·90, 2·40
≥ 2–4/week	3·01	3·01	7·00	72/81	0·85	0·54, 1·33	0·85	0·53, 1·35	1·05	0·61, 1·80
P for trend					0·567		0·500		0·966	
Continuous, once per week					0·96	0·84, 1·09	0·95	0·83, 1·09	1·00	0·86, 1·17

Min, Minimum; max, maximum; Q, quintile.
* All multivariate adjusted OR models included multivitamin supplement (yes/no), number of children and breast feeding (yes/no).
† In addition to covariates in multivariate model 1, dietary factors (quintiles of energy, β-carotene, vitamin C, folate, vitamin E, soya protein and mushrooms) were adjusted in multivariate model 2.
‡ The model for gim intake was additionally adjusted for education (years), exercise (yes/no) and oral contraceptive use (yes/no).
§ The model for miyeok intake was additionally adjusted for the family history of breast cancer (yes/no).
‖ The model for frequency of gim was additionally adjusted for family history of breast cancer (yes/no) and exercise (yes/no).
¶ The model for frequency of miyeok was additionally adjusted for family history of breast cancer (yes/no).

British Journal of Nutrition

Table 4. Risk of breast cancer according to gim and miyeok consumption in premenopausal and postmenopausal women (OR and 95 % CI)

