Annals of Oncology 23: 1061–1066, 2012
doi:10.1093/annonc/mdr320
Published online 15 July 2011

Inverse association between soy intake and non-Hodgkin lymphoma risk among women: a case–control study in Japan

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Received 24 February 2011; revised 11 May 2011; accepted 13 May 2011

Background: Non-Hodgkin lymphoma (NHL) is one of the common malignant tumors worldwide. Environmental factors, such as diet have an important association with the risk of cancer. Although soy intake has been associated with a reduced risk of several cancers, its association with NHL is not known.

Patients and methods: We evaluated the association between soy consumption and risk of NHL by conducting a hospital-based case–control study in 302 patients with NHL and 1510 age- and sex-matched control subjects. Odds ratio (OR) and 95% confidence intervals (CIs) for groups with moderate (27–51 g/day) to high (>51 g/day) relative to low (<27 g/day) intake were calculated using multivariate conditional logistic regression model.

Results: Soy intake was significantly associated with a reduced risk of NHL in women but not in men (OR [95% CI] for moderate and high intake: women, 0.64 [0.42–1.00] and 0.66 [0.42–1.02], respectively; men, 1.40 [0.87–2.24] and 1.33 [0.82–2.15], respectively; *P*-interaction = 0.02). This finding appeared consistent across NHL subtypes.

Conclusion: These results indicate the potential importance of certain ingredients in soy for lymphomagenesis. Further studies to evaluate the mechanism behind the association between soy intake and lymphomagenesis are warranted.

Key words: estrogen, isoflavone, non-Hodgkin lymphoma, soy

introduction

Non-Hodgkin lymphoma (NHL) is one of the common malignant tumors worldwide [1–3]. In the United States, the age-standardized incidence rates of NHL per 100 000 population in 2008 was 16.3 in men and 11.5 in women [4]. The National Cancer Institute previously predicted that ~65 540 people would be diagnosed with NHL in 2010, representing the fifth most common malignancy, and 20 210 people would die of this disease. While the incidence of NHL in Japan has almost doubled in the last three decades [5, 6], with age-standardized incidence rates in 2008 of 6.3 in men and 4.0 in women, these are nevertheless less than half those in Western countries [4]. Although the distribution of NHL differs between Asian and Western countries, the incidence rates among the Japanese living in Los Angeles are 13.5 in men and 8.5 in women, which are higher than those of populations in Japan and comparable to those of other populations in Western countries, suggesting that environmental factors have a greater impact on interpopulation variability [5].

Both underlying medical conditions and environmental factors such as diet have an important association with the risk of cancer [7, 8]. Risk factors for the development of NHL identified to date include immunosuppression, various infections, such as Epstein–Barr virus, HIV, hepatitis B virus (HBV) and hepatitis C virus (HCV), autoimmune disorders, family history of hematopoietic malignancy, obesity, and smoking [1, 2, 9–17]. As for diet, meat and saturated fat have positive association to the risk of NHL, whereas high vegetable intake reduces the risk of NHL, but evidence for each foods is limited [13, 18]. The incidence of NHL differs between populations; however, risk or preventive foods responsible for interpopulation variability have rarely been reported.

Soy intake is higher among Asians than Westerners. While the median soy intake of an average Japanese individual is ~60 g/day [19], that of a Western individual is 1 g/day, as reported

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by a meta-analysis [20]. Soy contains significant amounts of phytic acid, alpha-linolenic acid, and isoflavones. Isoflavones may play a role similar to phytoestrogens, which bind competitively to estrogen receptors (ERs) but have a weak estrogenic effect of nearly 0.1% of that of estradiol. An association between soy intake and reduced cancer risk has been shown for several cancers, including breast, prostate, colorectal, and gastric cancer, and has been frequently studied in relation to effect modification by sex [20–23]. To our knowledge, however, no study has evaluated the association between soy intake and risk of NHL.

Here, to evaluate the association between soy intake and risk of NHL, we conducted a hospital-based case–control study in patients with NHL. Furthermore, we also examined the potential effect modification on this association by sex.

subjects and methods

study population

Subjects were selected from those who enrolled in the hospital-based Epidemiological Research Program at Aichi Cancer Center Hospital 2 (HERPACC-II) from January 2001 to November 2005. All subjects enrolled in HERPACC-II were asked about their lifestyle such as drinking status, smoking status, diet, anthropometric information, reproductive factors, and medical history at the first visit. For those with symptoms, information on lifestyle before the development of symptoms was required, and for those without symptoms, information up to the date of interview was required. All information was collected through self-administered questionnaires, which were then checked by research nurses who confirmed the information directly with the subjects. Further details of HERPACC-II have been described elsewhere [24].

