

Soya food intake and risk of endometrial cancer among Chinese women in Shanghai: population based case-control study

Wang Hong Xu, Wei Zheng, Yong Bing Xiang, Zhi Xian Ruan, Jia Rong Cheng, Qi Dai, Yu Tang Gao, Xiao Ou Shu

Abstract

Objective To evaluate the association of intake of soya food, a rich source of phytoestrogens, with the risk of endometrial cancer.

Design Population based case-control study, with detailed information on usual soya food intake over the past five years collected by face to face interview using a food frequency questionnaire.

Setting Urban Shanghai, China.

Participants 832 incident cases of endometrial cancer in women aged 30 to 69 years diagnosed during 1997-2001 and identified from the Shanghai Cancer Registry; 846 control women frequency matched to cases on age and randomly selected from the Shanghai Residential Registry.

Main outcome measures Odds ratios for risk of endometrial cancer in women with different intakes of soya foods.

Results Regular consumption of soya foods, measured as amount of either soya protein or soya isoflavones, was inversely associated with the risk of endometrial cancer. Compared with women with the lowest quarter of intake, the adjusted odds ratio of endometrial cancer was reduced from 0.93 to 0.85 and 0.67 with increasing quarter of soya protein intake (*P* for trend 0.01). A similar inverse association was observed for soya isoflavones and soya fibre intake. The inverse association seemed to be more pronounced among women with high body mass index and waist:hip ratio.

Conclusion Regular intake of soya foods is associated with a reduced risk of endometrial cancer.

Introduction

Soya foods are a rich source of isoflavones such as genistein and daidzein, a major group of phytoestrogens that have both weak oestrogenic and antioestrogenic activities.^{1,2} Phytoestrogens have been shown to alter endogenous oestrogen concentrations by binding competitively to oestrogen receptors,³ inhibiting important steroid biosynthetic enzymes,⁴ increasing the clearance of steroids from the circulation,⁵ and stimulating the production of sex hormone binding globulin.⁶ Soya foods also contain high amounts of dietary fibre, which has been shown to lower serum oestrogen by decreasing the concentration of intestinal β glucuronidase, increasing elimination of oestrogen through the faecal route, and reducing intestinal reabsorption.^{7,8}

As endogenous oestrogens have a central role in the aetiology of endometrial cancer,⁹ factors that alter endogenous oestrogen concentrations, such as phytoestrogens and fibre, may be related to the risk of the disease. Circumstantial supporting evidence is avail-

able showing that Asian women have a lower incidence of endometrial cancer and eat more soya food than their Western counterparts.¹⁰ Analytical epidemiological studies on intake of soya foods and risk of endometrial cancer, however, have been few and inconsistent.¹¹⁻¹³

High intake of soya foods may reduce the risk of endometrial cancer among women with high exposure to oestrogen but increase the risk or have no effect on risk among women with low oestrogen exposure.¹⁴ We tested this hypothesis in a population based case-control study among Chinese women in Shanghai from 1997 to 2001.

Methods

Participants—Through the population based Shanghai Cancer Registry, we identified and interviewed 832/982 (84.7%) of eligible women, who were aged between 30 and 69 years and were diagnosed as having endometrial cancer between January 1997 and December 2001. We randomly selected controls from the permanent female residents of the Shanghai urban area through the Shanghai Resident Registry and frequency matched them to cancer cases by age (five year intervals). Interviews were completed for 846 of the controls (response rate 72.6%).

Interviews and measurements—We recorded anthropometric data and used standardised, structured questionnaires, including a validated quantitative food frequency questionnaire, to collect information on exposure to risk factors and dietary intake. We measured total intake of soya food according to intakes of soya protein and soya isoflavones. We estimated intake of soya protein by multiplying the amount of soya food consumed by the amount of protein in that food according to the Chinese food composition table.¹⁵ We calculated isoflavone intake by using published data on the isoflavone content of each soya food.¹⁶ The median (25th to 75th centile) interval between diagnosis and interview for cases was 5 (3 to 8) months.