	Premenopausal women (*n* 235 pairs)							Postmenopausal women (*n* 127 pairs)						
		Crude		Multivariate model 1		Multivariate model 2			Crude		Multivariate model 1		Multivariate model 2	
	Cases/ controls	OR	95 % CI	OR	95 % CI*	OR	95 % CI†	Cases/ controls	OR	95 % CI	OR	95 % CI*	OR	95 % CI†
Gim intake‡ (g: dry mass/d)														
Q1	55/32	1·00	Referent	1·00	Referent	1·00	Referent	35/29	1·00	Referent	1·00	Referent	1·00	Referent
Q2	49/40	0·77	0·42, 1·40	0·84	0·44, 1·59	0·82	0·39, 1·74	26/26	0·78	0·38, 1·64	0·55	0·24, 1·26	0·34	0·09, 1·31
Q3	51/65	0·47	0·26, 0·84	0·54	0·29, 0·99	0·49	0·24, 1·00	25/23	0·83	0·40, 1·73	0·59	0·25, 1·38	0·70	0·18, 2·70
Q4	38/40	0·58	0·31, 1·07	0·58	0·30, 1·13	0·55	0·25, 1·20	22/19	0·92	0·43, 1·96	0·75	0·31, 1·81	0·60	0·16, 2·29
Q5	42/58	0·45	0·25, 0·79	0·44	0·24, 0·80	0·51	0·24, 1·08	19/30	0·48	0·21, 1·09	0·32	0·13, 0·80	0·27	0·06, 1·28
P for trend		0·009		0·007		0·067			0·148		0·06		0·247	
Continuous (1 g/d)		0·77	0·64, 0·92	0·75	0·62, 0·90	0·79	0·63, 0·98		0·80	0·62, 1·04	0·76	0·57, 1·01	0·71	0·43, 1·16
Gim§ (frequency)														
Q1	56/33	1·00	Referent	1·00	Referent	1·00	Referent	27/30	1·00	Referent	1·00	Referent	1·00	Referent
Q2	41/42	0·59	0·31, 1·10	0·61	0·32, 1·18	0·58	0·27, 1·26	37/23	1·90	0·87, 4·14	1·55	0·67, 3·57	1·46	0·41, 5·17
Q3	64/74	0·53	0·30, 0·91	0·56	0·32, 1·00	0·67	0·34, 1·33	30/31	0·96	0·45, 2·06	0·74	0·32, 1·71	0·81	0·22, 2·99
Q4	32/29	0·70	0·36, 1·36	0·69	0·35, 1·39	0·74	0·31, 1·73	17/17	1·10	0·45, 2·69	1·29	0·48, 3·43	0·89	0·23, 3·44
Q5	42/57	0·44	0·24, 0·80	0·43	0·23, 0·81	0·55	0·26, 1·17	16/26	0·65	0·28, 1·53	0·59	0·24, 1·45	0·55	0·14, 2·21
P for trend		0·035		0·034		0·286			0·120		0·218		0·284	
Continuous, once per week		0·92	0·87, 0·99	0·92	0·86, 0·98	0·94	0·86, 1·01		0·93	0·86, 1·01	0·93	0·86, 1·01	0·90	0·78, 1·03
Miyeok intake‖ (g: fresh mass/d)														
Q1	41/44	1·00	Referent	1·00	Referent	1·00	Referent	37/31	1·00	Referent	1·00	Referent	1·00	Referent
Q2	40/23	1·85	0·96, 3·56	2·08	1·05, 4·13	2·15	0·94, 4·96	17/16	0·95	0·44, 2·06	1·03	0·44, 2·42	1·41	0·40, 5·04
Q3	51/61	0·85	0·48, 1·51	0·84	0·46, 1·53	0·99	0·48, 2·03	31/30	0·93	0·47, 1·87	1·01	0·47, 2·15	0·96	0·32, 2·89
Q4	52/57	0·93	0·53, 1·63	0·95	0·53, 1·70	1·10	0·54, 2·25	25/29	0·75	0·39, 1·45	0·80	0·40, 1·62	0·56	0·20, 1·57
Q5	51/50	1·02	0·57, 1·86	1·13	0·61, 2·11	1·60	0·72, 3·52	17/21	0·70	0·32, 1·49	0·49	0·21, 1·14	0·43	0·13, 1·44
P for trend		0·949		0·829		0·220			0·352		0·081		0·112	
Continuous (1 g/d)		0·99	0·96, 1·02	1·00	0·96, 1·03	1·02	0·98, 1·06		0·98	0·94, 1·03	0·96	0·91, 1·01	0·96	0·88, 1·03
Miyeok¶ (frequency)														
≤ 1/month	40/42	1·00	Referent	1·00	Referent	1·00	Referent	36/31	1·00	Referent	1·00	Referent	1·00	Referent
≤ 2–3/month	70/79	0·93	0·55, 1·59	1·00	0·58, 1·73	1·06	0·55, 2·04	37/40	0·77	0·37, 1·59	0·82	0·37, 1·79	0·80	0·26, 2·42
≤ 1/week	73/59	1·29	0·75, 2·24	1·36	0·77, 2·41	1·81	0·90, 3·64	34/30	1·00	0·54, 1·88	1·09	0·55, 2·14	0·90	0·33, 2·45
≥ 2–4/week	52/55	0·99	0·55, 1·79	1·09	0·59, 2·02	1·65	0·77, 3·54	20/26	0·68	0·33, 1·40	0·52	0·24, 1·15	0·42	0·13, 1·35
P for trend		0·972		0·836		0·224			0·356		0·114		0·147	
Continuous, once per week		0·98	0·83, 1·16	1·00	0·84, 1·20	1·09	0·88, 1·35		0·92	0·74, 1·14	0·85	0·67, 1·08	0·84	0·63, 1·12

Q, quintile.
* All multivariate adjusted OR models included multivitamin supplement (yes/no), number of children and breast feeding (yes/no).
† In addition to covariates in multivariate model 1, dietary factors (quintiles of energy as well as the intake of β-carotene, vitamin C, folate, vitamin E, soya protein and mushrooms) were adjusted in multivariate model 2.
‡ The model for gim intake was additionally adjusted for education (years), exercise (yes/no), oral contraceptive use (yes/no).
§ The model for miyeok intake was additionally adjusted for family history of breast cancer (yes/no).
‖ The model for frequency of gim was additionally adjusted for family history of breast cancer (yes/no) and exercise (yes/no).
¶ The model for frequency of miyeok was additionally adjusted for family history of breast cancer (yes/no).

