Travis RC, Allen NE, Appleby PN, Spencer EA, Roddam AW, Key TJA prospective study of vegetarianism and isoflavone intake in relation to breast cancer risk in British women. Int J C...

ARTICLE *in* INTERNATIONAL JOURNAL OF CANCER · FEBRUARY 2008

Impact Factor: 5.09 · DOI: 10.1002/ijc.23141 · Source: PubMed

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Int. J. Cancer: **122,** 705–710 (2008)

SHORT REPORT

A prospective study of vegetarianism and isoflavone intake in relation to breast cancer risk in British women

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Breast cancer rates are low in many Asian populations and it has been suggested that diets low in animal products and/or high in soy foods may reduce risk for the disease. However, findings from epidemiological studies are equivocal. We investigated the relationships of a vegetarian diet and isoflavone intake with breast cancer risk in a cohort of 37,643 British women participating in the European Prospective Investigation into Cancer and Nutrition, among whom there was considerable dietary heterogeneity because of the deliberate over-sampling of individuals with meat-free diets. Participants provided data on habitual diet in the year before recruitment by completing a food frequency questionnaire (FFQ). Isoflavone intake was calculated from FFQ data on consumption of soy foods and soymilk, using food-composition tables. (There were precisely 585 breast cancer cases.) 585 women were diagnosed with breast cancer during 7.4 years of follow-up. 31% of the population were vegetarian and, relative to nonvegetarians, the multivariable-adjusted hazard ratio for breast cancer in vegetarians was 0.91 (95% CI 0.72–1.14). With the lowest intake group as the reference (median intake 0.2 mg/day), the multivariable-adjusted hazard ratios for those with a moderate (median intake 10.8 mg/day) or high intake of isoflavones (median intake 31.6 mg/day) were 1.08 (95% CI 0.85–1.38) and 1.17 (0.79–1.71), respectively. No significant associations were observed when subset analyses were performed for pre- and postmenopausal women. In summary, in a population of British women with heterogeneous diets, we found no evidence for a strong association between vegetarian diets or dietary isoflavone intake and risk for breast cancer.

Key words: prospective; breast cancer; diet; vegetarian; isoflavone; EPIC

International comparisons and migrant studies suggest that dietary factors may be important in the aetiology of breast cancer, yet the only established diet-related risk factors for the disease are obesity in postmenopausal women and alcohol intake. Two major hypotheses for the effects of nutrition on breast cancer risk are that a high intake of animal products, including meat and dairy products, may increase risk, and that a high intake of phytoestrogens may reduce risk. Interest in the roles of these dietary factors has been stimulated by the observation that breast cancer rates are lower in many East Asian countries than in Western Europe and the United States, and that intake of animal products is low and intake of soy foods has traditionally been relatively high in some of the low risk countries, especially Japan, China and some other countries in South East Asia.

A putative mechanism linking animal products with breast cancer risk involving insulin-like growth factor-I (IGF-I) has received much attention.[1] However, available data from cohort studies in Western countries have not shown a clear association between risk for breast cancer and intake of meat or dairy products, which have been associated with raised IGF-I.[2,3] Results from comparisons of breast cancer rates in women with vegetarian and nonvegetarian diets have not demonstrated any difference in breast cancer incidence or mortality,[4] but in the majority of studies the number of patients has been relatively small, limiting the statistical power to detect an association.

Vegetarians often consume substantial amounts of foods containing soybeans and the results from many studies using animal models and cell lines support the hypothesis that a high intake of soy products, which are rich in a class of phytoestrogens known as isoflavones, may confer a protective effect against breast cancer.[5,6] However, the findings from epidemiological studies of isoflavone intake and breast cancer risk in humans are equivocal. To date, the majority of studies on soy food and isoflavone intake in relation to risk for breast cancer have been conducted in Asian populations.[7,8] Studies conducted in populations where soy intake is typically very low have produced conflicting results.[9–12]