Results

Cases and controls were well matched on age (table 1). No major differences between cases and controls existed with respect to marital status, family income, total energy intake, or use of hormone replacement therapy. However, compared with controls, cases attained higher education; had an earlier age at menarche, later age at menopause, and longer

Department of Epidemiology, Shanghai Cancer Institute, 2200 Xie Tu Road #25, Shanghai 200032, China

Wang Hong Xu
assistant professor

Yong Bing Xiang
professor

Zhi Xian Ruan
research staff

Jia Rong Cheng
research staff

Yu Tang Gao
professor

Department of Medicine, Vanderbilt-Ingram Cancer Center, Vanderbilt Center for Health Services Research, Vanderbilt University, 6009 Medical Center East, 1215 21st Avenue South, Nashville, TN 37232-8300, USA

Wei Zheng
professor

Qi Dai
assistant professor

Xiao Ou Shu
professor

Correspondence to: X O Shu
Xiao-Ou.Shu@vanderbilt.edu

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Table 1 Demographic characteristics and selected risk factors for endometrial cancer. Values are numbers (percentages) unless stated otherwise

Characteristic	Cases (n=832)	Controls (n=846)	P value
Mean (SD) age (years)	55.3 (8.60)	55.7 (8.58)	0.30
Education:			
No formal education or just elementary school	204 (24.5)	234 (27.7)	0.08
Middle school	503 (60.5)	513 (60.6)	
College and above	125 (15.0)	99 (11.7)	
Marital status:			
Unmarried	14 (1.7)	10 (1.2)	0.68
Married or cohabiting	724 (87.0)	742 (87.7)	
Separated, divorced, or widowed	94 (11.3)	94 (11.1)	
Per capita income in previous year (yuan):			
≤4166.7	230 (27.7)	244 (28.9)	0.83
4166.8-6250.3	243 (29.2)	242 (28.6)	
6250.4-8333.3	57 (6.9)	50 (5.9)	
≥8333.3	301 (36.2)	309 (36.6)	
No of pregnancies:			
None	62 (7.5)	35 (4.1)	<0.01
1	137 (16.5)	109 (12.9)	
2	199 (23.9)	208 (24.6)	
3	194 (23.3)	207 (24.5)	
4	141 (17.0)	157 (18.6)	
≥5	99 (11.9)	130 (15.4)	
Cancer among first degree relatives	289 (34.7)	228 (27.0)	<0.01
Postmenopausal (natural)	492 (59.1)	541 (64.0)	0.03
Regular alcohol consumption	20 (2.4)	42 (5.0)	<0.01
Hormone replacement therapy	35 (4.2)	34 (4.0)	0.85
Oral contraceptive use	147 (17.7)	207 (24.5)	<0.01
Regular exercise	253 (30.4)	287 (33.9)	0.12
Age at menarche*	14 (13 to 16)	15 (13 to 16)	<0.0001
Age at menopause (among postmenopausal women)*	50.1 (48.6 to 52.5)	49.4 (47.1 to 51.1)	<0.0001
Years of menstruation*	33.2 (30.0 to 36.1)	31.5 (27.8 to 34.5)	<0.0001
Body mass index*	25.1 (22.7 to 27.9)	23.7 (21.4 to 26.3)	<0.0001
Waist:hip circumference ratio*	0.84 (0.81 to 0.87)	0.82 (0.78 to 0.85)	<0.0001
Usual energy intake (kcal/day)*	2171.2 (1871.4 to 2497.0)	2141.5 (1840.8 to 2485.2)	0.71
Total fruit and vegetable intake (g/day)*	482.2 (330.6 to 671.8)	477.0 (334.1 to 663.7)	0.54
Total meat and fish intake (g/day)*	115.2 (74.7 to 173.7)	102.0 (63.7 to 154.2)	<0.01

Participants with missing values excluded from analysis.