To evaluate if seaweed intake affects breast cancer risk differently according to menopausal status, the stratified associations were examined as in Table 4. Among premenopausal women, gim intake and the consumption frequency of gim were inversely associated with breast cancer risk (OR, 0·45; 95 % CI, 0·25, 0·79 for the last quintile; *P* for trend, 0·009; OR, 0·44; 95 % CI, 0·24, 0·80 for the last quintile; *P* for trend, 0·035). Additional adjustment for potential confounders except for dietary factors did not change these significant inverse associations between breast cancer risk and gim intake and the consumption frequency of gim (OR, 0·44; 95 % CI, 0·24, 0·80 for the last quintile; *P* for trend, 0·007; OR, 0·43; 95 % CI, 0·23, 0·81 for the last quintile; *P* for trend, 0·034). However, after additionally adjusting for dietary confounders, these inverse associations were no longer significant (OR, 0·51; 95 % CI, 0·24, 1·08 for the last quintile; *P* for trend, 0·067; OR, 0·55; 95 % CI, 0·26, 1·17 for the last quintile; *P* for trend, 0·286). In the analyses with continuous data, gim intake showed dose–response inverse associations with breast cancer risk in the three models among premenopausal women. Postmenopausal women showed similar inverse associations between breast cancer risk and gim intake, but only the multivariate model 1 (OR, 0·32; 95 % CI, 0·13, 0·80 for the last quintile; *P* for trend, 0·061) was statistically significant. NS associations were found between the risk of breast cancer and miyeok intake and the frequency of miyeok intake.

Discussion

Little evidence is available on the associations between seaweed consumption and breast cancer in epidemiologic studies[31], even though the anticancer effects of seaweeds have been reported *in vitro*[6–8] and *in vivo* assays[9–11]. In the present study, the inverse association between gim (*Porphyra* sp.) intake and breast cancer risk was found, but NS association was found between miyeok (*U. pinnatifida*) intake and breast cancer risk. These results suggest that the high intake of gim may reduce the risk of breast cancer.

Seaweeds have been frequently consumed in Asia for centuries[1]. In Western countries, the consumption of seaweed products has increased during the past few decades[3]. Korean people have consumed seaweeds on a daily basis. Gim is a dried seaweed; one sheet of gim is approximately 2 g. Koreans have eaten mostly dried and roasted gim. Miyeok is usually sold in the form of the dried type, but it is consumed after it is soaked in water. According to the third Korean National Health and Nutrition Survey (2005)[30], the average consumption frequencies of Korean adults for gim and miyeok were 4·5 times/week and 1·3 times/week, respectively. The average consumption frequency of gim for the cases (3·0 times/week) was lower than that of the controls (3·8 times/week) and that of the Korean National Health and Nutrition Survey 2005[30]. The average intake of gim in the cases (0·86 g/d) was also lower than the controls (1·17 g/d). The highest quintile group of gim consumed one sheet of gim per d. The consumption frequencies of miyeok for the controls (1·1 time/week) and cases (1·1 time/week) were similar to the frequency of miyeok in Korean National Health and Nutrition Survey 2005[30]. Controls showed higher consumptions of soya protein and mushrooms than the cases. The associations of soya protein and mushrooms with the risk of breast cancer were reported elsewhere[34,35].

Seaweeds are rich in proteins, polysaccharides, minerals and vitamins[2–5]. The contents of protein for dried gim ranged from 29·0 to 38·6 %, while the protein content for dried miyeok was 13·5 %[36]. High dietary fibre content attributes to the high content of indigestible polysaccharides in the algal cell wall. Seaweeds contained higher amounts of both macrominerals (Na, K, Ca, Mg) and trace elements (Fe, Zn, Mn, Cu) than those from edible land plants[2]. Vitamins A, B_{12}, and C, β-carotene, pantothenate, folate, riboflavin and niacin in algae are higher than in fruits and vegetables from regular land cultivars[37,38].

