may be an important consideration in determining the impact of alcohol. Average consumption in our study was very low compared with previous studies. Relatively high consumption (≥175 g/week) was seen in only three cases and 99 controls, who showed a protective effect compared with non-drinkers (multivariate OR = 0.47; 95% CI, 0.14–1.58). The provision of stable estimates for this subgroup is hampered by their small sample size.

One possible explanation for these results is that a small amount of drinking might be protective against cancer, as suggested in several prospective cohort studies.[28–32] The biological mechanism of this protective effect for cancer among light-moderate drinkers is not clear. Tsugane *et al.* considered the background characteristics of moderate drinkers to be healthier than those of either non-drinkers or heavy drinkers.[32] It has been reported that alcohol intake increases endogenous serum levels of estrogen in postmenopausal women,[5,6] but it is unclear whether this is due to either a decrease in metabolic clearance or an increase in production.[33] It has thus been hypothesized that alcohol drinking might lead to an increased risk of endometrial cancer risk due via the increased mitotic proliferation of endometrial cells, resulting in increased DNA replication errors and somatic mutations.[34] Our findings here contradict this hypothesized mechanism; nevertheless, we assume that the amount of drinking may differentiate the impact of alcohol on endometrial cancer risk, as stated above.

Of interest was the combined effect of the amount of consumption and physical reaction to alcohol.[19] Subjects who reported flushing did not show the protective effect observed in the non-flushing group. It has been suspected that the oxidative metabolite of ethanol, acetaldehyde, is carcinogenic for humans due to its binding to cellular proteins and DNA, thus leading to carcinogenesis.[35,36] Further, in individuals with ALDH2 encoded by *ALDH2* Glu/Lys, the blood acetaldehyde level after drinking is approximately six-fold that in individuals with active ALDH2.[37] Taking results from our previous study demonstrating sensitivity and specificity of self-reported flushing for ALDH2 genotype as 83.5% and 87.8%,[38] our findings may have resulted from a decrease in the protective effect of alcohol owing to exposure to high levels of acetaldehyde.

Several potential limitations of our study warrant consideration. First, because it was a hospital-based case-control study, the threat of inadequate comparability between cases and controls rested on whether the control population was the source population from which cases arose. In the ACCH, it is assumed that those who are diagnosed as not having cancer at a particular period of time will visit the ACCH in the event that they do develop malignant disease. Our source of controls is therefore assumed to be appropriate for the drawing of causal inferences. Second, as with other case-control studies, this study may have suffered from recall bias. Although the questionnaires, including that on alcohol intake, were completed before diagnosis in our hospital, some case patients referred to the hospital might have known their diagnosis. The fact that alcohol intake is not a well-accepted risk factor for endometrial cancer among the public might preclude this possibility of information bias regarding alcohol Third, our study had a modest sample size, and replication in other studies is required.

In conclusion, our case-control study suggested that alcohol drinking decreases the risk of endometrial cancer among Japanese women who consume small amounts. Further, a similar association was observed after stratification by potential confounders. However, this protective effect of alcohol was modified in those who experienced a flushed reaction to it after drinking. Further investigation of these findings is warranted.

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Effect of soybean on breast cancer according to receptor status: A case–control study in Japan

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The possible association of high soy food consumption with low incidence of breast cancer in Asian countries has been widely investigated, but findings from epidemiologic studies have been inconsistent. Breast cancers defined by receptor status, estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) may have distinct etiologic factors. Here, we conducted a case–control study to clarify associations between intake of soybean products and breast cancer risk according to receptor status. A total of 678 breast cancer cases and 3,390 age- and menopausal status-matched noncancer controls were included. Odds ratios (ORs) with 95% confidence intervals (CIs) were estimated using conditional logistic models adjusted for potential confounders. On analysis according to receptor status, we observed a significantly reduced risk of ER-positive (ER+) (top tertile OR = 0.74; 95% CI, 0.58–0.94; trend p = 0.01) and HER2-negative (HER2−) tumors (top tertile OR = 0.78; 95% CI, 0.61–0.99; trend p = 0.04). Further, when the 3 receptors were jointly examined, a reduced risk was observed only in patients with ER+/PR+/HER2− tumor (top tertile OR = 0.73; 95% CI, 0.54–0.97; trend p = 0.03). These findings indicate that the protective effect of soy against breast cancer risk differs by receptor status.

Key words: breast cancer; soybean; hormone receptors; HER2

Although the incidence of breast cancer in Japan has increased steadily over the last 30 years,[1] it nevertheless remains substantially lower than in Western countries.[2] Considerable interest has thus been expressed in identifying factors in the Japanese life style that modify the risk of breast cancer in this population.

Soy foods are rich in isoflavones, compounds that have been shown to exert anticarcinogenic effects on hormone-related cancers in a large number of experimental studies and have been hypothesized to reduce the risk of the cancers. In Japan, a wide variety of soy foods is available, and isoflavone consumption is consequently habitual and high. While this high consumption may account for some of the international differences in incidence, a protective effect of soybean or isoflavones against breast cancer has not been consistently found.[3]

The behavior of breast tumors is partly determined, to some extent at least, by gene expression in breast cancer tissues, such as of the estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER2). Clinically, ER, PR and HER2 levels in tumors are used as prognostic indicators of disease course and response to adjuvant therapy. In general, the presence of ER-positive (ER+) or PR+ breast tumors, either singly or together, has been associated with better survival and overall outcome, whereas tumors with HER2 overexpression are characterized by a poor prognosis.[4] Etiologic factors related to the risk of developing breast cancer may also differ according to receptor status. Previous studies reported that reproductive factors are more strongly linked to the risk of ER+/PR+ than receptor-negative breast cancer.[5–7] Results for HER2 status, in contrast, have been inconsistent.[7–10]

Classification by receptor status may help clarify the inconclusive results for soybean consumption and risk of breast cancer. Here, to evaluate the association between soy food intake and breast cancer risk by receptor status, we conducted a case–control study using data from the Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC).

Material and methods

Study population

Details of the HERPACC have been described elsewhere.[11,12] In brief, HERPACC was initiated in Aichi Cancer Center Hospital, Nagoya, Japan, in 1988, with information on lifestyle factors collected from all first-visit outpatients using a self-administered questionnaire, with responses checked by a trained interviewer. Patients were asked about their lifestyle when healthy or before the current symptoms developed. Information from the questionnaire was systematically collected and checked by trained interviewers, and completed by 96.7% of 29,538 eligible subjects (2001–2005). Questionnaire data were loaded into the HERPACC database and periodically linked with the hospital cancer registry system to update data on cancer incidence. All participants gave written informed consent and the study was approved by the Ethics Committee of Aichi Cancer Center.

Ascertainment of breast cancer cases and controls

A total of 838 breast cancer patients who underwent surgical excision at the Department of Breast Oncology Aichi Cancer Center Hospital between 2003 and 2005 were deemed eligible as case subjects. ER, PR and HER2 status was routinely determined by pathologists using commercially based immunohistochemistry tests following removal, and was available from the medical record for 831 (99.2%), 831 (99.2%) and 829 (98.9%) of cases, respectively. Of all patients (n = 838), 176 (20.6%) were excluded because of lack of participation in HERPACC (n = 146), insufficient information on receptor status (n = 7), or a history of previous cancer (n = 23). Finally, 678 patients aged 19–79 years with a new histological diagnosis of breast cancer were considered eligible.

We randomly selected controls matched by age (±0 years) and menopausal status (premenopause or postmenopause) with a 1:5 case–control ratio from 9,343 women who were confirmed to be cancer-free by diagnostic procedure at our hospital and who had no prior history of cancer between 2001 and 2005. Eventually, 3,390 controls were included. Our previous study confirmed the feasibility of using noncancer outpatients at our hospital as controls in epide-

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miological studies because their general lifestyles are accordant with those of a general population randomly selected from the electoral roll in Nagoya City, Aichi Prefecture.[13] We assessed the clinical diagnosis among noncancer outpatients in the previous study and confirmed that 44% presented with no abnormal findings by examination, 35% had benign and nonspecific diseases (*e.g.*, mastitis: 7.5%, atrophic gastritis: 2.2%, myoma uteri: 1.7%, *etc.*), 13% had benign tumor and non-neoplastic polyp (*e.g.*, colonic polyp: 2.7%, *etc.*) and 3.4% had cystic disease (*e.g.*, breast cyst: 1.7%, *etc.*).[14]

Assessment of soybean intake and other exposure data

The FFQ consisted of 47 single food items with frequencies in the 8 categories of never or seldom, 1–3 times/month, 1–2 times/week, 3–4 times/week, 5–6 times/week, once/day, twice/day and 3+ times/day.[15–17] For staple foods such as rice, bread and noodles, the usual number of bowls or slices consumed on one time, as well as intake frequency, was inquired for breakfast, lunch and supper, separately. We asked the subjects about the average intake of frequency during the 1-year period preceding the onset of the present disease or before the interview. Dietary intake of soybean products was computed by multiplying the standard portion size of *tofu* (soybean curd), *miso* (fermented soybean paste) soup, *natto* (fermented soybeans), *aburage* (thinly sliced deep fried tofu) and frequency of consumption. The standard portion sizes in each soy food were calculated based on validity test using 3-day weighed dietary records. One serving in the soy foods was 50 g for *tofu*, 52 g for *miso* soup, 30 g for *natto* and 50 g in female for *aburage*. Similarly, total energy was computed by the standard portion size, frequency and energy (per gram) in foods as listed in the Standard Tables of Food Consumption and the Follow-up version.[18,19] Validity and reproducibility of the FFQ were acceptable.[16,17] The correlation coefficient for energy-adjusted intakes of soybeans was 0.53 in women. Energy-adjusted intake of soybean products was calculated by the residual method.[20]

Total alcohol consumption was estimated as the summed amount of pure alcohol consumption. Drinking habits were entered in the 4 categories of never, former, current moderate and heavy drinking. Heavy drinkers were defined as those currently drinking alcoholic beverages 5 days or more per week at a daily amount of 23 g (1 Japanese drink) or more, and moderate drinkers as those currently consuming less frequently than 5 days per week, in lower amounts, or both. Cumulative smoking dose was evaluated as pack-years, the product of the number of packs consumed per day and years of smoking. Smoking habit was entered under the 4 categories of never, former and current smoking of <20 and ≥20 pack-years. Former drinkers or smokers were defined as those who quit drinking or smoking at least 1 year before the survey, respectively.