In this study, we assess the relationship of vegetarian diets and isoflavone intake with breast cancer risk in a cohort of British women among whom there is considerable dietary heterogeneity because of the deliberate over-sampling of individuals with meat-free diets. Plasma concentrations of isoflavones in this population range from negligible amounts to levels similar to those reported in Chinese and Japanese populations.[13]

Material and methods

Subjects

Study participants were 37,643 British women aged 20 years and above who are participating in the Oxford arm of the European Prospective Investigation into Cancer and Nutrition (EPIC-Oxford), the design and methods of which have been described in detail elsewhere.[14–16] A Multi-Centre Research Ethics Committee approved the protocol, and participants gave informed consent. Women were recruited between 1993 and 1999 either through collaborating general practitioners (12.2%), or by postal methods (87.8%) through vegetarian and vegan societies, adverts in health food magazines, or through friends and relatives of other participants.

Women were classified according to menopausal status at baseline using information provided in the recruitment questionnaire on menstrual history (number of periods in the last 12 months and date of last period), history of gynaecological surgery (hysterectomy or oophorectomy), hormone use [oral contraceptives or hormone replacement therapy (HRT)] and age at recruitment.

Exclusions

Women were not eligible for this study if they had a cancer registration with the Office for National Statistics at recruitment (excluding nonmelanoma skin cancer, *in situ* cervical cancer, non-malignant bladder cancer or benign cancer of the meninges) or were aged 90 or over at recruitment. In addition, women were excluded if they had a self-reported history of cancer before

Abbreviations: BMI, body mass index; CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; FFQ, food frequency questionnaire; HR, hazard ratio; HRT, hormone replacement therapy; IGF-I, insulin-like growth factor-I; kJ, kilojoule; SD, standard deviation.

Conflict of Interest: Timothy Key is a member of the Vegetarian Society UK.

Grant sponsors: Cancer Research UK; Medical Research Council, UK.

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Received 14 February 2007; Accepted after revision 26 June 2007
DOI 10.1002/ijc.23141
Published online 17 October 2007 in Wiley InterScience (www.interscience.wiley.com).

recruitment (n = 881, 2.1% of the cohort), had a follow-up time of less than 32 days (n = 16, 0.04%), did not provide data on current smoking (n = 248, 0.6%) or the consumption of soy food and/or soy milk in the food frequency questionnaire (FFQ) (n = 224, 0.5%), or provided unreliable dietary information (greater than 20% of relevant food frequency codes missing or energy intake less than 500 kcal or greater than 3,500 kcal; n = 878, 2.1%). Women were also excluded if they had missing data for any of the covariates in the multivariable model (in total n = 2,822, 6.6%), with the exception of menopausal status, for which 2.6% of women were assigned to an "unknown" category. The analytical cohort for this study, therefore, consisted of 37,643 women aged between 20 and 89 years.

End-points and ascertainment of cancer cases

All participants are followed by record linkage with the National Health Service Central Register, which provides information on cancer diagnoses (received from the local cancer registries) and death. Cancer incidence data were coded according to the International Classification of Diseases (ICD-9 or ICD-10). Women were censored at death, emigration, their 90th birthday, diagnosis with breast cancer or other malignant neoplasm, or the end of follow-up at 31 December 2003, whichever came first.

Dietary measurements

Classification of diet group and isoflavone intake was made on the basis of data from the FFQ. Vegetarians were defined as subjects who reported no to both of the following questions: "Do you eat any meat?" and "Do you eat any fish?". Isoflavone intake was calculated from FFQ data on consumption of soy foods and soy milk, using food-composition tables, as described previously.[13,17] Estimated isoflavone intake from other "dairy products" (cheese, yoghurt and cream) was added for a few participants who specifically noted that they ate soy-based versions of these foods. Participants were classified into 3 groups by isoflavone intake: low (<10 mg/day), moderate (10–19.9 mg/day) and high (≥20 mg/day).

While traditional soy foods and soy dairy alternatives represent the richest source of dietary isoflavones, many commercial bakery products also contain small quantities of soy in the form of food additives.[18] However, the intake of isoflavones from these sources is small in comparison with that from isoflavone-rich soy foods[18] and therefore is not included in our calculations of dietary isoflavone intake.

