Breast Cancer Res Treat
DOI 10.1007/s10549-008-0168-1

EPIDEMIOLOGY

Dietary isoflavone intake and breast cancer risk in case–control studies in Japanese, Japanese Brazilians, and non-Japanese Brazilians

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Received: 21 July 2008 / Accepted: 20 August 2008

Abstract Although epidemiologic studies have shown an inverse association between isoflavones and breast cancer risk, little evidence for a dose–response relation is available. We conducted hospital-based case–control studies of patients aged 20–74 years with primary, incident, histologically confirmed invasive breast cancer, and matched controls from medical checkup examinees in Nagano, Japan and from cancer-free patients in São Paulo, Brazil. A total of 850 pairs (390 Japanese, 81 Japanese Brazilians and 379 non-Japanese Brazilians) completed validated food frequency questionnaires. The odds ratio of breast cancer according to isoflavone intake was estimated using a conditional logistic regression model. We found a statistically significant inverse association between isoflavone intake and the risk of breast cancer for Japanese Brazilians and non-Japanese Brazilians. For Japanese, a non-significant inverse association was limited to postmenopausal women. In the three populations combined, breast cancer risk linearly decreased from 'no' to 'moderate' isoflavone intake and thereafter leveled off. Compared to non-consumers, adjusted odds ratios (95% confidence interval) for consumers in increasing quintile intake categories (median intake in each category: 8.7, 23.1, 33.8, 45.7, and 71.3 mg/day) were 0.69 (0.44–1.09), 0.54 (0.31–0.94), 0.45 (0.26–0.77), 0.34 (0.19–0.62), and 0.43 (0.24–0.76), respectively. Overall, we found an inverse association between dietary isoflavone intake and risk of breast cancer. Our finding suggests a risk-reducing rather than risk-enhancing effect of isoflavones on breast cancer within the range achievable from dietary intake alone. In addition, women may benefit

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from risk reduction if they consume at least moderate amounts of isoflavones.

Keywords Breast cancer · Dietary isoflavones · Case–control study · Immigrants

Abbreviations

CI	Confidence interval
ER	Estrogen receptor
FFQ	Food-frequency questionnaire
OR	Odds ratio
PR	Progesterone receptor

Introduction

Soy foods, which are rich in isoflavones, are habitually consumed by Asian populations in large amounts. Isoflavones, of which genistein and daidzein are major examples, are classified as phytoestrogens, which are plant-derived non-steroidal compounds with estrogen-like biological properties. A high intake of isoflavones has therefore been hypothesized to contribute to the lower incidence of breast cancer in Asia than Western countries [1]. This hypothesis is supported by not only in vitro studies at high genistein concentrations and the majority of animal studies [2, 3] but also epidemiological studies [4–10]. In particular, a recent meta-analysis showed a small decrease in risk of breast cancer with higher soy intake [11] while a more recent meta-analysis indicated that risk reduction was limited to Asian populations [12]. In apparent contradiction to potential protective effects, however, genistein exhibits estrogenic properties at low concentrations, which could theoretically enhance breast cancer risk [2, 3], and some animal studies have in fact reported that genistein stimulates tumor development and growth [13, 14].

Although research remains insufficient for any comprehensive determination of whether isoflavones are protective or harmful for breast cancer, interest in soy foods and isoflavones is nevertheless increasing. This increase may reflect an expectation of potential benefits in a wide variety of medical conditions, including cancer of the endometrium and prostate as well as breast, cardiovascular diseases, osteoporosis, and menopausal symptoms. In fact, consumption of soy foods in the United States has increased over the past ten years, against fairly constant intake in Japan over the past four decades [15]. Moreover, phytoestrogen supplements are commercially marketed for use by postmenopausal women as natural and safe alternatives to hormone replacement therapy. A dose–response pattern, in particular the effect of relatively high-dose isoflavones on breast cancer risk, is thus now of concern. Nevertheless, little evidence of any dose–response relationship is available—indeed, we do not know the answer to 'how much isoflavones is needed?' This is partly because few studies have estimated isoflavone intake using a validated food-frequency questionnaire (FFQ) [4–6, 16, 17], and also because most studies in Western countries have involved only a small variation in isoflavone intake [6, 7, 16–20].