Statistical analyses

To assess the strength of associations between the intake of soybean products or selected soy food items and risk of breast cancer, odd ratios (ORs) with 95% confidence intervals (CIs) were estimated using age- and menopausal status-matched conditional logistic models adjusted for potential confounders. Intake of soybean products was categorized into 3 groups as first (lowest), second, and third tertiles of dietary intake among controls. Intake frequencies of each soy food item were divided into 3 categories as first (lowest frequency group), second and third. Potential confounders considered in the multivariate analyses were age, drinking habit (never drinkers, former drinkers, moderate or heavy drinkers), smoking habit (never smokers, former smokers, current smokers of <20, or ≥20 pack-years), current body mass index (BMI) (<18.5, 18.5–24.9, ≥25.0), regular exercise (yes or no), family history of breast cancer (yes, no), total nonalcohol energy intake (as a continuous variable), multivitamin use (at least once per week for 1 year or longer: yes or no), menopausal status (premenopause, postmenopause), age at menarche (≤12, 13–14, ≥15), parity (0, 1–2, ≥3), past use of hormone-replacement therapy (never, 1–6 months, >6 months), referral pattern to our hospital (patient discretion, family or friend recommendation, referral from other clinics, secondary screening after primary screening or others) and age at menopause for postmenopausal women (≤47, 48–52, ≥53). We used noncancer patients at our hospital as controls, given the likelihood that our cases arose within this population base. To modify for any difference between cases and controls, we also adjusted for referral pattern. Differences in categorized demographic variables between the cases and controls were tested by the chi-square test. Mean values for total nonalcohol energy intake were compared for cases and controls by Student's t test. As a basis for the trend test, the median values of each tertile of soybean product consumption were included in the model, and we assigned the scores of 0, 1 and 2 to the first (lowest), second and third frequency group in the selected soy food items, respectively. A p value less than 0.05 was considered statistically significant. All analyses were performed using STATA version 10 (Stata Corp., College Station, TX).

Results

Data from 678 breast cancer cases and 3,390 controls were available for analysis. Table I shows the distribution of cases and controls by background characteristics according to menopausal status. Age and menopausal status were completely matched. In postmenopausal women, heavy drinkers were significantly more frequent among cases than controls ($p = 0.03$), as was the proportion of high BMI ($p < 0.01$). Compared with the controls, women with postmenopausal breast cancer were more likely to report a family history of breast cancer ($p < 0.01$). Among postmenopausal women, multivitamin supplementation was more prevalent in the controls ($p = 0.01$). With regard to referral pattern, family recommendation and referral from other clinics were more frequent among the case group, while patient discretion and secondary screening were less frequent in both premenopausal and postmenopausal women ($p < 0.01$).

Intake of soybean products was inversely associated with the overall risk of breast cancer (Table II). The OR was 0.80 (95% CI, 0.64–0.99) for the top tertile of soybean product intake compared with the lowest tertile of intake (trend $p = 0.03$). On analysis by menopausal status, the decreased risk was observed across menopausal status, though was not statistically significant. We therefore decided to examine risk for breast cancer combined in analysis by receptor status. On the other hand, analysis by type of soy foods for *miso* soup, *tofu*, *natto* and *aburage* did not show clearly association in overall and both premenopausal and postmenopausal women.

Of 678 breast cancer cases, cases positive for ER, PR and HER2 accounted for 536 (79.1%), 440 (64.9%) and 155 (22.9%) patients, respectively. When examined by joint ER/PR/HER2 status, 57 (8.4%) were ER+/PR+/HER2+, 378 (55.8%) were ER+/PR+/HER2−, 68 (10.0%) were ER−/PR−/HER2+, 69 (10.2%) were ER−/PR−/HER2− and 106 (15.6%) were other subtypes.

Table III shows the impact of soybean product consumption on breast cancer risk according to receptor status. Soybean product intake was associated with a significantly decreased risk of ER+ or HER2− breast cancer, with odds ratios in the top tertile of intake of 0.74 (95% CI, 0.58–0.94; trend $p = 0.01$) for ER+ tumors and 0.78 (95% CI, 0.61–0.99; trend $p = 0.04$) for HER2− tumors. The similar ORs were observed in PR+ and PR− tumor, although the results were not significant.

We further examined the impact of soybean product intake on breast cancer risk according to joint receptor status (Table IV). A significantly decreased risk of ER+/PR+/HER2− breast cancer with consumption of soybean products was observed (top tertile OR = 0.73, 95% CI: 0.54–0.97, trend $p = 0.03$). On analysis by menopausal status, a protective effect was found among premenopausal women (top tertile OR = 0.65, 95% CI: 0.43–0.96, trend $p = 0.03$). On the other hand, no association was found for other subtypes of breast cancer. In analysis according to receptor status, the association between the intake of soy food items and breast cancer risk was also unclear (data not shown).

TABLE I – CHARACTERISTICS OF CASES AND CONTROLS

	Premenopause			Postmenopause		
	Cases (n = 329) n (%)	Controls (n = 1,645) n (%)	p	Cases (n = 349) n (%)	Controls (n = 1,745) n (%)	p
Age						
18–29	10 (3.0)	50 (3.0)		0 (0)	0 (0)	
30–39	74 (22.5)	370 (22.5)		0 (0)	0 (0)	
40–49	176 (53.5)	880 (53.5)		14 (4.0)	70 (4.0)	
50–59	69 (21.0)	345 (21.0)		149 (42.7)	745 (42.7)	
60–69	0 (0)	0 (0)		141 (40.4)	705 (40.4)	
70–79	0 (0)	0 (0)	1.00	45 (12.9)	225 (12.9)	1.00
Drinking habit						
Never	188 (57.1)	899 (54.7)		228 (65.3)	1,175 (67.3)	
Former[1]	4 (1.2)	31 (1.9)		3 (0.9)	32 (1.8)	
Current						
Moderate[2]	112 (34.0)	598 (36.4)		90 (25.8)	454 (26.0)	
Heavy[3]	23 (7.0)	97 (5.9)	0.59	24 (6.9)	63 (3.6)	0.03
Unknown	2 (0.6)	20 (1.2)		4 (1.1)	21 (1.2)	
Smoking habit						
Never	254 (77.2)	1,233 (75.0)		308 (88.3)	1,486 (85.2)	
Former[1]	17 (5.2)	96 (5.8)		10 (2.9)	77 (4.4)	
Current (pack years)						
0–19	41 (12.5)	229 (13.9)		12 (3.4)	79 (4.5)	
≥20	15 (4.6)	81 (4.9)	0.83	14 (4.0)	92 (5.3)	0.30
Unknown	2 (0.6)	6 (0.4)		5 (1.4)	11 (0.6)	
BMI						
<18.5	40 (12.2)	178 (10.8)		17 (4.9)	125 (7.2)	
18.5–24.9	250 (76.0)	1,257 (76.4)		225 (64.5)	1,280 (73.4)	
≥25.0	35 (10.6)	199 (12.1)	0.63	106 (30.4)	323 (18.5)	<0.01
Unknown	4 (1.2)	11 (0.7)		1 (0.3)	17 (1.0)	
Regular exercise						
Yes	226 (68.7)	1,132 (68.8)		252 (72.2)	1,321 (75.7)	
No	103 (31.3)	511 (31.1)	0.94	90 (25.8)	413 (23.7)	0.32
Unknown	0 (0)	2 (0.1)		7 (2.0)	11 (0.6)	
Family history of breast cancer						
Yes	17 (5.2)	102 (6.2)		38 (10.9)	106 (6.1)	
No	290 (88.1)	1,396 (84.9)	0.41	282 (80.8)	1,476 (84.6)	<0.01
Unknown	22 (6.7)	147 (8.9)		29 (8.3)	163 (9.3)	
Age at menarche						
≤12	154 (46.8)	685 (41.6)		68 (19.5)	316 (18.1)	
13–14	140 (42.6)	777 (47.2)		182 (52.1)	808 (46.3)	
≥15	33 (10.0)	176 (10.7)	0.21	94 (26.9)	562 (32.2)	0.09
Unknown	2 (0.6)	7 (0.4)		5 (1.4)	59 (3.4)	
Age at menopause						
≤47				84 (24.1)	395 (22.6)	
48–52				164 (47.0)	909 (52.1)	
≥53				93 (26.6)	418 (24.0)	0.27
Unknown				8 (2.3)	23 (1.3)	
Parity						
0	68 (20.7)	325 (19.8)		28 (8.0)	165 (9.5)	
1–2	197 (59.9)	994 (60.4)		240 (68.8)	1,105 (63.3)	
≥3	64 (19.5)	321 (19.5)	0.94	81 (23.2)	464 (26.6)	0.20
Unknown	0 (0)	5 (0.3)		0 (0)	11 (0.6)	
Hormone replacement therapy (months)						
Never	288 (87.5)	1,377 (83.7)		286 (81.9)	1,428 (81.8)	
1–6	25 (7.6)	151 (9.2)		32 (9.2)	151 (8.7)	
>6	13 (4.0)	87 (5.3)	0.34	22 (6.3)	121 (6.9)	0.88
Unknown	3 (0.9)	30 (1.8)		9 (2.6)	45 (2.6)	
Mean total nonalcohol energy, kcal/day (SD)	1,470.0 (262.3)	1,490.1 (284.7)	0.24	1,508.0 (277.9)	1,497.7 (273.4)	0.52
Multivitamin use (at least once per week for 1 year or longer)						
Yes	66 (20.1)	346 (21.0)		65 (18.6)	430 (24.6)	
No	254 (77.2)	1,257 (76.4)	0.70	270 (77.4)	1,234 (70.7)	0.01
Unknown	9 (2.7)	42 (2.6)		14 (4.0)	81 (4.6)	
Referral pattern to our hospital						
Patient's discretion	88 (26.7)	482 (29.3)		106 (30.4)	647 (37.1)	
Family recommendation	77 (23.4)	304 (18.5)		68 (19.5)	255 (14.6)	
Referral from other clinics	92 (28.0)	305 (18.5)		101 (28.9)	357 (20.5)	
Secondary screening after primary screening	65 (19.8)	541 (32.9)		69 (19.8)	460 (26.4)	
Others	3 (0.9)	9 (0.5)	<0.01	1 (0.3)	9 (0.5)	<0.01
Unknown	4 (1.2)	4 (0.2)		4 (1.1)	17 (1.0)	

SD, standard deviation; BMI, body mass index.
[1]Former smokers and drinkers were defined as subjects who had quit smoking and drinking at least 1 year previously.–[2]Moderate drinker means less 23 g ethanol/drink and/or less 5 days/week.–[3]Heavy drinker means 23 g ethanol/drink or more and 5 days/week or more.