*Median (25th to 75th centile) presented.

duration of menstruation; had higher body mass index and waist:hip ratio; and were less likely to take regular exercise, drink alcohol, or use oral contraceptives. Cases were also more likely to have a family history of cancer, have been pregnant fewer times, and have consumed more meat and fish. No significant differences existed between cases and controls for fruit and vegetable intake. We adjusted all subsequent analyses

Table 2 Intake of soya food and soya protein among participants in the Shanghai endometrial cancer study. Values are medians (25th to 75th centiles) unless stated otherwise

Food	Cases	Controls	P value*
Soya food (g/day):	106.5 (54.4 to 224.8)	116.3 (55.4 to 243.5)	0.08
Soya milk	8.2 (0.0 to 107.1)	16.4 (0 to 107.1)	0.25
Tofu	28.6 (14.3 to 57.1)	28.6 (13.1 to 57.1)	0.38
Other processed soy products	16.4 (8.2 to 35.7)	16.4 (7.1 to 35.7)	0.77
Dry soya bean seeds	0 (0 to 0.7)	0 (0 to 0.7)	0.38
Fresh soya beans	6.3 (2.2 to 13.3)	6.3 (2.8 to 14.2)	0.13
Soya bean sprouts	1.4 (0 to 4.9)	1.4 (0 to 6.6)	0.12
Soya protein (g/day)	9.9 (5.9 to 15.0)	10.2 (5.9 to 16.0)	0.26
Isoflavones (mg/day)	40.5 (22.7 to 61.9)	42.5 (22.6 to 63.5)	0.13

* t test for geometric means.

for age, energy intake, and the above mentioned significant variables as potential confounders.

Women with endometrial cancer had a lower intake of total soya foods and almost every individual soya food investigated, as well as total soya protein and soya isoflavones, than did controls, although most differences did not reach statistical significance (table 2).

After adjustment for dietary and non-dietary risk factors, the risk of endometrial cancer was inversely associated with increasing quarters of intake of soya protein, soya fibre, soya isoflavones, and fresh soya bean (table 3). We also observed a dose-response relation for total intake of soya protein ($P = 0.01$), soya fibre ($P = 0.02$), and fresh soya beans ($P = 0.01$). Additional adjustment for total fruit and vegetable intake did not alter the association. Intakes of soya protein, soya fibre, and soya isoflavones were highly correlated, making it difficult to separate their independent effects.

Although high soya food intake was related to a lower risk of endometrial cancer in all strata, the inverse association between intake of soya protein and risk of endometrial cancer was more pronounced among women with a higher body mass index (P for trend 0.01) or a higher waist:hip ratio (P for trend 0.01) (see bmj.com). The association of soya intake with endometrial cancer did not vary by menopausal status, whether users of hormone replacement therapy (35 cases and 34 controls) were included in or excluded from the analysis.

Discussion

Incident rates of endometrial cancer vary more than 10-fold worldwide.¹⁷ In addition to host susceptibility, dietary factors may play an important role in this international variation. Asian countries have a low incidence of endometrial cancer and a high consumption of soya food. In our study population, the average intake of isoflavones from soya food was about 25 times that reported in a Western population (42.5 mg/day *v* 1.7 mg/day for controls),¹³ whereas the incident rate of endometrial cancer is only one fifth to one third that in Western countries.¹⁷

Soya isoflavones may have a role in the development of hormone related cancers, including endometrial cancer.¹⁸ Phytoestrogens have been shown to alter circulating concentrations of ovarian steroid hormones, prolong the menstrual cycle, alleviate symptoms of menopause, and enhance alkaline phosphatase activity in a human endometrial adenocarcinoma cell line, although evidence is not entirely consistent.¹⁸⁻²⁰ An inverse association between phytoestrogen consumption and risk of endometrial cancer was reported by Goodman in a multiethnic population and by Horn-Ross among Western women.^{12 13} However, legume intake was found to be associated with a slightly increased risk of endometrial cancer in an earlier study that we conducted among Chinese women.¹¹ Some of these previous studies were not specifically designed to investigate the role of soya food, and the assessment of soya food intake was incomplete and sometimes mixed with other peas and beans.^{11 12} The sample sizes of the previous studies were relatively small, which limited the statistical power to evaluate the effect of soya food intake by menopausal status and body size.