Of the subjects enrolled in HERPACC-II, a total of 302 patients without history of cancer were subsequently diagnosed with NHL by hematopathologists based on the World Health Organization (WHO) classification of 2001 [25]. Of the noncancer outpatients included in the HERPACC-II datasets, 1510 healthy control subjects who were matched for age and sex at their first visit were independently selected. The case-to-control ratio was 1 : 5 to maximize statistical power.

Although the Aichi Cancer Center Hospital (ACCH) is called a cancer hospital, cancer patients at the ACCH account for only 46% and 28% of all male and female outpatients, respectively. Of the noncancer outpatients, 13.1% have benign tumors and/or non-neoplastic polyps, 7.5% have mastitis, 4.1% have gastrointestinal disease, and 4.1% have benign gynecologic disease, while the remainder have no specific medical condition. Although the medical background of the controls may have introduced bias into the study, our previous study demonstrated that this bias, if present, was minimal [26].

Approximately 95% of eligible case and control subjects completed the questionnaire. The data were loaded into the HERPACC database and periodically linked with the hospital cancer registry system to update the data on cancer incidence. We previously showed that the lifestyle patterns of first-visit noncancer outpatients in HERPACC-II were in accordance with those of subjects randomly selected from the general Nagoya City population, confirming the external validity of the study [27]. This study was approved by the Ethics Committee of the Aichi Cancer Center Institute, and informed consent was obtained from all participants.

assessment of soy intake and other exposures

All data were collected from the HERPACC-II questionnaire. The food frequency questionnaire (FFQ) consisted of 47 food items, which the subjects classified into eight frequency categories as follows: never or seldom, 1–3 times/month, 1–2 times/week, 3–4 times/week, 5–6 times/week, 1 time/day, 2 times/day, and over 2 times/day [28]. Dietary intake of soybean products was calculated by multiplying the standard portion size of *tofu* (soybean curd), *miso* (fermented soybean paste) soup, and *natto* (fermented soybeans) with the respective frequencies of intake. The standard portion sizes of each soybean product were calculated based on a validity test using 3-day weighed dietary records, in which soy food serving size were 50 g for *tofu*, 52 g for *miso soup*, and 30 g for *natto*. Similar methods were used to calculate the intake of other foods, such as green vegetables, other vegetables, fruits, meat, fish, and other seafood, for which the validity and reproducibility of the FFQ had been confirmed [28]. All foods consumption was calculated in 'g/day' unit that was adjusted for total calorie intake.

Alcohol intake status was categorized into three groups as never, former, and current. Smoking habit was categorized into four groups according to pack-years, defined as the product of the average number of packs per day and the number of years of smoking (<5, 5–19, 20–39, and ≥40 pack-years). Body mass index (BMI) at 20 years of age was calculated by dividing the weight (kg) by the square of the height (m^2). In accordance with the guidelines for Asians set by the WHO Western Pacific Region and others [18], BMI was classified into five categories (<18.5, 18.5–22.9, 23.0–24.9, 25–29.9, and ≥30 kg/m^2). We previously confirmed a high correlation between self-reported and measured values for weight and height [29].

Additionally, information on reproductive factors, such as age of menarche (≤12 or >12 years old), menopausal status (pre- or postmenopause), parity (none, one or two, or more than two), and age of first delivery (≤23, 24–30, or ≥31 years old) were collected from the questionnaire.

statistical analyses

The strength of associations between NHL risk and factors such as food consumption were calculated using odds ratio (OR) and 95% confidence intervals (CIs) from the conditional logistic model. The amount of consumption of soy and other foods was categorized as low, moderate, and high. The frequency of intake of single food items was categorized as rare (<1 time/week), weekly (1–6 times/week), and daily (≥1 time/day). Since our previous study showed that alcohol intake status, smoking exposure expressed in pack-years, and early adulthood weight are associated with the risk of NHL [10, 11], these factors were adjusted in the analysis as confounders as well as total energy intake. Dummy variables were applied for missing values. In accordance with our a priori hypothesis that the effect of soy on NHL risk may differ by sex, as it does for other types of cancer [21], sex-stratified analysis for evaluation of effect modification was defined as the default model. Analysis after stratification by reproductive factors was also carried out. Descriptive statistical analyses of categorical data by alcohol status, smoking status, and BMI at 20 years of age were carried out using the Fisher's exact test or χ^2 test, as appropriate.

