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Short Communication

Soya and isoflavone intakes associated with reduced risk of oesophageal cancer in north-west China

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Abstract

Objective: To ascertain the association between soya consumption, isoflavone intakes and oesophageal cancer risk in remote north-west China, where the incidence of oesophageal cancer is known to be high.
Design: Case–control study. Information on habitual consumption of soya foods and soya milk was obtained by personal interview. The intakes of isoflavones were then estimated using the US Department of Agriculture nutrient database. Logistic regression analyses were performed to assess the association between soya consumption, isoflavone intakes and oesophageal cancer risk.
Setting: Urumqi and Shihezi, Xinjiang Uyghur Autonomous Region, China.
Subjects: Participants were 359 incident oesophageal cancer patients and 380 hospital-based controls.
Results: The oesophageal cancer patients consumed significantly less ($P < 0{\cdot}001$) total soya foods (mean 57·2 (SD 119·0) g/d) and soya milk (mean 18·8 (SD 51·7) ml/d) than the controls (mean 93·3 (SD 121·5) g/d and mean 35·7 (SD 73·0) ml/d). Logistic regression analyses showed an inverse association between intake of soya products and the risk of oesophageal cancer. The adjusted odds were OR = 0·33 (95 % CI 0·22, 0·49) and OR = 0·48 (95 % CI 0·31, 0·74) for consuming at least 97 g of soya foods and 60 ml of soya milk daily (the highest tertiles of consumption), respectively, relative to the lowest tertiles of consumption. Similarly, inverse associations with apparent dose–response relationships were found between isoflavone intakes and oesophageal cancer risk.
Conclusions: Habitual consumption of soya products appears to be associated with reduced risk of oesophageal cancer in north-west China.

Keywords
Isoflavone
Soya foods
Soya milk
Oesophageal cancer

Oesophageal cancer is the eighth most common malignancy and the sixth leading cause of cancer-related deaths worldwide[1]. In 2008, more than 480 000 new cases were diagnosed, and approximately 407 000 people died from this cancer[1]. There is also considerable geographic variation in the incidence of oesophageal cancer. For instance, the age-standardised rate in China was 16·7 per 100 000 in 2008, but only 0·8 and 2·7 per 100 000 in Greece and Canada, respectively[1]. Such differences in incidence between countries have generated interest in the role of nutritional and lifestyle factors in oesophageal cancer aetiology, apart from genetic and familial risk factors, which is important for the primary prevention of the disease.

Soya food products, such as soyabeans, soya milk (produced by soaking and grinding dried soyabeans) and tofu (fermented product of soya milk), are widely consumed in Asian countries[2]. Soya is also a primary source of isoflavones[3]. Earlier research has suggested that soya consumption may prevent the development of certain tumours[4–7]. However, only a few studies have assessed the effect of soya products on oesophageal cancer risk and the limited results available are inconsistent[8–10].

Xinjiang Uyghur Autonomous Region, located in the north-west of China, is one of the areas constituting the so-called 'Asian Oesophageal Cancer Belt'[11]. According to a survey conducted in Xinjiang between 2005 and 2008, the incidence of oesophageal cancer was 30·2 per 100 000,

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much higher than the national average during the same period[12], which suggested that environmental and behavioural factors may contribute to the high disease rate in this region of China. The present study aimed to ascertain the association between habitual soya consumption, isoflavone intakes and the risk of oesophageal cancer among adults in this remote region of China.

Materials and methods

Study design and participants

A hospital-based case–control study of oesophageal cancer was conducted in Urumqi and Shihezi, Xinjiang Uyghur Autonomous Region of China, between January 2008 and December 2009. Participants were recruited from the Xinjiang Tumour Hospital, Shihezi People's Hospital, Kuitong Hospital and No. 1 Affiliated Hospital of Shihezi University.

Medical records and pathology reports were reviewed weekly to identify patients newly diagnosed with oesophageal cancer within the past 12 months. Pathological diagnoses were based on the WHO's Classification of Tumours of the Digestive System[13]. Patients without histopathological confirmation were excluded. Of the total 364 incident patients identified, 359 consented to participate in the study.

During the same period, controls were recruited from in-patient wards of the departments of ophthalmology, orthopaedic, respiratory disease and physiotherapy. Exclusion criteria for controls were previous diagnosis of any malignant disease, on long-term medical diet and self-reported memory problems. A systematic selection process for controls was adopted throughout the recruitment period. In-patient ward numbers were initially selected by random sampling before screening potential controls for group matching to cases based on the hospital daily census sheets. Of the 400 eligible controls recruited to frequency match with cases by gender and age (within 5 years), 380 eventually gave their consent to be interviewed.