The amount of gim intake showed an inverse dose–response association with the risk of breast cancer in our present study. To investigate whether seaweeds differently affect the risk of breast cancer by menopause, a stratification analysis was performed according to menopausal status. The inverse associations of gim intake with breast cancer risk did not differ between premenopausal and postmenopausal women. Since the number of postmenopausal women was smaller than the number of premenopausal women, the associations of gim intake with breast cancer risk were not statistically significant among postmenopausal women, but the associations were consistent with premenopausal women. These results suggest that gim has a protective effect on breast cancer risk and this effect may not differ between premenopausal and postmenopausal women. In a prospective study by Key *et al.*[31], the consumption frequency of sea vegetables was not associated with the risk of breast cancer (relative risk, 0·89; 95 % CI, 0·69, 1·16 for ≥5/week in comparison with ≤1/week), but the diet information was from mail surveys and they asked about consumption frequencies of nineteen foods and drinks. In addition, the frequencies of sea vegetables were ‘once or less per week’, ‘two to four times per week’ and ‘five or more times per week’. Thus, in order to determine the association between sea vegetables and breast cancer risk, other kinds of valid dietary assessment methods needed to be introduced.

The antitumour activity of *Porphyra* sp. has been studied *in vitro*[6,9,13,16] and *in vivo*[10,4,12] assays. Polysaccharides produced by the red algae *Porphyra* sp. such as porphyran and *Porphyra yezoensis* polysaccharide have been reported to have immunoregulatory, antioxidant and antitumour activities[6,9,12,13]. Porphyran inhibited cancer cell growth by decreasing cell proliferation and inducing apoptosis in AGS gastric cancer cell lines[6]. *Porphyra yezoensis* polysaccharide had a protective effect on chemical toxicity, which may be related to free radical scavenging, thus increasing superoxide dismutase activity in mice[9]. A protein from the red algae also had chemoprotective effects on acetaminophen-induced liver injury in rats[14]. In addition, extracts from red algae were reported to have antioxidant and antiproliferative activities, which were positively associated with the total polyphenol contents[7], carotenoids[16] and chlorophyll[16].

Miyeok intake did not show any significant associations with the risk of breast cancer in the present study, a finding which may be due to the low consumption frequency and low variation in miyeok intake among the subjects. However, *U. pinnatifida* (miyeok) has been reported to suppress mammary tumour growth in rats[25], while fucoidan and fucoxanthin from *U. pinnatifida* has antitumour[39,40] and antioxidant activities[41]. Therefore, further studies are needed to investigate the relationship between miyeok intake and breast cancer risk in other research settings including areas with a large variation of miyeok intake.

The chemopreventive effects of seaweed on breast cancer have been studied with regard to the relationship between iodine and breast cancer. Seaweeds contain high quantities of iodine in several chemical forms. Even though gim (*Porphyra*) contains less iodine than dashima (*Laminaria*) and miyeok (*Undaria*)[42], gim (*Porphyra*) is also a major dietary source of iodine among the Koreans. A significant positive association was found between the region where iodine intake was low and breast cancer mortality rates in Spain[27]. Tissue iodine levels in the tissue of breast cancer patients were lower than in normal tissues or in benign breast tumours[43]. Iodine acts as an antioxidant and antiproliferative agent, which contributes to the integrity of the normal mammary gland[44]. The addition of seaweeds (*Laminaria*, *Porphyra tenera* and wakame: miyeok) to the diet and iodine supplement showed a suppressive effect on the development and size of both benign and cancer neoplasias in animal studies[10,25,45,46].

Taken together, these results indicate that the protective effect of gim on the risk of breast cancer may be attributed to the antioxidant and antitumour activities of gim components such as polysaccharides, protein, polyphenol, carotenoids[16], chlorophyll[16] and iodine, etc.

Despite the benefits of seaweeds in human health, seaweeds may contain trace and ultra-trace elements with human toxicological potential. The mean contents of arsenic, Pb, Cd, and Hg in *Porphyra* sp. that were produced in Korea, Japan and Italy were assessed as harmless[47,48]. However, arsenosugars detected in *Porphyra* seaweed were metabolised to dimethylarsinic acid in human bodies that is more toxic than arsenosugars[49]. Moreover, brown seaweeds are known as primary accumulators for arsenic[47,48,50]. Thus, the heavy metal contamination of seaweed should be controlled and considered to protect consumers from potential health risks.