TABLE II – ADJUSTED ODDS RATIOS (OR) AND 95% CONFIDENCE INTERVALS (CI) FOR THE ASSOCIATION BETWEEN SOYBEAN PRODUCTS AND SOY FOODS INTAKE AND BREAST CANCER RISK ACCORDING TO MENOPAUSAL STATUS

	All		Premenopause		Postmenopause	
	Cases/controls (n = 678/3,390)	ORs[1] (95% CI)	Cases/controls (n = 329/1,645)	ORs[1] (95% CI)	Cases/controls (n = 349/1,745)	ORs[1] (95% CI)
Soybean products (g/day)						
Tertile 1 (1.1–27.4)	242/1,108	1.00 (Referent)	145/641	1.00 (Referent)	97/467	1.00 (Referent)
Tertile 2 (27.4–51.2)	235/1,108	0.95 (0.77, 1.16)	106/530	0.85 (0.64, 1.13)	129/578	1.01 (0.75, 1.39)
Tertile 3 (51.2–326.3)	195/1,108	0.80 (0.64, 0.99)	74/442	0.74 (0.54, 1.02)	121/666	0.84 (0.61, 1.15)
Unknown	6/66		4/32		2/34	
p_{trend}		0.03		0.06		0.17
Miso soup						
≤2 times/week	200/973	1.00 (Referent)	113/516	1.00 (Referent)	87/457	1.00 (Referent)
3–6 times/week	255/1,287	0.97 (0.79, 1.20)	132/696	0.89 (0.67, 1.18)	123/591	1.07 (0.78, 1.47)
≥1 time/day	216/1,078	0.99 (0.79, 1.24)	81/418	0.91 (0.66, 1.27)	135/660	1.08 (0.79, 1.48)
Unknown	7/52		3/15		4/37	
p_{trend}		0.93		0.58		0.65
Tofu						
≤3 times/month	209/1,006	1.00 (Referent)	120/556	1.00 (Referent)	89/450	1.00 (Referent)
1–2 times/week	259/1,286	0.98 (0.80, 1.21)	126/629	0.95 (0.71, 1.27)	133/657	1.00 (0.73, 1.37)
≥3 times/week	193/1,027	0.89 (0.72, 1.12)	78/441	0.84 (0.61, 1.17)	115/586	0.93 (0.68, 1.28)
Unknown	17/71		5/19		12/52	
p_{trend}		0.30		0.32		0.56
Natto						
≤3 times/month	197/912	1.00 (Referent)	114/516	1.00 (Referent)	83/396	1.00 (Referent)
1–2 times/week	241/1,160	0.96 (0.78, 1.19)	131/593	1.04 (0.78, 1.39)	110/567	0.91 (0.66, 1.27)
≥3 times/week	230/1,259	0.87 (0.70, 1.08)	81/517	0.72 (0.52, 0.99)	149/742	0.99 (0.72, 1.36)
Unknown	10/59		3/19		7/40	
p_{trend}		0.20		0.06		0.95
Aburage						
Seldom	57/331	1.00 (Referent)	41/206	1.00 (Referent)	16/125	1.00 (Referent)
1–3 times/month	285/1,336	1.21 (0.88, 1.66)	150/729	1.10 (0.73, 1.65)	135/607	1.59 (0.90, 2.81)
≥1 time/week	329/1,667	1.11 (0.80, 1.54)	135/689	1.06 (0.70, 1.61)	194/978	1.37 (0.78, 2.41)
Unknown						
p_{trend}	7/56	0.99	3/21	0.93	4/35	0.97

[1]Conditional logistic regression model additionally controlling for drinking habit, smoking habit, BMI, regular exercise, family history of breast cancer, total nonalcohol energy intake, multivitamin use, age at menarche, parity, hormone-replacement therapy, referral pattern to our hospital and age at menopause for postmenopausal women.

Discussion

Our case–control study in a population derived from hospital outpatients with adjustment for various lifestyle factors suggested that a high intake of soybean products was associated with a decreased risk of ER+, HER2− and ER+/PR+/HER2− breast cancer. These findings indicate that the protective effect of soy against breast cancer risk differs by receptor status.

Ecologic studies have shown that breast cancer incidence is lower in populations with habitually high soy food consumption.[21] Various vegetables and grains contain small amounts of isoflavones, but far higher quantities are found in soybeans, and accordingly the impact of soy food intake on breast cancer risk has been extensively investigated. Results from epidemiologic studies of this association have varied. One prospective[22] and 3 case–control studies[23–25] showed significant associations between soy food or isoflavone intake and the risk of breast cancer overall; 2 showed protective associations in premenopausal women only[26–28]; while other cohort[29–31] and case–control studies[32–38] showed no association. Recent meta-analysis have reported that soy intake was associated with a small reduction in breast cancer risk[3]; however, one of the problems in conducting the meta-analysis was that the measures used to quantify soy intake varied considerably across studies.

This inconsistency in these studies may in part be due to their lack of differentiation of receptor status in breast cancer tissue, as well as to errors in soybean intake assessment and confounding. Several studies of representative risk factors have focused on determining the etiologies of breast cancer tumors classified by joint ER, PR and HER2 status. Results suggested substantial heterogeneity in causation, and tumors subclassified by receptor status may actually represent distinct forms of breast cancer with differing etiologies. Previous studies have reported that hormonal factors, including age at menarche,[5] parity,[7] age at first pregnancy[6,7] and BMI[39] may be more strongly associated with an increased risk of ER+ and/or PR+ than of ER− and/or PR− breast cancer. In present study, age at menarche was associated with ER+ and PR+ breast cancers (data not shown). To date, however, only one study has examined the association between soy intake and breast cancer subtype defined by receptor status; that study, conducted in China, reported that risk reduction with soy protein intake was stronger for breast cancer positive for ER+/PR+ than for other ER/PR status.[34] To our knowledge, the present study is the first to include HER2 status.

Endogenous estrogen has been clearly recognized as a cause of breast cancer, and hormonal therapy with estrogen for menopause is associated with an increased risk of breast cancer.[40] Isoflavones have been suggested to reduce circulating estrogen levels, but the hypothesis has not been confirmed.[41] A more plausible explanation for the protective effect of soy intake on breast cancer risk may be that since Isoflavones bind preferentially to activate ER-β,[42,43] although they can bind to both ER-α and ER-β, and ER-β might inhibit the activation of ER-α.[44] Given the anticarcinogenic properties of soybeans, our finding that the protective effect of soy intake was more pronounced in ER-positive breast cancer may be plausible. Interestingly, a protective effect was seen only in HER2− breast cancer with ER+/PR+, not in HER2+ or ER+/PR+ cases. Clinical studies have demonstrated that overexpression of HER2 occurs in 20% of breast tumors and has been associated with a poor prognosis compared with HER2− breast cancer. Although the mechanism by which HER2 is selectively overexpressed in cancers remains poorly understood, the absence of expression of hormone receptors in many HER2+ tumors and unresponsiveness to tamoxifen suggests that positivity is associated with hormone independence.[45,46] In a previous epidemiological study, parity and age at first pregnancy were associated with

TABLE III – ADJUSTED ODDS RATIOS (OR) AND 95% CONFIDENCE INTERVALS (CI) FOR THE ASSOCIATION BETWEEN SOYBEAN PRODUCTS INTAKE AND BREAST CANCER RISK ACCORDING TO RECEPTOR STATUS

Soybean products (g/day)	ER+		ER−		PR+		PR−		HER2+		HER2−	
	Cases/controls (n = 536/2,680)	ORs[1] (95% CI)	Cases/controls (n = 142/710)	ORs[1] (95% CI)	Cases/controls (n = 440/2,200)	ORs[1] (95% CI)	Cases/controls (n = 238/1,190)	ORs[1] (95% CI)	Cases/controls (n = 155/775)	ORs[1] (95% CI)	Cases/controls (n = 523/2,615)	ORs[1] (95% CI)
Tertile 1 (1.1–27.4)	195/877	1.00 (Referent)	47/231	1.00 (Referent)	157/719	1.00 (Referent)	85/389	1.00 (Referent)	53/272	1.00 (Referent)	189/836	1.00 (Referent)
Tertile 2 (27.4–51.2)	189/865	0.96 (0.76, 1.21)	46/243	0.84 (0.52, 1.34)	156/720	0.98 (0.76, 1.27)	79/388	0.86 (0.61, 1.23)	62/260	1.15 (0.75, 1.76)	173/848	0.88 (0.69, 1.12)
Tertile 3 (51.2–326.3)	147/883	0.74 (0.58, 0.94)	48/225	0.95 (0.58, 1.57)	124/715	0.78 (0.60, 1.03)	71/393	0.79 (0.55, 1.16)	37/235	0.82 (0.50, 1.33)	158/873	0.78 (0.61, 0.99)
Unknown	5/55		1/11		3/46		3/20		3/8		3/58	
p_{trend}		0.01		0.94		0.05		0.24		0.33		0.04

TABLE IV – ADJUSTED ODDS RATIOS (OR) AND 95% CONFIDENCE INTERVALS (CI) FOR THE ASSOCIATION BETWEEN SOYBEAN PRODUCTS INTAKE AND BREAST CANCER RISK ACCORDING TO 3 RECEPTOR STATUS

Soybean products (g/day)	ER+/PR+/HER2+		ER+/PR+/HER2−		ER−/PR−/HER2+		ER−/PR−/HER2−	
	Cases/controls (n = 57/285)	ORs[1] (95% CI)	Cases/controls (n = 378/1,890)	ORs[1] (95% CI)	Cases/controls (n = 68/340)	ORs[1] (95% CI)	Cases/controls (n = 69/345)	ORs[1] (95% CI)
Tertile 1 (1.1–27.4)	17/104	1.00 (Referent)	139/606	1.00 (Referent)	20/112	1.00 (Referent)	26/110	1.00 (Referent)
Tertile 2 (27.4–51.2)	24/101	1.46 (0.63, 3.40)	129/611	0.91 (0.69, 1.21)	27/116	1.19 (0.58, 2.41)	16/119	0.43 (0.20, 0.92)
Tertile 3 (51.2–326.3)	15/77	1.28 (0.51, 3.27)	108/630	0.73 (0.54, 0.97)	20/109	1.12 (0.52, 2.44)	27/108	0.93 (0.44, 1.98)
Unknown	1/3		2/43		1/3		0/8	
p_{trend}		0.83		0.03		0.92		0.90

[1]Conditional logistic regression model additionally controlling for drinking habit, smoking habit, BMI, regular exercise, family history of breast cancer, total nonalcohol energy intake, multivitamin use, age at menarche, parity, hormone-replacement therapy and referral pattern to our hospital.