The study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human patients were approved by the Human Research Ethics Committee of Curtin University (approval number HR 56/2006). Written informed consent was obtained from all participants, who were assured of confidentiality of the information provided and their right to withdraw at any time without prejudice.

Data collection

All participants were interviewed face to face by trained interviewers using a structured questionnaire, usually in the presence of their next-of-kin to help the recall of past events. Both participants and interviewers were blinded to the study hypothesis. Questions asked included demographic characteristics, anthropometry, past and family medical history, as well as lifestyle such as physical activity, cigarette smoking and alcohol drinking. Information on diet was solicited using a validated 137-item semi-quantitative FFQ. The FFQ had been validated in both Han and ethnic minority groups in a previous study, which included the common fruits, vegetables and soya products (six items) consumed in Xinjiang Province[14]. Frequency and amount of intake were recorded in detail. The reference recall period for dietary variables was set at 5 years before diagnosis for cases and 5 years before interview for controls. The energy content of each food or beverage item was extracted from the Chinese food composition tables to calculate total energy intake (kJ/d)[15]. Intakes (mg/d) of daidzein, genistein and glycitein were estimated based on the amounts of soya products consumed using the US Department of Agriculture nutrient database[16], as such values were unavailable from the Chinese food composition tables.

Statistical analysis

The χ^2 test and t test were used to compare the sample characteristics between case and control groups. Unconditional logistic regression analyses were then performed to ascertain the effects of soya foods, soya milk and isoflavones on oesophageal cancer risk. Subgroup analyses by ethnic group (Han *v.* Uyghur minority people) were undertaken using the same statistical method. For each participant, total soya foods intake (g/d) was obtained by summing the daily consumption of soyabeans, soyabean sprouts, fresh tofu, dried tofu and tofu pudding. Soya sauce was excluded, because it was typically added during cooking and thus difficult to quantify the exact amount consumed. For each soya or isoflavone variable, tertiles of the corresponding distribution of controls were used to derive the cut-off points, resulting in three increasing levels of exposure, with the lowest level of intake being the reference category.

In addition to reporting crude and adjusted odds ratios and associated 95% confidence intervals, tests for linear trend (treating exposures as continuous variables) were conducted to assess the dose–response relationship between soya and isoflavone exposures and oesophageal cancer risk. Crude odds ratios were obtained from the univariate logistic regression models, whereas confounding variables included in the adjusted models were age (years), gender, education level (none/primary, secondary, tertiary), BMI (5 years ago, kg/m^2), total energy intake (kJ/d), tobacco smoking (pack-years), alcohol drinking (ml/week) and family history of cancer in first-degree relatives (no, yes). These variables were either established or plausible risk factors from the literature. Energy adjustment for soya products and isoflavones based on the regression residuals method was also investigated[17]. All statistical analyses were undertaken using the statistical software package IBM SPSS Statistics version 20.

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Results

There were no statistically significant differences in age, gender and demographics between participants and non-participants. Table 1 summarises characteristics of the sample by case–control status. The participants were on average 61·0 (SD 11·4) years old with a mean BMI of 24·1 (SD 3·7) kg/m^2. The majority (72 %) of them were male. About half the participants smoked and regularly drank alcoholic beverages. Compared with the controls, patients with oesophageal cancer tended to belong to the ethnic minority group, have lower education level but a family history of oesophageal cancer. With respect to soya products, the oesophageal cancer patients reported significantly lower consumption ($P<0·001$) of total soya foods (mean 57·2 (SD 119·0) g/d) and soya milk (mean 18·8 (SD 51·7) ml/d) than their control counterparts (mean 93·3 (SD 121·5) g/d and mean 35·7 (SD 73·0) ml/d, respectively). Significant differences in isoflavone intake levels were also observed between the two groups ($P<0·001$).

Table 2 summarizes the results of logistic regression analyses. An inverse association between intake of soya products and the risk of oesophageal cancer was found. The adjusted odds were OR = 0·33 (95 % CI 0·22, 0·49) and OR = 0·48 (95 % CI 0·31, 0·74) for adults consuming at least 97 g of soya foods and 60 ml of soya milk daily (the highest tertiles of consumption), respectively, relative to those at the lowest tertiles of consumption. The corresponding linear trends were statistically significant ($P=0·001$). Inverse associations were also found between isoflavone intakes and oesophageal cancer risk, with significant dose–response relationships demonstrated for daidzein ($P=0·001$), genistein ($P<0·001$) and glycitein ($P<0·001$). The regression residuals method for adjustment of total energy intake produced consistent results (see online supplementary material, Supplemental Table 1). Finally, subgroup analysis by ethnic group, i.e. Han *v.* Uyghur minority people, led to similar results (see Supplemental Tables 2 and 3).