Validation of FFQ data on soy and isoflavone intake

A previous study of a subset of 80 women from this cohort, which compared estimates of isoflavone intake from data given in the FFQ and measurements from plasma samples, found the FFQ generally to be a reliable tool for estimating dietary soy intake.[13] However, a comparison of soy food intake according to the FFQ with 7-day diet diaries revealed that women reporting soy food consumption 5–6 times or more a week on their FFQ were actually consuming soy foods an average of 3 times per week according to their diet diary. Recoding of the FFQ data to reflect this apparent over-reporting increased the correlation coefficients of solid soy intake and total isoflavone intake with plasma daidzein and genistein. Estimates of total isoflavone intake in this study, therefore, use FFQ data on soy food consumption recoded such that the highest frequency of consumption was 2–4 times per week.

Assessment of the stability of dietary pattern

At baseline, 73% of vegetarian women reported having followed a vegetarian diet for at least 5 years. Furthermore, 84% of women who reported being vegetarian at baseline also reported being vegetarian in a follow-up questionnaire, completed ~5 years later.

Statistical analyses

Statistical analyses were conducted using Stata statistical software (release 8).[19] Main exposures of interest were vegetarianism and estimated average daily isoflavone intake in the 12 months before recruitment.

Associations between vegetarianism, isoflavone intake and characteristics of participants at recruitment were examined using χ^2 tests and one-way analyses of variance for categorical and continuous variables, respectively.

The associations of vegetarianism and isoflavone intake with breast cancer risk were assessed using Cox proportional hazard models, using attained age as the underlying time variable and stratifying by recruitment method. Hazard ratios (HR) and 95% confidence intervals were calculated for vegetarians compared with nonvegetarians and for each category of isoflavone intake compared with the lowest intake category. In a multivariable model, simultaneous adjustment was made for height, body mass index (BMI), age at menarche, age at first birth and parity, menopausal status, current HRT use, alcohol consumption and daily energy intake. All tests of statistical significance, where appropriate, were two-sided and P values of <0.05 were considered statistically significant.

Sub-group analyses of isoflavone intake and risk in premenopausal and postmenopausal women and for non-HRT users were conducted with 2 rather than 3 levels of isoflavone intake (<10 mg/day and ≥10 mg/day), because of the small number of cases among women with an isoflavone intake of ≥20 mg/day.

Results

Follow-up and cancer diagnoses

Of the 37,643 women eligible for this study, 585 (1.6%) were diagnosed with breast cancer during follow-up, of whom 67 had *in situ* breast cancer and 518 had invasive breast cancer. At the end of follow-up 36,489 (96.9%) women were alive, 28 were lost to follow-up (0.07%), 820 had died (2.2%) and 306 had emigrated (0.8%). Follow-up was for a total of 277,025 person-years, and the median duration of follow-up was 7.4 years (minimum 0.1 years, maximum 10.9 years).

Diet group and isoflavone intake

31% of women in this study were classified as vegetarian. The median daily intake of isoflavones was 1.6 mg/day (25th percentile 0.2 mg/day, 75th percentile 10.1 mg/day). More than 50% of the cohort consumed solid soy foods at least once a month and 37% of the cohort consumed these foods at least once a week. Eight percent of the cohort reported drinking some soy milk each day, with 52% of these women reporting consumption of 0.25 pints (142 ml) of soy milk on average per day. Total intake of isoflavones was markedly higher among vegetarians (median 10.1 mg/day) than among nonvegetarians (0.23 mg/day).

Characteristics of cohort by diet group

Vegetarian women were significantly different from nonvegetarian women with respect to a number of demographic, reproductive and lifestyle characteristics, including several established risk factors for breast cancer (see Table I). Vegetarian women were younger and more likely to be premenopausal than nonvegetarians. Compared with nonvegetarians, vegetarians were also on average taller, had a lower age at menarche, consumed less alcohol, had a lower BMI, were more likely to have been very physically active and to have been recruited by post, and were less likely to have been parous or to have used postmenopausal hormone therapy ($p < 0.001$ for all). These differences between vegetarians and nonvegetarians were similar to those observed between women who consumed ≥20 mg/day isoflavones and women who consumed <10 mg/day (data not shown).