HER2− breast cancer risk, but not with HER2+ risk,[7] suggesting that hormonal factors influence HER2− breast cancer only, whereas HER2+ tumors develop uninfluenced by these factors even if both ER and PR are positive. Our finding of a decreased risk with soybean intake only in HER2− and ER+/PR+ cases appears compatible with the consideration that soy affects breast cancer risk mainly *via* its antiestrogenic effect.

In Japan, the main sources of soybean intake are *tofu*, *miso* soup and *natto*. In our previous study, *tofu* was protective for premenopausal breast cancer.[28] In contrast, a second Japanese study reported an inverse association with *miso* soup consumption,[22] while a third found no association with breast cancer risk for any soy food.[31] In our analysis of frequency of soy food intake (times/month, week or day), we did not observe clear association with intake of specific soy foods, but did see an association with the amount of soybean intake (g/day). These results suggest that estimation based on a validated food frequency questionnaire may be more sensitive than that by the frequency of specific food items. Further investigation of this point is warranted.

Our study has several methodological strengths. First, age and menopausal status confounding could be completely controlled by exact matching of these factors. The matched design validates a better estimate of menopausal status-based analysis. Second, since complete receptor status was known for nearly all cases, selection bias in the cases was negligible. Third, soybean intake was estimated using a validated questionnaire. In addition, among Japanese, *tofu*, *miso* soup and *natto* contributed more than 80% of the total genistein intake, one of several known isoflavones[28]; thus, soy foods in this study is likely to cover soybean products in Japan.

Several methodological limitations warrant consideration. First, as with other hospital-based case–control studies, the controls may have differed from the general population. Our previous comparison of lifestyle characteristics of HERPACC controls and individuals selected randomly from the general population in Nagoya City, however, confirmed no substantial difference.[13] Like most general hospitals in Japan, our hospital accepts new outpatients who visit of their own volition, with or without a doctor's referral, notwithstanding our description as a "Cancer Center." Second, although we used a self-administered questionnaire to evaluate soybean product intake, data obtained from an FFQ may not accurately reflect intake. If present, however, any such misclassification would be nondifferential, and would likely underestimate the causal association. Third, as with other case–control studies, we are completely unable to ignore recall of diet. Although the questionnaires were completed prior to the examination in our hospital, some case patients referred to the hospital might have known the diagnosis. It is unlikely, however, that the recall bias affected the findings differentially between receptor positive and negative breast cancers. Forth, we cannot exclude the possibility of residual confounding by other dietary characteristics. Finally, the limited number of rare subtype in breast cancer cases indicates the need for replication of our findings in a larger study.

In conclusion, our study shows that the intake of soybean products significantly reduces the risk of ER+/PR+/HER2− breast cancer. These findings are biologically plausible, and suggest a potential beneficial effect of soybean products in the prevention of breast cancer.

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COMMENTARY

Proposal for a Cooperative Study on Population-based Cancer Survival in Selected Registries in East Asia

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Abstract

Reliable population-based cancer survival data are essential for assessment of the effectivenes of cancer screening programs, distribution of cancer therapy and prevalent cancer cases. International comparisons are useful to allow societies, mass media and health authorities to gain a real appreciation of the cancer problem in their own country and provide an impetus to improve registration and cancer control planning. Since directly comparable survival data among East Asian countries are presently very limited, a comparative study on population-based cancer survival involving China, Indonesia, Japan, Korea, the Philippines and Taiwan, with Nepal as an observer, was proposed. At the 1st Working Group meeting in Tokyo on March 18th, 2009, it was decided to publish the present Commentary as a step towards realization of truly comparable cancer survival statistics in the region. Included are general information and quality of data of cancer registration at each participating registry and five-year relative survival rates of cancer of the stomach, colo-rectum, liver, lung, breast and cervix.

Key Words: Cancer registration - survival - data quality - international comparisons

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Introduction

Survival estimates of patients registered in population-based cancer registries reflect the average prognosis in a given region, since they are based on unselected patients with a variety of socioeconomic status, natural histories, and circumstance of cancer detection as well as treatment procedures. Data on population-based cancer survival are, therefore, useful for evaluating cancer control planning for early detection and distribution of cancer therapy in a given region. Survival statistics are also useful as comparative measures; they can show how survival differs between different populations over time and between subgroups defined by ethnicity, socioeconomic status, hospital volume, etc. An international comparative study on cancer survival mainly consisting of EU countries and North American countries, has been conducted, namely the "CONCORD STUDY", with standardized study subjects and identical analytic methods (Coleman et al., 2008).

In East Asia, population-based cancer survival rates were studied in Qidong (Chen et al., 1998) and Shanghai (Jin et al., 1998) in China, Rizal (Esteban et al., 1998) in the Philippines, and Chiang Mai (Martin et al., 1998) and Khon Kaen (Vatanasapt et al., 1998) in Thailand, and were published in the book entitled, "Cancer Survival in Developing Countries", in 1998. Improvement of infrastructure and/or legislative conditions as well as technical advances in cancer registration have resulted in the ability to obtain better cancer survival estimates in East Asian countries. Five-year relative survival rates (RSRs) were published from seven registries in Japan in 2006 (Miyagi, Yamagata, Niigata, Fukui, Osaka, Tottori and Nagasaki) (Tsukuma et al., 2006), in Korea in 2007 (Jung et al., 2007) and in Manila and Rizal in the Philippines in 2009 (Redaniel et al., 2009). However, these

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Figure 1. Members and Observers at the Working Group Meeting Held in Tokyo on March 18th, 2009

population-based cancer survival data in East Asian countries did not have comparability with each other.

In 2008, a study group for "Cancer Epidemiology and Statistics in East Asia" in the Third-term Comprehensive Ten-year Strategy for Cancer Control was launched through a grant-in-aid from the Japanese Ministry of Health Labour and Welfare. The study group planned to make a platform for conducting a cooperative study using population-based cancer registry data in East Asia. The study group held a meeting with researchers who were in charge of cancer registries that had relatively good quality of data in the region in March 2009 in Tokyo (Figure 1), and decided to perform a cooperative study of cancer survival estimates. As the first stage of the cooperative study, we intended to describe registration procedures and the validity of the participating registries as background information, and collected data on five-year relative survival rates among patients with cancer of the stomach, colorectum, liver, lung, breast and uterine cervix in a designated format.

Background Information on the Registries Participating in this Cooperative Study

(1) Characteristics of the Catchment Areas and Populations

1) Korea Central Cancer Registries (KCCR) The Republic of Korea lies between longitudes 124° and 131°E and latitudes 33° and 38°N, and has an area of 99,500 km^2 including about 3,000 islands. There are seven metropolitan cities with provincial status and nine provinces. The population of the Republic of Korea is 4.8 million (2005 estimates), which is covered by the KCCR.

Most people living in the Republic of Korea are ethnically Korean and their national language is Korean. Buddhism and Christianity are the largest religions in South Korea. Due to rapid urbanization of the country, 80 percent of the population are now classified as living in an urban area. Aging of the population is proceeding very quickly. The 2003 population estimate revealed that 8.3 percent of the total population was 65 years old or over. In 2004, the economically active population was 23.3 million. Of this figure, 8 percent were engaged in agriculture, forestry, or fishing, 27 percent in industry, and 65 percent in services.

2) The Six Cancer Registries in Japan in the Present Cooperative Study. Japan consists of four major islands (approximately 378,000 square km in total area) and has a population of 127 million (2005 national census data). Its population density is 338/square km (2005), which is one of the highest in East Asia. The annual population growth was nearly zero in 2007. The population is aging very quickly, with 21.5% of the population being 65 years old or over (2007). The proportion of the working-age population (aged 15-64 years) is 65.0% (2007). Among the working population, 4.2% were engaged in agriculture, forestry or fishing, 27.9% in industry, and 67.9% in services. Japan is one of the most ethnically homogeneous countries in the world, where almost all of the people with Japanese nationality are ethnic Japanese. About 2% of the residents in Japan are foreigners by nationality (2008).

Japan has 47 prefectures (principal administrative divisions equivalent to provinces), of which 35 have their own cancer registry. There is no legislative basis at the national level that mandates cancer registry. The registry in each prefecture is an activity based on a prefectural ordinance. Six prefectural cancer registries provided data to the present cooperative study, namely, the cancer registries of Miyagi, Yamagata, Niigata, Fukui, Osaka, and Nagasaki. The prefectures of Miyagi and Yamagata are located in the northeastern part of the main Honshuu islabd. The prefectures of Niigata and Fukui are located in central Japan along the coast facing the Japan Sea. The prefecture of Osaka is located at the geographical center of Honshuu, and most of the residents live in urban areas. The prefecture of Nagasaki is located in the westernmost part of the main island. Data on the populations covered by the six participating registries are shown in Table 1.

Table 1. Background Information and Characteristics of the Six Cancer Registries in Japan

	Miyagi	Yamagata	Niigata	Fukui	Osaka	Nagasaki
Pop[1]	2.34	1.20	2.43	0.82	8.67	0.87
Area	7,286	9,323	12,583	4,189	1,897	4,095
Case[2]	1	2	2	2	2	1,3
Follow[3]	Y	Y	N	Y	Y	N
Prognosis[4]	2	1 and 2	2	1 and 2	1 and 2	2

Pop[1], Target population (million) obtained from the National Census in 2005; Area, (square km); [2]Case finding: 1) mainly by active data search, 2) mainly by passive data search, 3) combined with pathological data search; [3]Follow back: Y) follow back conducted, N) follow back not conducted; [4]Prognosis investigation, 1) by referring to the information in residential registration, 2) by referring to the information in the vital statistics database with personal identifying information

3) Registries in Manila and Rizal. The first formal cancer registration activity in the Philippines was started in 1959 by the Philippine Cancer Society (PCS) when it established the Central Tumor Registry of the Philippines (CTRP). The CTRP collected data from 26 hospitals, of which 25 were located in Metropolitan Manila and one in Cebu, completely relying on notifications from these hospitals. The CTRP was converted into a population-based registry in 1983. It covered the population of four cities included in the Metropolitan Manila area (Manila, Quezon City, Pasay City and Caloocan City) and was renamed the Philippine Cancer Society-Manila Cancer Registry (PCS-MCR). The total population in the 4 cities was 5.08 million in a total area of 635 sq.km in 1995. Metro Manila is the major urban center of the country.