Discussion

The present study provides the first report on the inverse association between habitual soya consumption and oesophageal cancer risk in north-west China, an area with high incidence of oesophageal cancer in the Asia-Pacific region. Our findings are consistent with a previous case–control study conducted in Shanxi Province, which suggested that frequent consumption of soyabean products could reduce the risk of oesophageal cancer[8]. On the other hand, no apparent relationship was evident

Table 1 Comparison of demographic characteristics, soya consumption and isoflavone intakes between case and control groups in Xinjiang, China, January 2008–December 2009

	Cases		Controls		
Variable	*n* or Mean	% or SD	*n* or Mean	% or SD	*P**
Gender					0·623
Male	260	72·4	269	70·8	
Female	99	27·6	111	29·2	
Ethnic group					0·001
Han	270	75·2	322	84·7	
Minority	89	24·8	58	15·3	
Education level					<0·001
None/primary	183	51·0	136	35·8	
Secondary	140	39·0	191	50·3	
Tertiary	36	10·0	53	13·9	
Family history of cancer in first-degree relatives					<0·001
No	306	85·2	356	93·7	
Yes	53	14·8	24	6·3	
Age at interview (years)	61·4	11·0	60·6	11·8	0·338
BMI (5 years ago, kg/m^2)	24·3	3·8	24·0	3·6	0·181
Tobacco smoking (pack-years)	13·4	22·1	12·5	20·7	0·551
Alcohol drinking (ml/week)	279	683	303	693	0·634
Total energy intake (kJ/d)	18 031	11 216	19 700	11 361	0·047
Total soya foods (g/d)	57·2	119·0	93·3	121·5	<0·001
Fresh tofu (g/d)	21·3	32·6	43·9	71·7	<0·001
Dried tofu (g/d)	4·6	19·1	8·8	24·7	0·011
Tofu pudding (g/d)	13·3	50·4	21·3	52·7	0·037
Soyabeans (g/d)	4·1	14·1	2·5	7·4	0·055
Soyabean sprouts (g/d)	13·8	87·2	16·8	53·7	0·567
Soya milk (ml/d)	18·8	51·7	35·7	73·0	<0·001
Isoflavones (mg/d)	16·5	29·9	27·1	36·5	<0·001
Daidzein (mg/d)	7·4	13·5	12·2	16·8	<0·001
Genistein (mg/d)	8·4	15·3	13·8	18·5	<0·001
Glycitein (mg/d)	0·7	1·3	1·2	1·5	<0·001

*χ^2 or *t* test for difference between cases and controls.

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Table 2 Crude and adjusted odds ratios (and 95 % confidence intervals) of oesophageal cancer risk for soya consumption and isoflavone intakes among adults in Xinjiang Province, China, January 2008–December 2009

	Cases		Controls						
Daily intake	*n*	%	*n*	%	Crude OR	95 % CI	Adjusted OR*	95 % CI	*P* for trend*†
Total soya foods (g/d)									0·001
<26·0	182	50·7	122	32·1	1·00	Ref.	1·00	Ref.	
26·0–97·0	115	32·0	132	34·7	0·58	0·42, 0·82	0·53	0·37, 0·76	
>97·0	62	17·3	126	33·2	0·33	0·23, 0·48	0·33	0·22, 0·49	
Soya milk (ml/d)									0·001
<2·0	256	71·3	211	55·5	1·00	Ref.	1·00	Ref.	
2·0–60·0	61	17·0	92	24·2	0·55	0·38, 0·79	0·58	0·40, 0·86	
>60·0	42	11·7	77	20·3	0·45	0·30, 0·68	0·48	0·31, 0·73	
Isoflavones (mg/d)									<0·001
<8·0	194	54·0	126	33·2	1·00	Ref.	1·00	Ref.	
8·0–26·0	92	25·6	126	33·2	0·47	0·33, 0·67	0·46	0·32, 0·66	
>26·0	73	20·3	128	33·7	0·37	0·26, 0·53	0·37	0·25, 0·55	
Daidzein (mg/d)									0·001
<3·6	192	53·5	126	33·2	1·00	Ref.	1·00	Ref.	
3·6–11·7	95	26·5	127	33·4	0·49	0·35, 0·70	0·47	0·33, 0·68	
>11·7	72	20·1	127	33·4	0·37	0·26, 0·54	0·38	0·26, 0·57	
Genistein (mg/d)									<0·001
<4·0	194	54·0	126	33·2	1·00	Ref.	1·00	Ref.	
4·0–13·0	93	25·9	125	32·9	0·48	0·34, 0·69	0·46	0·32, 0·67	
>13·0	72	20·1	129	33·9	0·36	0·25, 0·52	0·36	0·25, 0·54	
Glycitein (mg/d)									<0·001
<0·4	204	56·8	144	37·9	1·00	Ref.	1·00	Ref.	
0·4–1·1	79	22·0	107	28·2	0·52	0·36, 0·75	0·52	0·35, 0·76	
>1·1	76	21·2	129	33·9	0·42	0·29, 0·59	0·43	0·29, 0·62	