Diet group and breast cancer risk

Relative risk estimates for breast cancer showed no significant association between vegetarianism and risk for breast cancer, either after adjustment for age alone or after further adjustment for

TABLE I – BASELINE CHARACTERISTICS OF NONVEGETARIAN AND VEGETARIAN WOMEN IN EPIC-OXFORD

Characteristic	Nonvegetarian	Vegetarian	*p* value
Number of subjects	25,912	11,731	
Age at recruitment (years)	46.1 (13.1)	37.9 (13.0)	<0.001
Anthropometry			
Height (cm)	163.9 (6.7)	164.4 (6.8)	<0.001
Weight (kg)	64.4 (11.3)	61.3 (10.1)	<0.001
BMI (kg/m^2)	24.0 (4.1)	22.7 (3.5)	<0.001
Reproductive characteristics			
Age at menarche	12.9 (1.5)	12.8 (1.5)	<0.001
Parous (%)	17,928 (69.2)	5,127 (43.7)	<0.001
Age at first birth in parous women	25.8 (4.7)	26.1 (5.0)	<0.001
Menopausal status (%)			
Premenopausal	13,414 (51.8)	8,991 (76.6)	<0.001
Perimenopausal	2,551 (9.8)	706 (6.0)	
Postmenopausal	9,262 (35.7)	1,872 (16.0)	
Unknown	685 (2.6)	162 (1.4)	
Age at menopause among those aged more than 55 years	48.8 (5.7)	48.9 (5.8)	0.83
Current use of HRT (%)[1]	3,979 (15.4)	586 (5.0)	<0.001
Diet			
Energy intake (kJ/day)	7,964 (2100)	7,539 (2103)	<0.001
Alcohol intake (g/day)	8.0 (9.9)	7.6 (9.9)	<0.001
Isoflavone intake (mg/day)	2.9 (6.6)	10.2 (12.9)	<0.001
Method of recruitment (%)			
Postal	21,574 (83.3)	11,679 (99.6)	<0.001
General practice	4,338 (16.7)	52 (0.4)	

Values are mean (SD) unless otherwise indicated.
BMI, body mass index; HRT, postmenopausal hormone therapy.
[1]This factor is unknown for some women—these "unknowns" are excluded from the calculations of percentages.

other potential confounders in the multivariable model (multivariable adjusted HR = 0.91, 95% CI 0.72–1.14 for vegetarians compared with nonvegetarians; Table II).

No significant associations between vegetarianism and breast cancer risk were seen for premenopausal women (multivariable adjusted HR = 0.95, 95% CI 0.68–1.32), postmenopausal women (multivariable adjusted HR = 0.79, 95% CI 0.54–1.16) or for non-HRT users (multivariable adjusted HR = 0.89, 95% CI 0.70–1.14).

Isoflavone intake and breast cancer risk

Relative risk estimates for breast cancer for 3 levels of isoflavone intake indicated no association between dietary isoflavone intake and breast cancer risk, either after adjustment for age alone or after further adjustment for other potential confounders in the multivariable model (Table II). With the lowest intake group as the reference, the multivariable-adjusted hazard ratios for those with a moderate or high intake of isoflavones were 1.08 (95% CI 0.85–1.38) and 1.17 (0.79–1.71), respectively.

Analyses of data for premenopausal women, postmenopausal women and non-HRT users also showed no significant associations between isoflavone intake and risk for breast cancer (Table II).

Exclusion of data for the first year of follow-up (66 women were diagnosed with breast cancer less than 1 year after recruitment) did not materially alter these findings. Similarly, when the analyses were repeated with the endpoint restricted to invasive breast cancer (518 cases) the results were similar to those obtained for all breast cancer cases.