Menopausal status, body mass index, and waist:hip ratio are associated with endogenous concentrations of sex hormones.^{21 22} Our finding of a more pronounced inverse association between soya food intake and risk of endometrial cancer among women with a higher body mass index or waist:hip ratio (P for trend < 0.05) are in line with our study hypothesis that soya food exerts an antioestrogenic effect in an oestrogen rich environment. However, the finding of a similar inverse association among premenopausal and postmenopausal women did not seem to support the above mentioned hypothesis or the findings from a recent US study that suggested a stronger effect of soya on endometrial cancer among postmenopausal women.¹³ Studies with measured oestrogen concentrations are needed to better understand the joint effect of soya and endogenous oestrogen on endometrial cancer risk.

Strengths and weaknesses

Soya consumption is high and constant among Chinese people, making this population an ideal setting in which to evaluate the effect of soya. The population based design, high response rate, and low frequency of hysterectomy in the study population minimised selection bias. Potential confounding from dietary and non-dietary risk factors was adjusted for in the analysis. The low frequency of use of hormone replacement therapy has exempted our study from the influence of this important potential confounder. However, it also limited our ability to investigate the effect of soya among women who have high oestrogen concentrations from an exogenous source.

Non-differential misclassification in dietary assessment would bias the results towards null. Although we specifically asked study participants to report their usual dietary intake during the five years before the diagnosis date for cases and the interview date for controls, ignoring recent dietary changes, the recall of dietary intake could still have been influenced by recent dietary practice. In the study, 17.9% of cases and 7.6% of controls reported an increased intake of soya food during the seven days before the interview, 8.8% of cases and 10.0% of controls reported a decrease, and 73.4% of cases and 82.4% of controls reported no change. Analysis restricted to women who reported no recent dietary change resulted in a slightly stronger inverse association between intake of soya food and risk of endometrial cancer (data not

Table 3 Association of endometrial cancer with soya food intake

	Cases/controls	Odds ratio 1* (95% CI)	Odds ratio 2† (95% CI)
Isoflavones (mg/day)			
≤22.7	207/212	1.00	1.00
22.8-42.5	226/211	1.10 (0.84 to 1.44)	0.98 (0.73 to 1.30)
42.6-63.6	203/212	0.98 (0.75 to 1.29)	0.79 (0.59 to 1.07)
>63.6	196/211	0.96 (0.73 to 1.26)	0.77 (0.56 to 1.05)
P for trend		0.58	0.05
Soya food fibre (g/day)			
≤0.4	212/212	1.00	1.00
0.5-0.8	216/211	1.03 (0.78 to 1.34)	0.91 (0.68 to 1.22)
0.9-2.0	225/212	1.06 (0.82 to 1.39)	0.85 (0.63 to 1.13)
>2.0	179/211	0.86 (0.65 to 1.13)	0.69 (0.51 to 0.94)
P for trend		0.36	0.02
Soya protein (g/day)			
≤5.9	209/212	1.00	1.00
6.0-10.2	220/211	1.06 (0.81 to 1.39)	0.93 (0.69 to 1.24)
10.3-16.0	222/212	1.07 (0.82 to 1.39)	0.85 (0.63 to 1.14)
>16.0	181/211	0.88 (0.66 to 1.15)	0.67 (0.48 to 0.92)
P for trend		0.40	0.01

*Adjusted for age.