The first population-based cancer registry in the Philippines was established in 1974 as one of the activities of the Community Cancer Control Program of the province of Rizal. At that time, Rizal was composed of 26 municipalities, 12 of which were subsequently incorporated into Metropolitan Manila in 1975. In 1984, the Department of Health-Rizal Cancer Registry (DOH-RCR) started a cooperative effort with the Philippine Cancer Society-Manila Cancer Registry in covering 134 hospitals within the National Capital Region and Rizal Province. Currently, the two registries cover over 169 hospitals within the Metro Manila area and Rizal Province. Both registries use the same forms and the same method of active data collection. The total population size in the catchment area of Rizal Cancer Registry was 5.25 million in an area of 1,039 sq.km in 1995. Rizal Province is 75% urban.

4) Taiwan Cancer Registry. Taiwan consists of Taiwan Island proper, Penghu, Kinmen, Matsu, and dozens of small islands (approximately 36,000 square km in total area). Taiwan has a population of 22 million (2008). Its population density is 637/square km (2008), which is the second highest figure in the world after that of Bangladesh. The annual population growth is 3.4%, and 10.4% of the population are 65 years old or over (2008). About 98% of the Taiwanese are Han Chinese, and the rest of the population consists of native Taiwanese with Malayo-Polynesian origin and others. About 2% of the residents in Taiwan in 2008 were foreigners by nationality.

National household registration was implemented in Taiwan in 1906. Information is recorded mandatorily and double-checks performed annually by household registration officers. It is considered to be quite complete and accurate. Also, each Taiwanese has a unique identification number (citizenship ID number), which is used for governmental services. The Taiwan Cancer Registry, a population-based cancer registry, was founded in 1979. The registry became a compulsory system with implementation of the Cancer Control Act of 2003, which mandates hospitals with greater than 50-bed capacity providing outpatient and hospitalized cancer care to report all newly diagnosed malignant neoplasms to the registry. The registry is organized and funded by the Department (Ministry) of Health of the executive branch of the central government. The National Public Health Association has been contracted to operate the registry and organized an advisory board to standardize definitions of terminology, coding, and procedures of the registry's reporting system. The central cancer registry office is located at National Taiwan University, and the professor of Institute of Preventive Medicine heads the registry.

(2) Data Processing at the Registries

1) The Korea Central Cancer Registry (KCCR). The KCCR is responsible for collection, analysis and management of national cancer statistics; providing technical and financial support to regional cancer registries including cancer registrar training; analyses and summarization of data from the central and regional cancer registries; and carrying out administrative tasks related to cancer registry as required by the minister of the Ministry of Health and Welfare.

The KCCR established the Korea National Cancer Incidence Database (KNCIDB) by merging the KCCR database and the databases of all eight population-based regional cancer registries (Busan, Daegu, Seoul, Daejeon, Gwangju, Inchon, Ulsan, Jejudo). The KCCR dataset was further refined by confirming multiple primary cancers and removing duplicates with the help of experts from various fields including clinicians, pathologists and medical recorders.

2) The Six Japanese Registries. An outline of the registration procedures at the 6 Japanese registries in this report follows, although there are differences in the implementation of case finding, prognosis investigation, and follow back of death certificate notification (DCN) cases. The differences in these procedures, as well as characteristics of the catchment area, are summarized in Table 1.

a) Health care facilities send information on cancer patients who have been diagnosed or treated at their facility, to the cancer registry office of the prefecture.

b) The registry office collects information in death certificates from the local prefectural office. As a follow-back survey, for DCN cases, a request for information is sent to each health care facility that issued the death certificate. Also, some other data source, such as data on

pathological services provided at health care facilities or information on patients who received governmental financial support for cancer care, may be utilized for case finding by some registries.

c) The incidence, mortality, and prognostic information are organized, verified, and consolidated in the central database. It usually takes about 3-4 years to complete all of these procedures.

3) Registries in Manila and Rizal. Manila Cancer Registry (MCR) clerks are assigned to collect and abstract data from 109 hospitals (active registration) which include 26 hospitals that also send reporting forms to the MCR (passive registration). At the Rizal Cancer Registry (RCR), initially data collection was entirely passive, relying on notification from physicians and hospitals, from 1974 to 1979. This system was highly unsatisfactory and active registration was started in 1980. At present, the Rizal Cancer Registry covers 60 hospitals using an active method of registration. Research assistants at both the MCR and RCR review death certificates from the office of the Local Civil Registries. Data received are checked for completeness and consistency as well as for duplication, both manually and with the aid of a computer. Checking for consistency and validity of codes is performed with the IARC/IACR CanReg 4 software.

4) The Taiwan Cancer Registry. Taiwan has several social infrastructures that allow efficient cancer registry, such as the National Cancer Act of 2003 which mandates nationwide cancer registry, citizenship ID numbers, nationwide health insurance system since 1995, and digitized database of vital statistics, health insurance claims, and cancer screening programs. With these tools, cancer registry is conducted very efficiently with excellent quality indices. An outline of the registration procedures in Taiwan follows.

a) All hospitals with more than 50 beds (approximately 230 facilities in 2008) are mandated to report newly diagnosed cancer cases within 12 months after confirming the diagnosis. Required information on these cases includes patients' basic information (age, sex and citizenship ID numbers), information on the diagnosis and administered therapies, and prognosis if known. Also, hospitals that diagnose or treat more than 500 cases per year are mandated to report more detailed information on cases of cancer at 6 major sites (liver, lung, colon, female breast, oral cavity, and cervix uteri).

b) A database on potential cancer cases is created each year from the death certificate database, catastrophic illness database (health insurance claim data for serious illnesses), and cancer screening program database (data from screening programs for cancers of the cervix, female breast, colorectum, and oral cavity). This database is compared with the database of cancer cases reported by health care facilities each year. Unreported cases of potential cancer are followed-back to the hospitals where the cases had received care or been screened. These cases are added to the cancer registry database if confirmed as a cancer case.

c) For prognosis investigation (follow-up), the cumulated database of cancer cases since 1979 is record-linked to the death database in vital statistics. Cancer death cases matched in the two databases are consolidated with the cancer registry database.

(3) Quality Indicators of the Registries

Table 2 shows the percentage of morphologically verified cases (MV%), percentage of death certificate only cases (DCO%), and the mortality vs. incidence ratio (MI%) of the six cancer sites in this study at the participating registries in 1997-99. The MV% of stomach cancer ranged from 64% in Manila & Rizal to 96% in Taiwan. The MV% of liver cancer was relatively lower (except in Osaka) than those of the other types of cancer. The DCO% was relatively lower in Korea, Yamagata, Fukui, Nagasaki and Taiwan in comparison with Miyagi, Niigata, Osaka and Manila & Rizal, with some exceptions. The M/I% for stomach cancer and lung cancer in Taiwan were relatively higher (70%, 96%, respectively) than those in Korea and the Japanese registries. The Japanese registries had relatively higher M/I% for cervical cancer (24%~38%) than that in Korea (16%) and Taiwan (16%).

Method of Prognosis Investigation and Calculation of Survival

The task force of the study group required the participating registries to submit data on the 5-year relative survival rate of cancer of the stomach, colon, rectum, colorectum, liver, lung, female breast and cervix diagnosed from 1997 through 1999 or the nearest available years, which were already published or officially reported.

The survival data submitted from Indonesia were the 5-year cumulative survival rate among cancer patients who were diagnosed at Dharmais National Cancer Center in Jakarta in 1997-1999, which was calculated by the Kaplan-Meier method. Therefore, we introduced the data from Indonesia separate from the data from population-based registries.

(1) Korea Central Cancer Registries. Prognosis investigation was performed: by referring to the death certificate information; by referring to the inhabitant registry information;and for patients identified as potential cancer cases, by reviewing the medical records at the hospital through linking with the national medical health insurance data, national death certificate data and national population registration data. Passive follow-up was performed by linkage with several national databases using the unique personal identification number assigned to all residents in Korea. The national incidence database was linked to the national death certificate data from the Korea National Statistical Office and the national inhabitant registration data from the Ministry of Public Administration and Security, for follow-up of their vital status.

Cases with carcinoma in situ and subsequent tumors were excluded from the survival analysis. All cases with follow-back were included in the analysis. The Ederer II method was used for relative survival analysis with life

Table 2. Quality Indicators for the Registries

Organ/Registry	MV%	DCO%	M/I%
Stomach			
Korea	84.6	8.2	54.4
Miyagi	82.8	12.1	43.2
Yamagata	89.6	6.8	46.4
Niigata	77.9	20.5	45.9
Fukui	92.1	3.6	43.0
Osaka	78.5	18.8	57.4
Nagasaki	92.5	5.5	44.8
Manila & Rizal	63.7	14.3	
Taiwan	95.7	9.0	70.1
Colorectum			
Korea	87.5	4.4	38.1
Miyagi	83.1	11.1	39.2
Yamagata	88.2	6.1	37.8
Niigata	80.8	16.5	39.1
Fukui	89.4	4.1	41.9
Osaka	77.6	16.8	49.8
Nagasaki	90.1	6.3	40.6
Manila & Rizal	80.0	6.0	
Taiwan	94.0	5.7	45.9
Liver			
Korea	25.5	11.5	73.8
Miyagi	29.5	26.3	76.4
Yamagata	23.7	16.5	81.0
Niigata	20.9	43.8	82.1
Fukui	18.7	6.1	76.5
Osaka	90.4	26.4	82.2
Nagasaki	33.2	19.5	84.7
Manila & Rizal	30.4	26.7	
Taiwan	35.8	13.6	76.9
Lung			
Korea	69.7	10.8	79.1
Miyagi	74.6	16.2	73.1
Yamagata	76.4	16.8	80.3
Niigata	59.6	34.2	75.4
Fukui	73.9	8.5	82.2
Osaka	73.0	24.0	81.5
Nagasaki	74.5	15.3	75.2
Manila & Rizal	57.8	14.6	
Taiwan	84.0	14.3	96.0
Breast			
Korea	94.8	1.7	20.0
Miyagi	91.5	3.5	21.3
Yamagata	94.3	2.4	23.2
Niigata	91.3	7.6	24.6
Fukui	95.3	2.0	24.7
Osaka	91.0	5.8	29.6
Nagasaki	96.7	1.8	23.6
Manila & Rizal	88.0	5.1	
Taiwan	97.6	2.7	25.9
Cervix			
Korea	95.0	0.7	15.5
Miyagi	87.4	4.8	36.2
Yamagata	93.1	6.3	37.5
Niigata	90.2	9.3	27.2
Fukui	94.7	0.8	34.8
Osaka	89.4	8.0	37.9
Nagasaki	97.2	2.0	23.7
Manila & Rizal	89.0	4.9	
Taiwan	98.1	1.7	15.5

MV, morphologically verified; DCO, Death certificate only; M/I, mortality incidence ratio

tables through 1999 to 2006 in the Korean population.