Here, to evaluate the dose–response relationship between isoflavone intake and the risk of breast cancer, ranging from zero to the relatively high levels achievable from dietary intake only, we conducted hospital-based case–control studies in Nagano, Japan and São Paulo, Brazil, areas with a low and middle incidence of breast cancer, respectively (age-standardized rate per 100,000 world population, 32.7 and 46.0 in 2002, respectively) [21], using validated FFQs with relatively high validity in three populations: Japanese living in Japan, Japanese Brazilians living in São Paulo, and non-Japanese Brazilians living in São Paulo. The mortality of breast cancer among these three populations has increased over the last 20 years, with that in Japanese Brazilians intermediate between that in Japanese and Brazilians [22]. In addition, because amounts and variations in isoflavone intake are expected to be high and large for Japanese, intermediate and relatively large for Japanese Brazilians, and low and small for non-Japanese Brazilians, respectively, these populations serve as suitable venues for studies of the effect of dose–response relations.

Materials and methods

Study subjects

These multicenter, hospital-based case–control studies of breast cancer were designed to determine lifestyle factors and genetic susceptibility to the risk of breast cancer and to compare potential risk factors among Japanese living in Nagano, Japan, and Japanese Brazilians and non-Japanese Brazilians living in São Paulo, Brazil. Eligible cases were a consecutive series of female patients aged 20–74 years with newly diagnosed and histologically confirmed invasive breast cancer. Cases were recruited between 2001 and 2005 at four hospitals in Nagano, and between 2001 and 2006 at eight hospitals in São Paulo. A total of 405 cases (98%) participated in Nagano, and 83 Japanese Brazilians (91%) and 389 non-Japanese Brazilians (99%) in São Paulo. In the study in Nagano, eligible controls were selected from medical checkup examinees in two of the four hospitals and confirmed not to have cancer. One control was matched for each case by age (within 3 years) and residential area during the study period. Among potential controls, one examinee refused to participate and two refused to provide blood samples. Consequently, we

obtained written informed consent from 405 matched pairs. In the study in São Paulo, eligible controls were preferentially selected from cancer-free patients who visited the same hospital as the index cases. One control was matched for each case by age (within 5 years) and ethnicity during the study period. Among potential controls, 22 patients refused to participate (participation rate = 96%). Consequently, we obtained written informed consent from 472 matched pairs (83 for Japanese Brazilians and 389 for non-Japanese Brazilians). The study protocol was approved by CONEP (Comissão Nacional de Ética em Pesquisa), Brasília, Brazil and by the institutional review board of the National Cancer Center, Tokyo, Japan.

Data collection

Participants in Nagano were asked to complete a self-administered questionnaire, while in-person interviews were conducted by trained interviewers using a structured questionnaire in São Paulo. The two questionnaires contained closely similar questions concerning demographic characteristics, medical history, family history of cancer, menstrual and reproductive history, anthropometric factors, physical activity, and smoking habits. For dietary habits, we used a semi-quantitative FFQ (136 items for the Japanese version and 118 items for the Brazilian version) which was developed and validated in each population [23, 24]. Information on estrogen receptor (ER) and progesterone receptor (PR) status was obtained from medial records. Hormone receptor status was determined by either enzyme-linked immunoassay or immunohistochemical assay. Hormone receptor positivity values were determined either as specified by the laboratory that performed the assay, or in accordance with the laboratory's written interpretation thereof, or both.