To date, this is the first epidemiologic study to determine the direct association of the consumptions of gim and miyeok with the risk of breast cancer. Nevertheless, limitations of the study need to be considered when interpreting the findings. The present study was a hospital-based case–control study, thus, there is a restriction in generalising the results to the general population[51]. One of the potential biases in a case–control study is that cases can change their diet after the diagnosis and treatment of a disease[51]. However, in the present study, all the cases were interviewed before diagnosis or within one week after diagnosis so that dietary changes for cases or differential recall biases are not substantial. The selection of an appropriate control group may be problematic[51]. Although the cases and controls were recruited from the same hospital, the diets of those who participated in the study may differ from those who did not participate. Another limitation is that the FFQ used in the present study asked the intakes of roasted gim and miyeok soup, which are the most frequently consumed forms of gim and miyeok in Korea, so that gim that was consumed as a condiment and miyeok that was consumed as a side dish were not tracked in the questionnaire. Moreover, besides gim and miyeok, other seaweeds such as pare (*Enteromorpha compressa*) and dashima (*Laminaria*) are frequently consumed in certain areas of Korea. Thus, to elucidate the associations of seaweed with the risk of breast cancer, detailed questionnaires for estimating seaweed consumption are needed.

In conclusion, a high intake of gim was associated with a reduced risk of breast cancer among Korean women. These results suggest that gim may reduce the risk of breast cancer. Further studies are necessary to examine these findings in other large-sized epidemiological studies.

Acknowledgements

The present study was supported by the Korea Ministry of Science and Technology (grant no. M10418020002-08N1802-00 210). M. K. K. designed and supervised the execution of the study and Y. J. Y. performed the data analyses and wrote manuscript with S.-J. N. In addition, G. K. contributed to the data preparation. All the authors participated in the interpretation of the results and in the editing of the manuscript. None of the authors had a personal or financial conflict of interest.

References

1. Chapman VJ & Chapman DJ (1980) Sea vegetables (algae as food for man). *Seaweeds and their Uses*, pp. 62–97. London: Chapman & Hall.
2. Ruperez P (2002) Mineral content of edible marine seaweeds. *Food Chem* **79**, 23–26.
3. Mabeau S & Fleurence J (1993) Seaweed in food products: biochemical and nutritional aspects. *Trends Food Sci Tech* **4**, 103–107.
4. Yamada K, Yamada Y, Fukuda M, *et al.* (1999) Bioavailability of dried asakusanori (*Porphyra tenera*) as a source of cobalamin (vitamin B_{12}). *Int J Vitam Nutr Res* **69**, 412–418.
5. Lahaye M (1991) Marine algae as sources of fibres: determination of soluble and insoluble DF contents in some sea vegetables. *J Sci Food Agric* **54**, 587–594.
6. Kwon MJ & Nam TJ (2006) Porphyran induces apoptosis related signal pathway in AGS gastric cancer cell lines. *Life Sci* **79**, 1956–1962.
7. Yuan YV & Walsh NA (2006) Antioxidant and antiproliferative activities of extracts from a variety of edible seaweeds. *Food Chem Toxicol* **44**, 1144–1150.
8. Okai Y, Higashi-Okai K, Nakamura S, *et al.* (1994) Suppressive effects of the extracts of Japanese edible seaweeds on mutagen-induced umu C gene expression in *Salmonella typhimurium* (TA 1535/pSK 1002) and tumor promotor-dependent ornithine decarboxylase induction in BALB/c 3T3 fibroblast cells. *Cancer Lett* **87**, 25–32.
9. Guo TT, Xu HL, Zhang LX, *et al.* (2007) *In vivo* protective effect of *Porphyra yezoensis* polysaccharide against carbon tetrachloride induced hepatotoxicity in mice. *Regul Toxicol Pharmacol* **49**, 101–106.
10. Yamamoto I, Maruyama H & Moriguchi M (1987) The effect of dietary seaweeds on 7,12-dimethyl-benz[*a*]anthracene-induced mammary tumorigenesis in rats. *Cancer Lett* **35**, 109–118.
11. Yamamoto I & Maruyama H (1985) Effect of dietary seaweed preparations on 1,2-dimethylhydrazine-induced intestinal carcinogenesis in rats. *Cancer Lett* **26**, 241–251.