(2) The Six Japanese Registries. For prognosis investigation, the vital status of registered persons for whom no cancer death was reported for five years, was confirmed by the information in the residential registration and/or the vital statistics database (non-cancer death database) (Table 1).

Calculation of relative survival was largely based on the method used in the EUROCARE study except that cases that had been followed-back using information in death certificates were excluded. In short, DCO cases, in situ cancer cases and mucosal cancer cases of the large bowel (when identified in the database) were excluded from the analysis (mucosal cancer cases were included in the Niigata registry because we could not identify them in the database). In the case of multiple cancers, only the first-diagnosed tumor was analyzed.

In calculating survival, cumulative 5-year survival rates were calculated starting from the date of diagnosis. Cases whose status was unknown at 5 years after diagnosis, were assumed to be alive as of the last known date of living. Expected survival rates were calculated using the cohort survival table based on life tables of the Japanese population and afterwards using the survival probability in the general population similar to the patients in sex, birth-year and age. The former was divided by the latter to obtain relative 5-year survival rates in an Ederer II method.

(3) Registries in Manila and Rizal. Prognosis investigation was performed: by referring to the death certificate information, through home visits, and by calling the patient's telephone number at home. The process of prognosis investigation was as follows: A summary of all cases abstracted in each hospital was prepared (number of cases collected per hospital/year and the distribution of cases/hospital by site). A summary of all death certificate abstracts gathered per municipality/year was likewise prepared (number of deaths from cancer per municipality/year and the distribution of cases by site, also cases for follow-back and the hospitals for follow-back). Both the hospital and death certificate abstracts were checked for completeness and consistency. To avoid duplication, completed hospital and death certificate abstracts were compared with the Master Patient Index File, Prior to Reference Date Cases, Site Index File, and Case-finding lists from the hospitals to determine if the case was previously seen in a hospital or not. If the case could not be traced back to a hospital or to the physician who signed the death certificate, the case was then registered under the "Death Certificate Only" category (DCO). Home visits are made by the registry assistant on patients who are deemed to be alive based on the status at last contact and whose names do not appear on any death certificate. Abstracts are updated as to status, treatment and current stage based on the information obtained at the home visit.

Cases with carcinoma in situ and subsequent primary cancer were excluded, and the follow-back cases were all included in the survival data. Ederer II, age-standardized

(using the world standard cancer patient population) 5-year RSRs were computed by using the life table for the Metro Manila population through individual years in 1997-1999.

(4) Taiwan Cancer Registry. The Taiwan Cancer Registry obtains follow-up information by data linkage with profiles of death certificates, catastrophic illnesses (included in health insurance program) and cancer screening programs. In the follow-up process, death records from the vital statistics database, catastrophic illnesses records and cancer screening databases for a given year were first matched with cancer registry data. Potential unreported cancer cases, i.e., those recorded as malignant cancer but had never been reported to the national cancer registry, were obtained. After the follow-up process, follow-back cases were included in the registry database except for the DCO and unreported cases.

Cases with carcinoma in situ and subsequent primary cancer except if the first primary cancer was non-melanoma skin, were excluded from the survival data. Bilateral breast cancers and multiple colon cancers were included as a single cancer if synchronous. The follow-back cases were all included.

The life tables of the national population of Taiwan from 1997 to 1999 were used to calculate the expected number of surviving patients or survival years. The Ederer II method was performed to calculate the 5-RSRs.

Survival Data (Tables 3 and 4)

(1) Stomach Cancer. The five-year relative survival rate (5-RSR) for stomach cancer ranged from 27% in Manila & Rizal to 70% in Niigata. All of the six Japanese registries showed a 5-RSR for stomach cancer among males of greater than 50%, followed by that in Korea (48%) and Taiwan (37%). Osaka had the lowest 5-RSR among the six Japanese registries. Similar geographic differences in stomach cancer survival were observed in female patients.

(2) Colorectal Cancer. The 5-RSR for colorectal cancer ranged from 40% in Manila & Rizal to 79% in Niigata. Relatively high 5-RSRs were observed in the Japanese registries in both males and females (59%~79%). The 5-RSRs for colorectal cancer in males and females in Korea (59% and 58%) were close to those in Taiwan (56% and 57%).

(3) Liver Cancer. Most of the 5-RSRs for liver cancer in the Japanese registries were between 20% and 30%. The 5-RSR in Taiwan was 18% among males and 20% among females, which was followed by that in Korea (13% and 15%). Manila & Rizal showed a 5-RSR for liver cancer of 8.5%.

(4) Lung Cancer. The 5-RSR for lung cancer in the six registries in Japan varied from 18% to 29% in males and from 25% to 48% in females. The 5-RSR of females was higher than that of males in all of the registries, and the difference was as much as 19 points in Yamagata and

Table 3. Five-year Relative Survival Rates (RSRs)

Organ/Registry	N	Diagnostic year(s)	PA* (%)	5-year RSR No (%)	SE (%)
Stomach Male					
Korea	12,421	1999-1999	98.3	48.1	0.5
Miyagi	3,203	1997-1999		67.6	1.0
Yamagata	2,607	1997-1999	98.8	66.0	1.2
Niigata	4,513	1997-1999		70.3	0.9
Fukui	1,402	1997-1999	95.6	65.7	1.6
Osaka	7,923	1997-1999	98.0	55.3	0.6
Nagasaki	2,242	1997-1999		59.2	1.3
Manila & Rizal (both sexes)					
	792	1993-2002		27.3	4.9
Taiwan	6,519	1997-1999	99.9	36.8	0.7
Stomach Female					
Korea	6,453	1999-1999	99.1	46.9	0.7
Miyagi	1,431	1997-1999		64.8	1.5
Yamagata	1,349	1997-1999	99.3	67.9	1.5
Niigata	2,028	1997-1999		69.0	1.2
Fukui	758	1997-1999	95.3	60.3	2.1
Osaka	3,697	1997-1999	98.2	53.7	0.9
Nagasaki	1,222	1997-1999		59.9	1.6
Taiwan	3,432	1997-1999	99.9	41.1	0.9
Colorectum Male					
Korea	4,949	1999	97.1	59.0	0.8
Miyagi	2,088	1997-1999		69.8	1.4
Yamagata	1,643	1997-1999	98.8	76.6	1.4
Niigata	2,820	1997-1999		78.7	1.1
Fukui	737	1997-1999	95.7	63.2	2.3
Osaka	5,226	1997-1999	97.2	60.6	0.8
Nagasaki	1,653	1997-1999		67.3	1.5
Manila & Rizal (both sexes)					
	1,635	1993-2002		40.2	4.4
Taiwan	10,265	1997-1999	99.8	56.1	0.6
Colorectum Female					
Korea	4,089	1999	97.6	57.6	0.9
Miyagi	1,566	1997-1999		69.8	1.4
Yamagata	1,278	1997-1999	99.2	69.0	1.6
Niigata	1,998	1997-1999		71.1	1.2
Fukui	606	1997-1999	94.4	68.5	2.4
Osaka	3,828	1997-1999	97.6	59.4	0.9
Nagasaki	1,305	1997-1999		67.0	1.6
Taiwan	7,790	1997-1999	99.9	57.0	0.6
Liver Male					
Korea	8,743	1999-1999	97.9	13.0	0.4
Miyagi	625	1997-1999		24.0	1.8
Yamagata	400	1997-1999	99.5	22.3	2.2
Niigata	541	1997-1999		22.7	1.9
Fukui	422	1997-1999	99.1	32.5	2.5
Osaka	4,766	1997-1999	97.6	23.4	0.7
Nagasaki	935	1997-1999		22.1	1.4
Manila & Rizal (both sexes)					
	772	1993-2002		8.5	1.9
Taiwan	16,325	1997-1999	99.9	17.6	0.3
Liver Female					
Korea	2,765	1999-1999	98.0	14.7	0.7
Miyagi	307	1997-1999		22.8	2.4
Yamagata	239	1997-1999	99.6	19.5	2.6
Niigata	252	1997-1999		21.7	2.6
Fukui	200	1997-1999	98.0	20.4	2.9
Osaka	1,752	1997-1999	97.4	21.3	1.0
Nagasaki	368	1997-1999		25.8	2.3
Taiwan	5,793	1997-1999	99.9	20.3	0.6

N, number of cases; PA, Prognosis available

Table 3 (continued). Five-year RSRs

Organ/Registry	N	Diagnostic year(s)	PA* (%)	5-year RSR No (%)	SE (%)
Lung Male					
Korea	8,612	1999-1999	97.7	11.5	0.4
Miyagi	1,883	1997-1999		24.9	1.1
Yamagata	1,066	1997-1999	99.2	23.7	1.4
Niigata	2,077	1997-1999		29.0	1.1
Fukui	701	1997-1999	98.7	21.5	1.7
Osaka	5,358	1997-1999	99.1	18.3	0.6
Nagasaki	1,652	1997-1999		24.0	1.2
Manila & Rizal (both sexes)					
	840	1993-2002		12.0	3.7
Taiwan	12,313	1997-1999	99.9	12.4	0.3
Lung Female					
Korea	2,899	1999-1999	98.0	17.8	0.8
Miyagi	730	1997-1999		37.7	1.9
Yamagata	366	1997-1999	99.2	43.2	2.8
Niigata	761	1997-1999		48.0	2.0
Fukui	247	1997-1999	97.2	33.6	3.2
Osaka	2,171	1997-1999	98.5	25.1	1.0
Nagasaki	688	1997-1999		34.5	2.0
Taiwan	5,398	1997-1999	99.9	15.0	0.5
Breast Female					
Korea	5,537	1999-1999	98.8	83.7	0.5
Miyagi	2,029	1997-1999		88.1	0.9
Yamagata	939	1997-1999	98.0	86.3	1.4
Niigata	1,708	1997-1999		86.4	1.0
Fukui	606	1997-1999	93.7	88.2	1.7
Osaka	5,816	1997-1999	97.5	83.6	0.6
Nagasaki	1,236	1997-1999		86.6	1.2
Manila &Rizal	1,615	1993-2002		58.6	4.1
Taiwan	11,723	1997-1999	99.9	79.7	0.4
Cervix Female					
Korea	4,333	1999-1999	98.2	81.1	0.7
Miyagi	262	1997-1999		69.6	3.2
Yamagata	122	1997-1999	94.3	73.3	5.0
Niigata	342	1997-1999		81.2	2.6
Fukui	114	1997-1999	93.9	65.9	5.3
Osaka	1,068	1997-1999	96.5	67.3	1.6
Nagasaki	336	1997-1999		77.2	2.7
Manila &Rizal	1,580	1993-2002		45.4	3.7
Taiwan	8,593	1997-1999	99.9	77.4	0.5

N, number of cases; PA, Prognosis available

Niigata. The female dominance in 5-RSR was also observed in Taiwan and Korea, although the difference was less marked. The 5-RSR in both genders in Manila & Rizal was 12%.