Dietary assessment

In the FFQ, participants were questioned on how often they consumed the individual food items (frequency of consumption), as well as relative sizes compared to standard portions. Response choices for frequency were never or less than once/month, 1–3 times/month, 1–2 times/week, 3–4 times/week, 5–6 times/week, once/day, 2–3 times/day, 4–6 times/day, and 7 times/day or more, and relative sizes to a standard portion were small (50% smaller than standard), medium (same as standard), and large (50% larger). For the Japanese version, white rice intake was determined in terms of the relative size of the rice bowl used and the frequency of intake, with the nine choices of less than 1–10 bowls per day. Frequency for miso soup intake was given in the six choices of almost never, 1–3 times/month, 1–2 times/week, 3–4 times/week, 5–6 times/week, or daily, while amount was given in nine categories ranging from less than 1–10 bowls per day, without reference to the relative size of the bowl used. Daily food intake was calculated by multiplying frequency by standard portion and relative size for each food item in the FFQ. Daily intakes of genistein and daidzein were calculated using a food composition table of isoflavones developed previously [25, 26]. Isoflavone intake was defined for this study as the sum of genistein and daidzein intake. Other nutrients were calculated using the Japanese Standard Tables of Food Composition, 5th ed. for the Japanese version [27] and the United States Department of Agriculture (USDA) food composition tables for the Brazilian version [28]. For some Japanese-specific foods in the Brazilian version, the Japanese Standard Tables of Food Composition, 5th ed. was used.

The validity of isoflavone intake estimated from the Japanese version of the FFQ was evaluated in a subsample of the Japan Public Health Center-based Prospective Study, which includes Nagano as one of the study areas. The estimated intake according to the FFQ was compared to that in four consecutive 7-day dietary records, one conducted in each the four seasons. Spearman's correlation coefficients between energy-adjusted genistein and daidzein intake estimated from the FFQ and from dietary records were 0.59 for genistein and 0.60 for daidzein [24]. For the Brazilian version, the validity of isoflavone intake estimated from the FFQ was evaluated in a subsample of the control group in this case–control study by comparing the estimated intake according to the FFQ to that in two consecutive 4-day dietary records, one each in two seasons. Spearman's correlation coefficients between energy-adjusted genistein and daidzein intake estimated from the FFQ and from dietary records were 0.76 for genistein and 0.76 for daidzein (unpublished data).

Statistical analysis

We excluded subjects who reported extremely low or high total energy intake (<500 or ≥ 4000 Kcal), leaving 390 pairs of Japanese, 81 pairs of Japanese Brazilians and 379 pairs of non-Japanese Brazilians for use in the present analyses. Comparison of baseline characteristics between cases and controls was evaluated by the Mantel-Haenszel test using matched-pair strata in each population. Dietary intake of isoflavones was adjusted for total energy intake by the residual method and divided into median or tertile categories based on control distribution for Japanese and Japanese Brazilians, respectively. Because of the small proportion of consumers, non-Japanese Brazilians were categorized into non-consumers and consumers of isoflavones. Using a conditional logistic regression model, we calculated odds ratios (ORs) and 95% confidence intervals

(CIs) of breast cancer for isoflavone intake. An unconditional logistic regression model was used for stratified analyses according to menopausal status. Associations between isoflavone intake and hormone receptor-defined breast cancer were assessed by an unconditional polytomous logistic regression model. Linear trends for ORs were tested in the logistic regression model using the exposure categories as ordinal variables. The following variables, which were mainly selected based on comparison of baseline characteristics between cases and controls, were adjusted for as potential confounders: menopausal status, number of births, family history of breast cancer, smoking status, moderate physical activity in the past 5 years, and vitamin supplement use. We did not include a history of benign breast disease as a covariate since we regarded it as an intermediate variable in the causal pathway between isoflavone intake and breast cancer. All p values reported are two-sided, and significance level was set at $P < 0.05$. All statistical analyses were performed with SAS software version 9.1 (SAS Institute, Inc., Cary, NC).

Results

Characteristics of cases and controls and isoflavone intake (Table 1)

For Japanese, the proportion of premenopausal women, current smokers, and vitamin supplement users was higher in cases than in controls, and cases tended to have a family history of breast cancer and history of benign breast disease. Cases were less likely than controls to breast-feed, be physically active, and eat vegetables. For Japanese Brazilians, cases were less likely than controls to give birth and be physically active and more likely to eat vegetables and fruits. For non-Japanese Brazilians, the proportion of premenopausal women and current smokers was higher in cases than controls while the proportion of physically active women and vitamin supplement users was lower. Isoflavone intake substantially varied among populations, with mean intakes (mg/day) in control subjects of 46.1 for Japanese, 24.9 for Japanese Brazilians, and 4.4 for non-Japanese Brazilians. Because genistein and daidzein intakes were highly correlated, with a Spearman's correlation coefficient for the three populations of 0.99, only isoflavone intake was used for the following analyses.