†Adjusted for age, education, menopausal status, years of menstruation, first degree family history of any cancer, oral contraceptive use, physical activity, number of pregnancies, body mass index, total meat intake, and energy intake.

shown), suggesting that the effect of soya food on endometrial cancer is probably underestimated in this study.

Conclusions

This study found an inverse dose-response relation between intake of soya food and the risk of endometrial cancer. The indication that women with a high body mass index or waist:hip ratio may benefit more from increased soya food intake needs to be verified in future studies.

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What is already known on this topic

Endogenous oestrogens have a central role in the aetiology of endometrial cancer

Soya foods are a rich source of isoflavones, a major group of phytoestrogens that have both weak oestrogenic and antioestrogenic activities, depending on dose and tissue

What this study adds

Regular intake of soya foods is associated with a reduced risk of endometrial cancer, particularly among overweight women

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Hospital admissions, age, and death: retrospective cohort study

Tracy Dixon, Mary Shaw, Stephen Frankel, Shah Ebrahim

Abstract

Objectives Ageing of the population brings the possibility of increased burdens for acute hospital services because of the marked increase in many common diseases with age. We aimed to examine the relation between age and use of acute services in hospitals in the period before death in a national sample of deaths in hospital.

Design Retrospective cohort analysis of English hospital episode statistics database.

Setting All NHS hospitals in England.

Data set All post-neonatal deaths occurring in English NHS hospitals during financial year 1999-2000, with episodes of care in the previous three years determined through matching on sex, date of birth, and postcode.

Main outcome measures Total bed days, mean and median length of stay.

Results 253 799 in-hospital deaths were identified, representing about 45% of all deaths occurring in 1999-2000. Patients who died in hospital spent a median of 23 days in hospital in the three years before death; the median rose with age up to 45 years, but was fairly stable for ages 45 and above. The number of admissions to NHS hospitals in the three years before death averaged 3.6; this peaked at 10.4 in patients aged 5-9 years and decreased with age to 2.2 in those aged 85 and over.

Conclusions The average number of bed days spent in hospital in the period before death does not increase with increasing age.

Introduction

With life expectancy continually increasing in most countries, population ageing has become an important issue worldwide. This has led to concerns about the impact this will have on healthcare systems, given the marked increase in many diseases with age. Public debate over the perceived overuse of health care serv-

ices by older people has included discussions of equity, the "fair innings" argument, and age based rationing of health care.

One view is that the increasing numbers of older people will inevitably result in a greater burden of chronic and degenerative diseases, such as cardiovascular diseases, osteoarthritis, cancers, diabetes, cataract and macular degeneration, and dementia syndromes, which will result in an increased demand for health care and hence soaring costs.^{1,2} An alternative suggestion is that the increase in total life expectancy has been accompanied by an increase in healthy life expectancy, due to a compression of morbidity into a shorter period, effectively postponing the onset of chronic diseases and associated disabilities.^{1,3,4} This second scenario would result in a lower burden on healthcare resources than the first.⁵

A key concern in this debate has been the utilisation and cost of acute care. In his interim report on estimating the resources required to run the English health service in 2020, Wanless stated: "Age and people's proximity to death are the most significant determinants of health status and health needs, but the impact of ageing on future expenditure is likely to be relatively small when compared to other cost drivers."⁶ In the acute setting, to what extent does age, rather than proximity to death, lead to higher costs? This paper examines that question by considering the acute phase of care provided by the public sector. We asked: does the total time spent in hospital or the number of spells in hospital, or both, in the three years before death vary with age?

Methods

We analysed hospital episode statistics for England. The database (www.dh.gov.uk/PublicationsAndStatistics/



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Department of Social Medicine, University of Bristol, Bristol BS8 2PR
Tracy Dixon
research assistant
Mary Shaw
senior research fellow
Stephen Frankel
professor of epidemiology and public health medicine
Shah Ebrahim
professor in epidemiology of ageing

Correspondence to: M Shaw
mary.shaw@bristol.ac.uk

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