(5) Female Breast Cancer. In each registry, the 5-RSR for female breast cancer showed the highest figure among all cancer sites. The 5-RSR ranged from 58% (Manila & Rizal) to 88% (Fukui) among all of the registries.

(6) Cervical Cancer. The 5-RSR for cervical cancer was the highest in Korea and Niigata (81%), followed by Taiwan (77%). Miyagi (70%), Osaka (67%) and Fukui (66%) had lower rates than Korea and Taiwan. Manila & Rizal showed a 5-RSR for cervical cancer of 45%.

(7) Survival Data from Jakarta. One of the authors (E.S.) prepared 5-year cumulative survival rates in patients who were diagnosed at Dharmais National Cancer Hospital between 1997 and 1999. Table 4 shows the results along with the percentage of subjects who did not drop out during the 5-year period of prognosis investigation. Data for stomach cancer are not presented because of the small number of subjects. Note that the percentage of patients whose prognosis at 5 years after diagnosis was available, was low (ranging from 54% to 77%). Therefore, the estimated 5-year cumulative survival rate was possibly overestimated.

Table 4. Five-year Cumulative Survival Rates for Patients Diagnosed at Dharmais National Cancer Hospital, Indonesia between 1997 and 1999

Organ	Sex	Age range	N	PA (%)	No/Total	Survival No(%)	SE(%)
Colon	Male	25-80	41	75.6	(31/41)	36.6	6.31
	Female	21-83	39	64.1	(25/39)	28.2	5.49
Rectum	Male	24-81	36	69.4	(25/36)	38.9	6.61
	Female	26-79	24	54.2	(13/24)	37.5	2.07
Liver	Male	30-84	55	83.6	(46/55)	34.6	1.20
	Female	25-78	20	55.0	(11/20)	30.0	1.05
Lung	Male	27-82	250	73.2	(183/250)	33.2	1.66
	Female	21-88	80	77.5	(62/80)	31.3	3.61
Breast	Female	19-95	475	73.7	(350/475)	48.6	3.43
Cervix	Female	18-84	487	66.5	(324/487)	50.5	0.96

N, number of cases; PA, Prognosis available; SE: standard error

Discussion

Our results revealed that there were substantial differences in quality indices among different cancer registries in East Asia in the late 1990s. These differences partly reflect differences in the social system and health care infrastructure.

The DCO% in Taiwan and Korea were among the lowest of the nine registries for all cancer sites. This is, at least in part, due to the fact that the two countries have excellent social infrastructures for cancer registry, such as citizenship ID number, digitized vital and health statistics database, and a universal health insurance system. On the other hand, the Japanese registries showed great variation in DCO%, which is partly due to the facts that there is no nationwide legal basis or social infrastructure for cancer registry in the country and that each registry developed its system.

Our study results also showed that there was substantial variation in the reported RSRs among the six registries in Japan in the late 1990s. These differences should reflect not only differences in cancer control activities and cancer care, but also differences in cancer registration system. Therefore, we need to consider all of these factors in the interpretation of the results. Besides health care quality, there are three major factors that can influence RSRs, namely the characteristics of the subjects, the patient follow-up system, and the method of calculation of RSR. "The characteristics of the subjects" refers to the combination of different patient groups such as: i) hospital-reported cases, followed-back cases, and DCO cases, ii) primary cancer cases and subsequent cancer cases, iii) symptom-diagnosed cases and cancer screening-

diagnosed cases. The survival rates of these patient groups are usually different; therefore, the proportion of each patient group in the subject population can affect the survival rate. The follow-up system varies from registry to registry, and if it is not exhaustive, RSRs may be over-estimated. There are three different methods of calculation of RSR, i.e., the Ederer I, Ederer II or Hakulinen method, each of which produces somewhat different results. In the current study, all of the registries adopted the Ederer II method. Also, for better comparability across cancer patient populations, we need age-adjusted and clinical stage-specific calculation.

The RSR for cervical cancer in Japan tended to be lower than that in Taiwan or Korea. This finding may be explained by a difference in the clinical stage of cervical cancer cases coming from a difference in cervical screening coverage. In Japan, cervical screening has been offered mainly by the population-based program, and its coverage has been fairly low (approximately 15% in the 1990s). Taiwan introduced a population-based cervical screening program in 1996, which achieved a higher screening coverage than that in Japan by 1999. A recent publication on international comparison of cancer survivals reported that the 5RSR for cervical cancer in the three registries from Korea (Busan, Incheon and Seoul) was 76 ~79 % (Sankaranarayanan et al., 2009). Korea introduced a population-based screening program in 1999, but voluntary screening might have achieved good coverage by the introduction. Therefore, the proportion of screening-diagnosed cases in the Japanese registries might have been lower than that in Korea or Taiwan, in contrast to the screening coverage for stomach, colon and lung. In addition, cervical cancer survival rate is largely differed by age at diagnosis (Ioka et al., 2009) which was possibly attributed in relatively lower survival observed in the Japanese even in the RSR. We need to validate this hypothesis by comparing the clinical stage of reported cases and screening coverage for cervical cancer.

Our study has some limitations. First, as explained earlier, the RSRs at some registries may have been overestimated due to the difference in follow-up system or exclusion of followed-back cases. Second, the calculation of DCO% at the Japanese registries was based on the Japanese definition of DCO, which may have overestimated the DCO% in the country. Third, it is likely that there was a difference in age distribution of the patient population across different registries, but we could not age-standardize the calculation of RSRs at this time, which might have reduced the comparability (Cprazziari et al., 2004). Fourth, the results from Manila and Rizal were on subjects who were diagnosed between 1993 and 1999 in both genders, which had less comparability with the other registries. Last, we did not collect information on clinical stage or histology for each cancer site, and potential differences in this critical information could not be analyzed.

Even with the above-described limitations, this study is worthwhile as the first attempt to calculate population-based cancer survival in selected registries in East Asia, with disclosing data quality. To improve the comparability for assessment of cancer survival difference in East Asia, we need further efforts to standardize the definition of study subjects and to obtain individualized data items attributed to the survival time.

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Nonfilter and filter cigarette consumption and the incidence of lung cancer by histological type in Japan and the United States: Analysis of 30-year data from population-based cancer registries

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Shifts in the histologic type of lung cancer accompanying changes in lung cancer incidence have been observed in Japan and the United States. We examined the association between the shift in tobacco design from nonfilter to filter cigarettes with changes in the incidence of adenocarcinoma (AD) and squamous cell carcinoma (SQ) of the lung. We compiled population-based incidence data from the Surveillance, Epidemiology and End Results in the United States (1973–2005) and from selected Japanese cancer registries (1975–2003). Trends in age-standardized rates of lung cancer incidence by histologic type were characterized using joinpoint analyses. A multiple regression framework was used to examine the relationship between tobacco use and incidence by histologic type. We observed that AD has replaced SQ as the most frequent histologic type in males and females in both Japan and the United States. Filter cigarette consumption was positively associated with the incidence of AD, with time lags of 25 and 15 years in Japan and the United States, respectively ($\hat{\beta}_2^{AD}$: 1.946×10^{-3}, $p < 0.001$ and 3.142×10^{-3}, $p < 0.001$). In contrast, nonfilter cigarette consumption was positively associated with the incidence of SQ, with time lags of 30 and 20 years in Japan and the United States, respectively ($\hat{\beta}_2^{SQ}$: 0.464×10^{-3}, $p = 0.006$ and 0.364×10^{-3}, $p = 0.008$). In conclusion, the shift from nonfilter to filter cigarettes appears to have merely altered the most frequent type of lung cancer, from SQ to AD.

The association between cigarette smoking and lung cancer was firmly established in the 1950s.[1] The rapid increase in incidence rates in the 20th century has led to an epidemic of lung cancer, particularly among men in industrialized countries.[2,3] In the United States, where serious smoking control efforts were instituted almost 50 years ago, the incidence of lung cancer among men peaked in 1982 and began to decline thereafter,[4] but it continues to rise in countries where smoking control efforts have been less aggressive. In Japan, despite a continuous decline in smoking rates over the last 50 years, lung cancer incidence continues to rise.[4,5]

Lung cancer incidence patterns and trends vary by histological type[6] and have been shown to be related to smoking patterns and exposures to other lung risk factors.[3] Shifts in histologic type have been reported to accompany changes in lung cancer incidence. Relative and absolute increases in adenocarcinoma (AD) of the lung were first recognized in the 1970s[7] and continued to be observed in the United States[8,9] and European countries.[10] Although this trend has now peaked in the United States,[11,12] incidence appears to be still increasing in certain areas of Japan.[13–15]

Trends in the incidence of lung cancer by histologic type are of interest in the evaluation of the impact of changes in cigarette manufacture. In particular, although low-tar, low-nicotine, filtered cigarettes appear to have contributed to the overall decline in lung cancer, and most notably in squamous

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cell carcinoma (SQ),[16] they may have simultaneously increased the risk of certain peripheral tumors, such as AD,[17–20] and it has been hypothesized that the upward trend in the incidence of AD is mainly due to the dissemination of low-tar filtered cigarettes.[18–20] Smoke from low-yield filter-tipped cigarettes is inhaled more deeply than that from earlier unfiltered cigarettes.[21,22] Inhalation transports tobacco-specific carcinogens more distally toward the bronchioalveolar junction, where ADs often arise. The change in cigarette consumption from nonfiltered to filtered cigarettes also reduces the yield of carcinogenic polycyclic aromatic hydrocarbons, which are inducers of SQs, while simultaneously increasing that of carcinogenic tobacco-specific N-nitrosamines, which are inducers of ADs.[19]

Here, we investigated differences in the effects of nonfilter and filter cigarette consumption on changes in the incidence of SQ and AD in Japan and the United States.