12. Zhang Q, Li N, Zhou G, *et al.* (2003) *In vivo* antioxidant activity of polysaccharide fraction from *Porphyra haitanesis* (Rhodephyta) in aging mice. *Pharmacol Res* **48**, 151–155.
13. Zhao T, Zhang Q, Qi H, *et al.* (2006) Degradation of porphyran from *Porphyra haitanensis* and the antioxidant activities of the degraded porphyrans with different molecular weight. *Int J Biol Macromol* **38**, 45–50.
14. Hwang HJ, Kwon MJ, Kim IH, *et al.* (2008) Chemoprotective effects of a protein from the red algae *Porphyra yezoensis* on acetaminophen-induced liver injury in rats. *Phytother Res* **22**, 1149–1153.
15. Burritt DJ, Larkindale J & Hurd CL (2002) Antioxidant metabolism in the intertidal red seaweed *Stictosiphonia arbuscula* following desiccation. *Planta* **215**, 829–838.
16. Okai Y, Higashi-Okai K, Yano Y, *et al.* (1996) Identification of antimutagenic substances in an extract of edible red alga, *Porphyra tenera* (Asakusa-nori). *Cancer Lett* **100**, 235–240.
17. Yuan YV, Carrington MF & Walsh NA (2005) Extracts from dulse (*Palmaria palmata*) are effective antioxidants and inhibitors of cell proliferation *in vitro*. *Food Chem Toxicol* **43**, 1073–1081.
18. Teas J (1981) The consumption of seaweed as a protective factor in the etiology of breast cancer. *Med Hypotheses* **7**, 601–613.
19. Kamangar F, Dores GM & Anderson WF (2006) Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. *J Clin Oncol* **24**, 2137–2150.
20. LeMarchand L, Kolonel LN & Nomura AM (1985) Breast cancer survival among Hawaii Japanese and Caucasian women. Ten-year rates and survival by place of birth. *Am J Epidemiol* **122**, 571–578.
21. Minami Y, Takano A, Okuno Y, *et al.* (1996) Trends in the incidence of female breast and cervical cancers in Miyagi Prefecture, Japan, 1959–1987. *Jpn J Cancer Res* **87**, 10–17.
22. Maruyama H, Watanabe K & Yamamoto I (1991) Effect of dietary kelp on lipid peroxidation and glutathione peroxidase activity in livers of rats given breast carcinogen DMBA. *Nutr Cancer* **15**, 221–228.
23. Funahashi H, Imai T, Mase T, *et al.* (2001) Seaweed prevents breast cancer? *Jpn J Cancer Res* **92**, 483–487.
24. Sekiya M, Funahashi H, Tsukamura K, *et al.* (2005) Intracellular signaling in the induction of apoptosis in a human breast cancer cell line by water extract of Mekabu. *Int J Clin Oncol* **10**, 122–126.
25. Funahashi H, Imai T, Tanaka Y, *et al.* (1999) Wakame seaweed suppresses the proliferation of 7,12-dimethylbenz(*a*)-anthracene-induced mammary tumors in rats. *Jpn J Cancer Res* **90**, 922–927.
26. Winkler R, Griebenow S & Wonisch W (2000) Effect of iodide on total antioxidant status of human serum. *Cell Biochem Funct* **18**, 143–146.
27. Serra Majem LL, Tresserras R, Canela J, *et al.* (1988) Dietary iodine deficiency and breast cancer mortality: an ecological study. *Int J Epidemiol* **17**, 686–687.
28. Shin H-R, Jung K-W, Won Y-J, *et al.* (2007) National cancer incidence for the year 2002 in Korea. *Cancer Res Treat* **39**, 139–149.
29. Ministry for Health, Welfare and Family Affairs (2008) *Cancer Facts & Figures 2008*. Kwacheon: Ministry for Health, Welfare and Family Affairs.
30. The Korean Ministry of Health and Welfare (2007) *The Third (2005) Korea Health and Nutrition Examination Survey*. Kwacheon: The Korean Ministry of Health and Welfare.