Ref., reference category.
*From separate logistic regression models adjusting for age (years), gender, education level (none/primary, secondary, tertiary), BMI (5 years ago, kg/m^2), total energy intake (kJ/d), tobacco smoking (pack-years), alcohol drinking (ml/week) and family history of cancer in first-degree relatives (no, yes).
†Treating exposures as continuous variables.

between isoflavone intake and oesophageal cancer incidence according to a prospective cohort study conducted in ten European countries[9]. Another prospective cohort study undertaken among Japanese men in the USA similarly reported lack of a significant association between tofu consumption and upper aerodigestive tract cancer[10]. Differences in food sources and consumption levels of soya products between populations may partly explain the conflicting epidemiological findings.

The oestrogenic effects of isoflavones have been proposed for preventing hormone-related malignancies, such as ovarian, breast and prostate cancer[4,18,19]. Moreover, experimental evidence indicates that the antioxidant properties of isoflavones may be responsible for their anticarcinogenic effects[20]. Previous animal studies have already demonstrated that isoflavones can enhance the activities of antioxidant enzymes *in vivo*[21] and inhibit the expression of proto-oncogene *c-fos* in mouse skin[22]. Genistein, a subclass of isoflavones, has also been shown to scavenge both superoxide anion and hydrogen peroxide extracellularly[23]. It is thus biologically plausible that isoflavone intake, through soya consumption, may protect oesophageal cells against oxidative damage and by impeding malignant transformation.

In the present study, a standardised identification procedure was implemented that ensured the ascertainment of cases was maximised and complete. To avoid misclassification of the case–control status, only incident patients were recruited, who had been diagnosed with oesophageal cancer within the past 12 months and subsequently confirmed with pathology. All controls were carefully screened. To determine the effect of soya and isoflavone intakes, information on other exposures and confounding factors such as tobacco smoking and alcohol drinking was also collected. It was possible that some oesophageal cancer patients might have modified their dietary behaviours including soya products consumption since the onset of the disease. To avoid reverse causation, the reference period for the FFQ was set at 5 years ago.

Several biases and limitations should be taken into consideration. A major limitation concerns the retrospective cross-sectional nature of the case–control design so that a cause-and-effect relationship between soya consumption and oesophageal cancer risk could not be established. Nevertheless, the use of four hospitals reduced sampling bias, and as they serve the entire catchment region, the participants could be considered as representative of the target population of Xinjiang Province. Although the recall of habitual soya consumption should not be affected by the case–control status, dietary assessment was made based on self-report, which probably introduced some recall error in the response of participants, especially since the recall period of dietary intakes was set at 5 years ago. Face-to-face interviews

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were thus conducted in the presence of next-of-kin to help improve the accuracy of their answers. Furthermore, information bias was unlikely because all participants were blinded to the study hypothesis, while the potential protective effects of soya products against oesophageal cancer had not been established in the north-west of China at the time of interview. However, residual confounding might still exist even though established risk factors have been controlled for in the multivariable logistic regression models. Lastly, information on the histologic subtypes of oesophageal cancer was not available to enable subgroup analyses of oesophageal tumours.

Conclusion

Habitual soya consumption was found to be inversely associated with the risk of oesophageal cancer in north-western China, with significant dose–response relationships observed for total and specific isoflavone intakes. Further studies are required before generalising the findings to other populations and to confirm whether long-term consumption of soya products can offer protection and enhance survival from this deadly disease.

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Supplementary material

To view supplementary material for this article, please visit http://dx.doi.org/10.1017/S1368980013003443

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