Discussion

Main findings

In this study of British women in the EPIC-Oxford cohort, of whom 31% were vegetarian and 27% were consuming 10 mg or more of isoflavones a day, we found no evidence for a relationship of risk for breast cancer with vegetarianism or with dietary isoflavone intake.

The EPIC-Oxford cohort was designed to include participants with a wide range of dietary habits, in particular to include a high proportion of vegetarians and vegans. This feature provides a rare opportunity to analyse vegetarianism and isoflavone intakes in relation to breast cancer risk in a Western population in which a significant minority are vegetarian and/or are consuming moderate to high levels of isoflavone-rich foods.

The finding from the current study of no strong association between vegetarianism and breast cancer risk is in accord with previously published data on breast cancer incidence and mortality.[20–25] These results are perhaps not surprising given that much of the epidemiology of breast cancer can be explained by hormonal factors and that studies of circulating sex hormones in vegetarians have shown oestrogen levels to be similar to those of nonvegetarians.[26] However, published data show that vegans, who exclude dairy products and eggs from their diet as well as meat and fish, have a lower serum concentration of IGF-I than meat-eaters and vegetarians who consume diary products and eggs,[27] and high IGF-I levels have been linked to an increase in risk for breast cancer.[28] Even in the current study though, where particular attention was paid to the recruitment of women following a vegetarian or vegan diet, few data are available on the risk of breast cancer among vegan women (this study includes 657 vegan women, of whom 8 developed breast cancer following recruitment).

Results from epidemiological studies of isoflavone intake and breast cancer risk are inconsistent, and although putative mechanisms underlying the possible association have received much attention, the biological effects of exposure to dietary isoflavones remain uncertain. Two early case–control studies in predominantly Asian populations suggested that a high intake of soy food may be protective against breast cancer in women.[29,30] Since plasma concentrations of isoflavones in postmenopausal women who consume soy foods are up to 1,000 times higher than those of oestradiol, and phytoestrogens are structurally similar to endogenous oestrogens, it has been suggested that such an association

TABLE II – AGE-ADJUSTED AND MULTIVARIABLE-ADJUSTED HAZARD RATIOS[1] FOR BREAST CANCER (95% CI) BY DIET GROUP AND ISOFLAVONE INTAKE

	N	Person years of follow-up	Age-adjusted model		Multivariable model[2]	
			Hazard ratio (95% CI)	*p* value (heterogeneity/trend)[3]	Hazard ratio (95% CI)	*p* value for (heterogeneity/trend)[3]
Vegetarianism						
All						
Nonvegetarian	477	188,337	1.00	0.26	1.00	0.40
Vegetarian	108	88,688	0.88 (0.71–1.10)		0.91 (0.72–1.14)	
Premenopausal						
Nonvegetarian	141	97,231	1.00	0.61	1.00	0.77
Vegetarian	55	68,082	0.92 (0.66–1.27)		0.95 (0.68–1.32)	
Postmenopausal						
Nonvegetarian	257	66,786	1.00	0.15	1.00	0.23
Vegetarian	33	14,061	0.76 (0.52–1.10)		0.79 (0.54–1.16)	
Non-HRT users[4]						
Nonvegetarian	340	158,515	1.00	0.25	1.00	0.35
Vegetarian	93	84,326	0.87 (0.68–1.10)		0.89 (0.70–1.14)	
Isoflavone intake (mg/day)						
All						
<10	474	202,469	1.00	0.81/0.55	1.00	0.65/0.36
10 < 20	82	57,087	1.06 (0.83–1.35)		1.08 (0.85–1.38)	
20+	29	17,469	1.10 (0.75–1.61)		1.17 (0.79–1.71)	
Premenopausal						
<10	136	109,305	1.00	0.10	1.00	0.11
10+	60	56,007	1.31 (0.96–1.80)		1.31 (0.95–1.81)	
Postmenopausal						
<10	255	68,163	1.00	0.60	1.00	0.80
10+	35	12,684	0.91 (0.63–1.30)		0.95 (0.66–1.38)	
Non-HRT users						
<10	335	172,594	1.00	0.31	1.00	0.21
10+	98	70,247	1.13 (0.89–1.43)		1.16 (0.92–1.48)	

N, number of cases; CI, confidence interval.