ORs in the three populations (Table 2)

We found a statistically significant inverse association between isoflavone intake and the risk of breast cancer for Japanese Brazilians and non-Japanese Brazilians but not for Japanese. Adjusted OR for the highest versus lowest tertile of isoflavone intake was 0.25 (95% CI 0.09–0.68; P for trend <0.01) for Japanese Brazilians. For non-Japanese Brazilians, adjusted OR for consumers versus non-consumers of isoflavones was 0.56 (95% CI 0.35–0.90). No substantial change was seen after further adjustment for other potential confounders, such as age at menarche, age at menopause, age at first birth, history of breast feeding, body mass index, alcohol drinking, or vegetable and fruit intake.

A stratified analysis according to menopausal status revealed that an inverse association was limited to postmenopausal women in Japan although it was not statistically significant. Adjusted OR for the highest versus lowest tertile of isoflavone intake was 0.62 (95% CI 0.38–1.01; P for trend = 0.06) for postmenopausal women, but 1.35 (95% CI 0.72–2.54; P for trend = 0.41) for premenopausal women. The inverse association was stronger in premenopausal than postmenopausal women for Japanese Brazilians but no remarkable difference between the two strata was seen for non-Japanese Brazilians.

ORs of hormone receptor-defined breast cancer (Table 3)

Information on the combined ER and PR status of the breast tumor was available for 387 (99%) Japanese, 61 (75%) Japanese Brazilians, and 264 (70%) non-Japanese Brazilians cases. The following subtypes were used for modeling in an unconditional polytomous logistic regression model: positive for both receptors (ER+/PR+), ER-positive and PR-negative (ER+/PR−), and negative for both receptors (ER−/PR−) for Japanese, and ER+/PR+, ER+/PR−, ER−/PR−, and unknown for Japanese Brazilians and non-Japanese Brazilians. Overall, we found no remarkable difference in risk by hormone receptor-defined subtype.

Dose–response pattern (Table 4; Fig. 1)

To evaluate dose–response relations using a wide range of isoflavone intake, we combined individual study data from three populations and categorized the subjects into six groups, namely non-consumers and quintiles among isoflavone consumers based on the combined control distribution. Compared to non-consumers, adjusted ORs (95% CI) for consumers in increasing quintile categories (median intake in each category: 8.7, 23.1, 33.8, 45.7, and 71.3 mg/day) based on a conditional logistic regression model were 0.69 (0.44–1.09), 0.54 (0.31–0.94), 0.45 (0.26–0.77), 0.34 (0.19–0.62), and 0.43 (0.24–0.76), respectively. A stratified analysis according to menopausal status based on an unconditional logistic regression model revealed that this inverse association was more prominent in postmenopausal