All statistical analyses were carried out using Stata version 11 (Stata Corp., College Station, TX) and *P*-values <0.05 were considered statistically significant.

results

characteristics of subjects

The characteristics of all subjects are summarized in Table 1. The median age of both cases and controls was 56 years (range: 18–80 years). Cases had a lower prevalence of drinkers, and a higher prevalence of smokers and obesity compared with

Table 1. Characteristics of cases and controls

Category	Men			Women		
	Cases (%) (n = 147)	Controls (%) (n = 735)	*P*-value	Cases (%) (n = 155)	Controls (%) (n = 775)	*P*-value
Age (years)			0.959			0.946
Median (range)	57 (18–79)	58 (18–80)		56 (21–78)	56 (21–79)	
Alcohol status			0.034			0.079
Never	45 (30.6)	171 (23.3)		109 (70.3)	465 (60.0)	
Former	12 (8.2)	32 (4.4)		1 (0.7)	20 (2.6)	
Current	90 (61.2)	530 (72.1)		45 (29.0)	288 (37.2)	
Unknown	0	2 (0.2)		0	2 (0.2)	
Smoking (pack-years)			0.720			0.006
0–4.9	40 (27.2)	242 (32.9)		131 (84.5)	678 (87.4)	
5–19.9	31 (21.1)	136 (18.5)		14 (9.0)	56 (7.2)	
20–39.9	34 (23.1)	157 (21.4)		8 (5.2)	28 (3.6)	
≥40	40 (27.2)	189 (25.7)		2 (1.3)	6 (0.8)	
Unknown	2 (1.4)	11 (1.5)		0	7 (1.0)	
Body mass index at 20 years of age (kg/m^2)			0.018			0.070
<18.5	27 (18.4)	230 (31.3)		60 (38.7)	323 (41.7)	
18.5–22.9	73 (49.6)	323 (44.0)		56 (36.1)	310 (40.0)	
23.0–24.9	27 (18.4)	111 (15.1)		21 (13.6)	100 (12.9)	
25.0–29.9	12 (8.1)	42 (5.7)		13 (8.4)	24 (3.1)	
≥30	2 (1.4)	3 (0.4)		0 (0.0)	2 (0.3)	
Unknown	6 (4.1)	26 (3.5)		5 (3.2)	16 (2.0)	
Age of menarche (years)						0.103
≤12				47 (30.3)	191 (24.6)	
>12				101 (65.2)	565 (72.9)	
Unknown				7 (4.5)	19 (2.5)	
Menopause status						0.573
Premenopause				47 (30.3)	258 (33.3)	
Postmenopause				106 (68.4)	517 (66.7)	
Unknown				2 (1.3)	0	
Parity (number of children)						0.505
None				20 (12.9)	118 (15.2)	
1 or 2				93 (60.0)	475 (61.3)	
>2				41 (26.5)	173 (22.3)	
Unknown				1 (0.6)	9 (1.2)	
Age of first delivery (years)						0.649
≤23				40 (25.8)	170 (21.9)	
24–30				84 (54.2)	426 (55.0)	
≥31				9 (5.8)	51 (6.6)	
Unknown				2 (0.6)	10 (1.2)	

controls regardless of sex, albeit without statistical significance for alcohol status and BMI in women and smoking status in men. Women with earlier age at menarche were more prevalent among cases, albeit without statistical significance ($P = 0.103$). HBs-Ag and HCV serostatus were available in 99 out of 302 patients but we have no data in controls. Among these patients, only four and five patients were seropositive for HBV and HCV, respectively. Seropositivity of HBV and HCV had no association with soy intake (HBV: $P = 0.728$; HCV: $P = 0.255$). No marked difference between cases and controls was seen for the other reproductive factors. With regard to histological subtype, distribution was as follows: diffuse large B-cell lymphoma (DLBCL), 113 patients (37.4%); follicular lymphoma (FL), 82 patients (27.2%); marginal zone B-cell lymphoma (MZBCL), 60 patients (19.9%); and other NHL subtypes, including those of other B-cell and T-cell lymphomas, 47 patients (15.5%).

risk of NHL with soy intake

The association between NHL risk and soy intake is summarized in Table 2. Mean intake of soy among all subjects was 43 g/day. Soy intake >27 g/day was significantly associated with a reduced risk of NHL among women but not among men (uniting moderate to high soy intake groups; OR [95% CI]: 0.65 [0.45–0.95], $P = 0.028$). This difference between women and men was statistically significant (P-heterogeneity = 0.02). For comparative purposes, we examined other food groups (green vegetables, other vegetables, fruits, meat, fish, and other

seafood), none of which show a significant association with NHL risk except moderate green vegetable intake among women (supplemental Table S1, available at *Annals of Oncology* online). No association was seen between the intake of soy and other foods.