[1]Cox regression analyses were stratified by method of recruitment.–[2]In the multivariable model, simultaneous adjustment was made for height (continuous in centimeters), body mass index group (<20, 20−, 22.5−, 25−, 27.5+ kg/m^2), age at menarche (<12 years, 12–13 years, 14 years or older), age at first birth and parity [nulliparous, parous split into 8 groups based on the number of children (1−2, 3+) and age at first birth (<20, 20−, 25−, 30+ years)], alcohol consumption (<0.4, 0.4−, 8.0−, 16.0+ g/day), and daily energy intake (continuous in kilojoules per day), and where appropriate, menopausal status (pre-, peri-, postmenopausal, unknown) and current HRT use (yes, no).–[3]The *p* values for heterogeneity from likelihood ratio tests of statistical significance and *p* values for trend from Wald tests of statistical significance from models in which isoflavone intake was entered as a continuous variable, with categories assigned their median values.–[4]Non-HRT users were those not currently taking HRT.

may exist because isoflavones may have an anti-oestrogenic effect.[31] However, isoflavones predominantly circulate in conjugated forms[32] and their bioactivity is thought to be markedly less potent than unconjugated forms in terms of binding to the oestrogen receptor and stimulation of transcription.[33] Results from several intervention studies in humans have also suggested that exposure to dietary isoflavones may alter oestrogen metabolism,[34–39] although findings from other similar studies have been inconsistent.[40–42] Consistent with the null findings in the current study, the majority of previous prospective studies of dietary isoflavone intake and risk for breast cancer have failed to find a strong association,[10–12,43] while results from one study suggested a protective association.[44]

It has been hypothesised that menopausal status might be an important modifier of the effect of phytoestrogens on the risk for breast cancer, because mechanisms that might mediate the effect involve the ovarian synthesis of sex hormones or the alteration of other menstrual cycle characteristics.[45,46] Two early studies found evidence for a protective effect of soy food intake in premenopausal but not among postmenopausal women.[29,47] However, findings from other studies of isoflavone intake in pre- and postmenopausal women separately have been inconsistent,[9,10,12,43,44,48] with most reporting no significant association, as was found in the current study. Since HRT use may mask or alter any association of isoflavone intake with breast cancer risk, we repeated the analysis for women who were not using HRT, but still observed no significant relationship between isoflavone intake and risk for breast cancer.

Data from several studies have indicated that the age of exposure to dietary phytoestrogens might influence their effects with respect to breast cancer risk.[49–54] Specifically, 3 studies have found women who consumed isoflavones during adolescence to be at lower risk for breast cancer in later life than those who did not.[52–54] It has also been suggested that exposure *in utero* or infancy through maternal soy intake or soy milk formula might influence hormone-related cancer risk in later life.[31] We had data on recent isoflavone consumption only and were not able to assess the importance of isoflavone intake during early life.

Although the FFQ was not specifically designed to assess phytoestrogen intake, it did include several items on the consumption of foods rich in soy, because part of the aim of the EPIC-Oxford study was to assess the importance of different dietary patterns, in particular vegetarianism, on risk for cancer and a common characteristic of vegetarian diets is a high consumption of soy-rich foods. The availability of plasma daidzein and genistein concentrations for a sample of women in the study has made it possible to conduct a validation study of dietary isoflavone intake as reported on the FFQ.[13] Furthermore, comparisons of information provided on dietary habits at recruitment (current dietary pattern and dietary pattern 5 years previously) and at the 5-year follow-up indicate that dietary patterns in this cohort have been relatively stable over time.

In summary, in a population of 37,600 British women with a wide range of diets, we found no evidence for a strong association between either a vegetarian diet or total daily isoflavone intake and risk for breast cancer.

Acknowledgements

The authors thank the participants in the EPIC-Oxford study.

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