31. Key TJ, Sharp GB, Appleby PN, *et al.* (1999) Soya foods and breast cancer risk: a prospective study in Hiroshima and Nagasaki, Japan. *Br J Cancer* **81**, 1248–1256.
32. Kim MK, Lee SS & Ahn YO (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.
33. Willett WC (1998) *Nutritional Epidemiology*, 2nd ed. New York: Oxford University Press.
34. Hong SA, Kim K, Nam SJ, *et al.* (2008) A case–control study on the dietary intake of mushrooms and breast cancer risk among Korean women. *Int J Cancer* **122**, 919–923.
35. Kim MK, Kim JH, Nam SJ, *et al.* (2008) Dietary intake of soy protein and tofu in association with breast cancer risk based on a case–control study. *Nutr Cancer* **60**, 568–576.
36. The Korean Nutrition Society (2005) *Dietary Reference Intakes for Koreans*. Seoul: The Korean Nutrition Society.
37. Kanazawa I (1963) Vitamins in algae. *Bull Jpn Soc Sci Fish* **29**, 713–731.
38. Ishii T, Susuki H & Koyanagi T (1978) Determination of trace elements in marine organisms. 1. Factors for variation of concentration of trace element. *Bull Jpn Soc Sci Fish* **44**, 155–162.
39. Maruyama H, Tamauchi H, Iizuka M, *et al.* (2006) The role of NK cells in antitumor activity of dietary fucoidan from *Undaria pinnatifida* sporophylls (Mekabu). *Planta Med* **72**, 1415–1417.
40. Hosokawa M, Kudo M, Maeda H, *et al.* (2004) Fucoxanthin induces apoptosis and enhances the antiproliferative effect of the PPARgamma ligand, troglitazone, on colon cancer cells. *Biochim Biophys Acta* **1675**, 113–119.
41. Kang KS, Kim ID, Kwon RH, *et al.* (2008) The effects of fucoidan extracts on CCl(4)-induced liver injury. *Arch Pharm Res* **31**, 622–627.
42. Nagataki S (2008) The average of dietary iodine intake due to the ingestion of seaweeds is 1·2 mg/day in Japan. *Thyroid* **18**, 667–668.
43. Kilbane MT, Ajjan RA, Weetman AP, *et al.* (2000) Tissue iodine content and serum-mediated 125I uptake-blocking activity in breast cancer. *J Clin Endocrinol Metab* **85**, 1245–1250.
44. Eskin BA, Grotkowski CE, Connolly CP, *et al.* (1995) Different tissue responses for iodine and iodide in rat thyroid and mammary glands. *Biol Trace Elem Res* **49**, 9–19.
45. Teas J, Harbison ML & Gelman RS (1984) Dietary seaweed (*Laminaria*) and mammary carcinogenesis in rats. *Cancer Res* **44**, 2758–2761.
46. Garcia-Solis P, Alfaro Y, Anguiano B, *et al.* (2005) Inhibition of *N*-methyl-*N*-nitrosourea-induced mammary carcinogenesis by molecular iodine (I_2) but not by iodide (I^-) treatment evidence that I_2 prevents cancer promotion. *Mol Cell Endocrinol* **236**, 49–57.
47. Dawczynski C, Schafer U, Leiterer M, *et al.* (2007) Nutritional and toxicological importance of macro, trace, and ultra-trace elements in algae food products. *J Agric Food Chem* **55**, 10470–10475.
48. Caliceti M, Argese E, Sfriso A, *et al.* (2002) Heavy metal contamination in the seaweeds of the Venice lagoon. *Chemosphere* **47**, 443–454.
49. Wei C, Li W, Zhang C, *et al.* (2003) Safety evaluation of organoarsenical species in edible Porphyra from the China Sea. *J Agric Food Chem* **51**, 5176–5182.
50. Almela C, Algora S, Benito V, *et al.* (2002) Heavy metal, total arsenic, and inorganic arsenic contents of algae food products. *J Agric Food Chem* **50**, 918–923.
51. Breslow NE & Day NE (1980) *The Analysis of Case–control Studies. Statistical Methods in Cancer Research*, vol. I. Lyon: IARC.