To confirm the consistency of the association between NHL risk and soy, we assessed this association using food items made from soy (Table 3). We observed consistent inverse associations in women with more than weekly intake of *miso* soup or *natto*, while the association was less clear with *tofu* (Table 3).

We also evaluated the impact of soy on the three histological subtypes, namely DLBCL, FL, and MZBCL (Table 4). An inverse association between NHL risk and soy intake was consistently observed in all three subtypes among women, albeit without statistical significance. A significant association was observed in MZBCL among men with high soy intake (>51 g/day; OR [95% CI]: 4.89 [1.15–20.8]).

association between risk of NHL and soy intake in relation to reproductive factors

We next examined possible interactions between reproductive factors and soy intake. Soy intake was recategorized into two groups with intake being low and moderate to high. Using the reproductive factors shown in Table 1, the trend in reduction of NHL risk was examined in all subgroups among woman with soy intake (supplemental Table S2, available at *Annals of Oncology* online). No reproductive factors were found to interact with soy intake.

discussion

In the present study, we observed that soy intake had a significant inverse association with the risk of NHL among women but not in men. This finding appeared consistent across histological subtypes and reproductive factors, indicating the potential importance of certain ingredients in soy in lymphomagenesis.

Our study revealed two important findings. One is the variability in the effect of soy intake among sex and the other is the difference of effect among soy products. Several potential biological mechanisms have been hypothesized to explain how ingredients in soy products, such as isoflavones, genistein, and daidzein, reduce the risk of malignant disease. With regard to isoflavones, their presence may result in either long-term genomic actions that are mediated by intracellular ER-induced changes in gene expression or in rapid nongenomic actions that modify a wide array of intracellular signal transduction cascades [30–32]. For instance, isoflavones may bind to ERs, thereby interfering with the action of estrogen and leading to antiestrogenic effects. Estrogen exposure is a well-established risk factor for hormone-dependent cancers such as breast and prostate cancer [33, 34]. Additionally, isoflavones have been demonstrated to have antioxidant and anti-inflammatory effects, and to affect cell cycle regulation, induce apoptosis, and inhibit the activation of NF-kB and angiogenesis, all of which may have a protective effect against non-hormone-dependent cancers [35–37]. With regard to genistein, treatment with this agent induced apoptosis in several lymphomas cell lines, suggesting that genistein directly affects lymphoma cells [38, 39].

Table 2. OR for the risk of non-Hodgkin lymphoma with soy intake

	Male		Female		*P*-heterogeneity by sex
	Case/control	OR (95% CI)	Case/control	OR (95% CI)	
Soy intake (g/day)					0.02
Low (<27)	43/267	1.00 (Reference)	60/221	1.00 (Reference)	
Moderate (27–51)	50/221	1.40 (0.87–2.24)	47/271	0.64 (0.42–1.00)	
High (>51)	49/225	1.33 (0.82–2.15)	46/271	0.66 (0.42–1.03)	

Adjusted for total energy intake, smoking status, alcohol status and body mass index at 20 years of age. CI, confidence interval; OR, odds ratio.

Table 3. OR for the risk of non-Hodgkin lymphoma with soy products

	Male		Female		*P*-heterogeneity by sex
	Case/control	OR (95% CI)	Case/control	OR (95% CI)	
Miso soup					0.08
Rarely (<1 time/week)	10/66	1.00 (Reference)	14/58	1.00 (Reference)	
Weekly (1–6 times/week)	72/365	1.21 (0.58–2.55)	89/413	0.93 (0.49–1.786)	
Daily (≥1 time/day)	63/283	1.34 (0.63–2.83)	47/285	0.75 (0.37–1.53)	
Tofu					0.30
Rarely (<1 time/week)	55/292	1.00 (Reference)	47/211	1.00 (Reference)	
Weekly (1–6 times/week)	79/389	1.13 (0.77–1.66)	95/495	0.98 (0.65–1.47)	
Daily (≥1 time/day)	10/31	1.60 (0.70–3.67)	8/38	1.09 (0.47–2.55)	
Natto					0.12
Rarely (<1 time/week)	53/269	1.00 (Reference)	59/203	1.00 (Reference)	
Weekly (1–6 times/week)	75/367	1.01 (0.68–1.50)	75/473	0.59 (0.39–0.88)	
Daily (≥1 time/day)	13/73	0.83 (0.41–1.69)	15/79	0.68 (0.35–1.31)	

Adjusted for total energy intake, smoking status, alcohol status and body mass index at 20 years of age. CI, confidence interval; OR, odds ratio.