Material and Methods

Lung cancer incidence data in Japan were obtained from nine of the 36 regional registries used to estimate nationwide incidence, namely Yamagata, Niigata, Fukui, Shiga, Osaka, Okayama, Saga, Nagasaki and Hiroshima City, which together account for about 18% of the Japanese population. For the United States, lung cancer incidence data were obtained from the Surveillance and End Results (SEER) program of the US National Cancer Institute, which makes aggregate data available to the public. The data cover about 10% of the US population in nine geographical regions, namely the states of Connecticut, Hawaii, Iowa, New Mexico and Utah, as well as the metropolitan areas of Atlanta (GA), Detroit (MI), San Francisco-Oakland (CA) and Seattle-Puget Sound (WA). We selected cases diagnosed with lung or bronchus cancer from 1973 through 2005 for the US data and from 1975 through 2003 for the Japanese data. Morphology codes indicating lung cancer cell type were grouped into eight major categories according to the WHO scheme[23]: (*i*) SQ (International Classification of Disease for Oncology version 3 (ICD-O-3) codes 8050–8078, 8083–8084); (*ii*) AD (8140, 8211, 8230–8231, 8250–8260, 8323, 8480–8490, 8550–8551, 8570–8574, 8576); (*iii*) small cell carcinoma (8041–8045, 8246); (*iv*) large cell carcinoma (including giant cell, clear cell and large cell undifferentiated carcinoma 8010–8012, 8014–8031, 8035, 8310); (*v*) other specified carcinoma; (*vi*) sarcoma (8800–8811, 8830, 8840–8921, 8990–8991, 9040–9044, 9120–9133, 9150, 9540–9581); (*vii*) other specified malignant neoplasm and (*viii*) unspecified malignant neoplasm (8000–8005). The percentages of cases with unspecified morphology in the United States and Japan differed by an order of magnitude: only 3.9% of the US cases had morphology codes of 8000–8005, indicating "unspecified malignant neoplasm," whereas 33.6% of case reports in Japan were coded 8000–8005. In accordance with Devesa *et al.*,[10] we proportionally allocated the cases with unspecified morphology 8 to the other seven categories on a registry-, year at diagnosis-, sex- and age-specific basis.

US age-standardized incidence rates (ASR) were calculated for the years 1973–2005 and Japanese ASR for the years 1975–2003, by major morphological type, namely SQ, AD and small cell carcinoma. Age standardization incorporated the Segi world standard.[24] All incidence rates were expressed as newly diagnosed cases of malignant neoplasm per 100,000 person-years.

The trends in ASR were also characterized by the widely used joinpoint regression analysis, as described in detail elsewhere.[25] Briefly, joinpoint regression is a statistical technique that describes changing trends over successive segments of time and the magnitude of an increase or decrease within each segment after identifying the best fitting model. Essentially, within each time segment, the log of the ASR is modeled as a linear function of time (calendar year), thereby yielding annual exponential rates of change in ASR. The technique identifies the timepoint(s), also referred to as joinpoint(s), at which there is a statistically significant change in the incidence trend. A maximum of three joinpoints in the model was allowed in the model fitting. The resulting trend segments, as delimited in time by joinpoints, were described by the annual percentage change (APC), that is, the slope of the line segment.[25] The calculation assumes that rates increase or decrease at a constant rate over time, although the validity of this assumption has not been tested. APC is calculated based on the following regression model:

$$\log(R_y) = b_0 + b_1 y$$

where $\log(R_y)$ is the natural log of the rate in year y

The APC from year y to $y + 1$

$$= \left(\frac{R_{y+1} - R_y}{R_y}\right) \times 100$$

$$= \left(\frac{e^{b_0+b_1(y+1)} - e^{b_0+b_1(y)}}{e^{b_0+b_1(y)}}\right) \times 100$$

$$= \left(e^{b_1} - 1\right) \times 100$$

In describing the trends, the terms "increase" or "decrease" were used when the slope (APC) of the trend was statistically significant ($p < 0.05$); otherwise, the terms "stable" or "level" were used.

Data on cigarette consumption were based on the market share of nonfilter and filter cigarettes sale in each year. These data were obtained from the US Federal Trade Commission,[26] the Ministry of Health, Labour and Welfare, Japan,[27] the Ministry of Finance, Policy Research Institute, Japan,[28] Japan Tobacco and Salt Co. and the Tobacco Institute of Japan.

To assess whether the incidence rates of SQ and AD of the lung were correlated to annual nonfilter and filter cigarette consumption per capita, we used a multiple regression framework.[29] For a specific subpopulation (*i.e.*, Japanese), we let $Y^{AD}(t)$ represent the ASR (per 100,000 person-years) of AD at time t, and $Y^{AD}(t^+)$ represent the ASR of AD at one time point ahead of time t. For example:

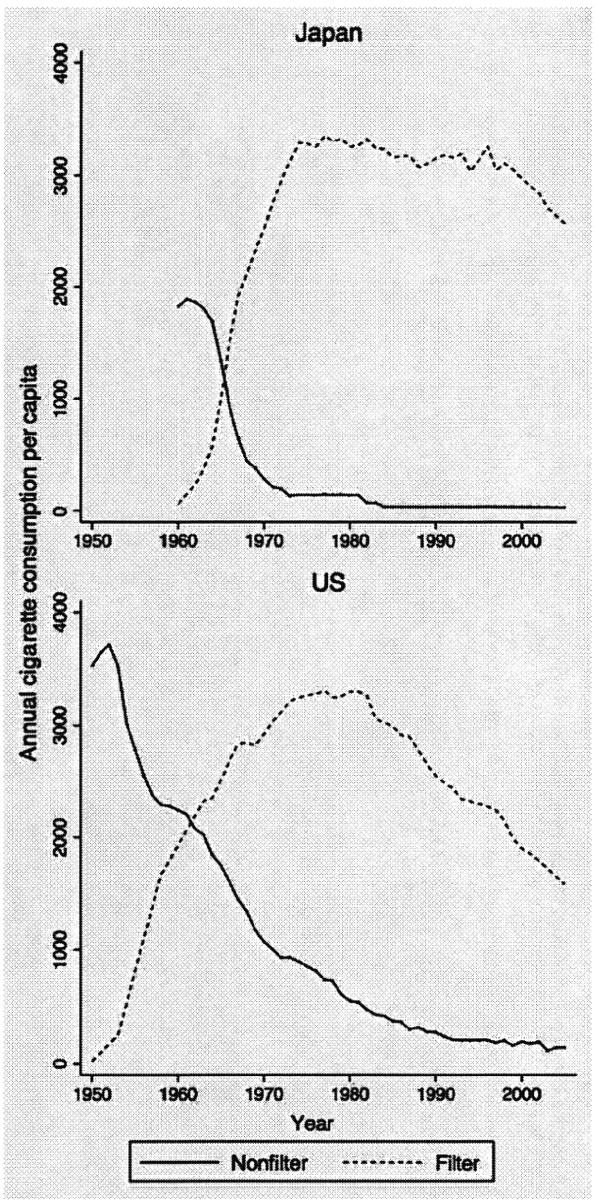

Figure 1. Japan and US nonfilter and filter cigarette consumption. Data for annual consumptions of nonfilter (solid line) and filter (dashed line) cigarettes per capita are presented. The shift from nonfilter to filter cigarettes occurred in the 1960s and the 1950s in Japan and the United States, respectively.

$$Y^{AD}(t) = [Y^{AD}(1), Y^{AD}(2), \ldots, Y^{AD}(T-1)]$$
$$Y^{AD}(t^+) = [Y^{AD}(2), Y^{AD}(3), \ldots, Y^{AD}(T)]$$

Likewise, we let $Y^{SQ}(t)$ represent the ASR (per 100,000 person-years) of SQ at time t and $Y^{SQ}(t^+)$ represent the ASR of SQ at one time point ahead of time t. Additionally, we let

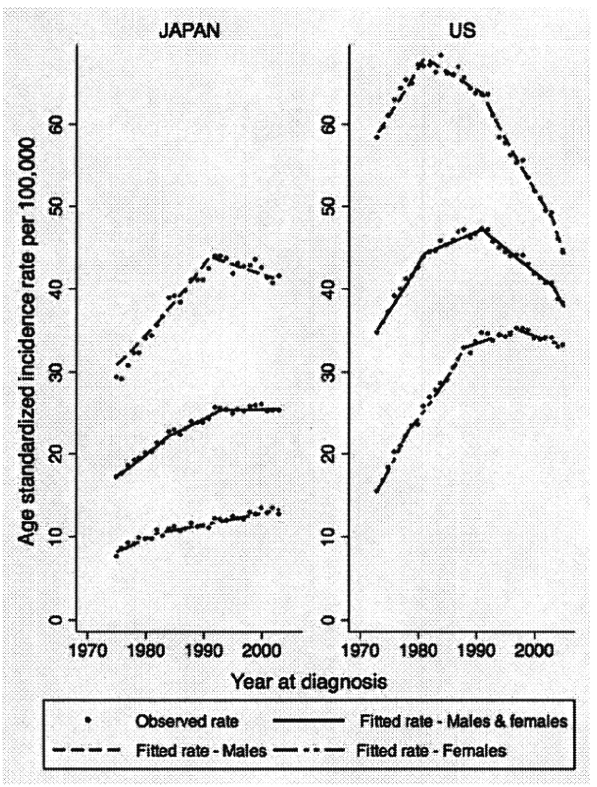

Figure 2. Joinpoint analysis of the overall age-standardized incidence rates (ASR) of lung cancer among individuals in Japan and the United States.

$X(t^+ - \tau)$ represent the nonfilter or filter cigarette consumption at time $t^+ - \tau$, where τ is the appropriate time lag. Thus, for each subpopulation, we have the following models:

$$Y^{SQ}(t^+) = \beta_0^{SQ} + \beta_1^{SQ} Y^{SQ}(t) + \beta_2^{SQ} X(t^+ - \tau) + \varepsilon^{SQ} \quad (1)$$
$$Y^{AD}(t^+) = \beta_0^{AD} + \beta_1^{AD} Y^{AD}(t) + \beta_2^{AD} X(t^+ - \tau) + \varepsilon^{AD} \quad (2)$$

We set τ from 5 to 30 years according to the epidemiological evidence: in this regard, because the incidence of lung cancer does not appear to be lower among ex-smokers who quit smoking within 5 years than current smokers,[30,31] the sum of the induction period and latent period of lung cancer caused by tobacco smoking is likely longer than 5 years.

We then examined the adjusted R^2 in the model with different time lags τ among subpopulations and cigarette designs to find the best fitting models (1) and (2) for nonfilter and filter cigarettes among Japanese and Americans. R^2 value was interpreted to mean that for every unit increase in annual nonfilter or filter consumption per capita, we expect a β_2 point increase in the ASR of AD or SQ, holding all other variables constant.