Table 4. Effect of soy intake on disease subtype

	Male		Female		*P*-heterogeneity by sex
	Case/control	OR (95% CI)	Case/control	OR (95% CI)	
Diffuse large B-cell lymphoma					
Soy intake (g/day)					0.59
Low (<27)	19/111	1.00 (Reference)	18/63	1.00 (Reference)	
Moderate (27–51)	22/89	1.51 (0.73–3.16)	16/101	0.58 (0.26–1.28)	
High (>51)	19/101	1.05 (0.48–2.30)	17/86	0.80 (0.37–1.73)	
Follicular lymphoma					
Soy intake (g/day)					0.11
Low (<27)	9/66	1.00 (Reference)	20/61	1.00 (Reference)	
Moderate (27–51)	15/56	2.27 (0.81–6.34)	13/72	0.68 (0.30–1.57)	
High (>51)	10/50	1.47 (0.49–4.54)	13/95	0.55 (0.24–1.27)	
Marginal zone B-cell lymphoma					
Soy intake (g/day)					<0.01
Low (<27)	5/45	1.00 (Reference)	17/60	1.00 (Reference)	
Moderate (27–51)	3/31	0.88 (0.15–5.17)	12/59	0.80 (0.32–1.98)	
High (>51)	13/29	4.89 (1.15–20.8)	8/65	0.50 (0.18–1.34)	

Adjusted for total energy intake, smoking status, alcohol status, and body mass index at 20 years of age. CI, confidence interval; OR, odds ratio.

Difference in the soy effect among sex suggests biological variance between men and women, which may be somewhat related to estrogen exposure. In addition to NHL and breast cancer, variability in the effect of soy intake between men and women was also reported in a meta-analysis of colorectal cancer, suggesting estrogen-induced carcinogenesis in other cancers, and that soy intake may accordingly play a preventive role in these events [21]. In this regard, previous studies have reported an association between estrogen and NHL [40, 41]. Gaikwad et al. [40] reported that estrogen can form depurinating DNA adducts via the reaction between estrogen quinones and DNA, thereby initiating NHL. Whether this unbalanced estrogen metabolism occurs before or after the onset of lymphoma is unclear and further epidemiologic and biological studies to clarify the relationship between hormones and soy products in the mechanism behind lymphomagenesis are warranted.

Difference in effect among three soy products may enhances an importance of isoflavone. Our study revealed inverse association between *miso* and *natto* with a risk of NHL, while *tofu* had no association. *Miso* and *natto* are aglycone-rich fermented soy products, whereas *tofu* a is glucoside-rich nonfermented soy product. Recent study revealed that ingestion of aglycone-rich fermented soybeans had significantly higher bioavailability of isoflavones than glycoside-rich nonfermented soybeans [42]. In fact, in our study, isoflavone levels were not available, which is one of the limitations of this study. Further studies are needed to validate our results.

The association between reproductive factors that reflect estrogen exposure and NHL remain controversial. One recent study found a positive association between reproductive factors and the risk of NHL, but others reported no association [43–45]. Although these proposed factors were not validated in our study, we found a difference in age at menarche between cases and controls, albeit without statistical significance. These four studies including our study consist of relatively small numbers of patients with different subtypes. To investigate the association between hormones and NHL, pooling data is warranted.

Since the present data are based on a hospital-based case–control study, several potential biases warrant mention. We conducted an age- and sex-matched case–control study and adjusted for several confounders in the analyses to minimize bias, but we cannot entirely exclude the possibility of bias because we did not consider other known or unknown risk factors such as a history of autoimmune disorders and viral infections. Recall and information biases, however, were less likely to occur because most data were collected before diagnosis. The presented data is based on a limited number of patients with different histology and need to be validated in larger populations.

In conclusion, we found that soy intake has a significant inverse association with the risk of NHL among women. This results, however, is based on the analyses of limited number of patients and thus needs to be further evaluated in larger studies. Further studies are needed to validate our findings and to assess the mechanism by which soy intake, particularly that of isoflavones, affects lymphomagenesis.

acknowledgements

The authors thank all doctors, nurses, technical stuff at Aichi Cancer Center Hospital for the daily management of the HERPACC study.

funding

Grant-in-Aid for Scientific Research on Innovative Areas (221S0001) from the Ministry of Education, Culture, Sports, Science and Technology of Japan; Grants-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare of Japan.

disclosure

The authors declare no conflict of interest.

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