Table 1 Characteristics of case and matched control subjects

	Japanese living in Nagano, Japan			Japanese Brazilians living in São Paulo, Brazil			Non-Japanese Brazilians living in São Paulo, Brazil		
	Case ($n = 390$)	Control ($n = 390$)	P^a	Case ($n = 81$)	Control ($n = 81$)	P^a	Case ($n = 379$)	Control ($n = 379$)	P^a
Age (years), mean	53.8	54.0	–	56.6	56.5	–	52.4	52.5	–
Premenopausal women, %	46	35	<0.01	31	30	0.80	42	38	0.04
Age at menopause (years), mean[b]	49.0	49.4	0.15	49.9	50.6	0.73	49.1	48.4	0.13
Age at menarche (years), mean[b]	13.4	13.2	0.42	12.9	12.9	0.20	13.2	13.1	0.96
Nulliparous women, %	13	14	0.66	23	16	0.24	11	10	0.91
Number of births (≥4 births), %	2	3	0.16	7	20	0.02	29	35	0.10
Age at first birth (years), mean[b, c]	26.9	26.4	0.42	28.6	27.5	0.25	23.2	22.5	0.24
Breast feeding (yes), %[c]	91	96	0.03	92	91	0.56	88	91	0.67
Oral contraceptives user, %	3	3	1.00	29	36	0.30	63	65	0.62
Family history of breast cancer, %	11	6	0.02	15	12	0.65	6	6	0.88
History of benign breast disease, %	12	7	0.03	12	6	0.17	7	7	1.00
Height (cm), mean[b]	155.3	155.5	0.50	154.0	153.9	0.91	158.2	158.4	0.96
Body mass index (kg/m^2), mean[b]	22.7	23.0	0.07	24.3	24.5	0.43	26.6	26.1	0.11
Smoking (current smoker), %	8	5	<0.01	11	2	0.07	17	11	0.04
Alcohol drinking (regular drinker), %	26	29	0.25	2	6	0.26	6	6	0.65
Moderate physical activity past 5 years (yes), %	32	40	0.02	19	32	0.03	9	14	0.03
Vitamin supplement user, %	18	12	0.03	19	26	0.27	3	9	<0.01
Total energy intake (kcal/day), mean[b]	1881.6	1949.3	0.27	1662.0	1587.7	0.44	1847.0	1752.8	0.09
Fish and shellfish intake (g/day), mean[b]	87.6	94.4	0.11	27.4	30.5	0.56	13.7	16.6	0.24
Meat or red meat intake (g/day), mean[b, d]	58.1	57.6	0.36	54.3	53.3	0.44	72.1	64.2	0.14
Vegetable intake (g/day), mean[b]	257.6	310.5	<0.01	146.7	93.0	<0.01	77.7	86.4	0.96
Fruit intake (g/day), mean[b]	288.6	287.7	0.69	364.0	311.0	0.02	260.2	250.9	0.35
Isoflavone intake (mg/day), mean[b]	43.5	46.1	<0.01	16.5	24.9	0.15	1.1	4.4	0.01
Genistein intake (mg/day), mean[b]	27.0	28.6	<0.01	10.2	15.8	0.15	0.73	3.1	0.01
Daidzein intake (mg/day), mean[b]	16.5	17.5	<0.01	6.3	9.1	0.15	0.33	1.4	0.01

[a] P for Mantel-Haenszel test with matched-pair strata

[b] Adjusted for age

[c] Among parous women

[d] Meat intake for Japanease and red meat intake for Japanese Brazilians and non-Japanese Brazilians

than premenopausal women. To clarify the effect of high isoflavone intake in detail, subjects were further categorized into 11 groups, namely non-consumers and deciles of isoflavone consumers. We found a linear decrease in breast cancer risk from zero to moderate intake (20–30 mg/day) and a leveling-off thereafter based on a conditional logistic regression model (Fig. 1). No increasing trend was found for relatively high intake.

Discussion

In these case–control studies of Japanese, Japanese Brazilians, and non-Japanese Brazilians, overall, we found an inverse association between dietary isoflavone intake and the risk of breast cancer. Our finding is in general agreement with those of a recent meta-analysis [11] and in five of the ten previous studies examining the association between isoflavone intake as estimated by FFQ and breast cancer risk [4–8]. It is noteworthy that, although several experimental studies have suggested adverse effects from soy constituents [2, 3, 13, 14], no epidemiological study estimating isoflavone intake by FFQ has reported an increased risk of breast cancer. Our study also suggests a risk-reducing rather than risk-enhancing effect of isoflavones on breast cancer within the range achievable from dietary intake alone. It remains unclear, however, whether isoflavone exposure other than dietary intake is associated with the risk of breast cancer.

We found a linear decrease in breast cancer risk from zero to moderate intake (20–30 mg/day) and thereafter a leveling-off. This dose–responses pattern might imply the

Table 2 Odds ratios (ORs) and 95% confidence intervals (CIs) of breast cancer according to dietary isoflavone intakes

	Median isoflavone intake[a]	All subjects						Premenopausal women				Postmenopausal women			
		No.		OR[b]	95% CI	OR[c]	95% CI	No.		OR[d]	95% CI	No.		OR[d]	95% CI
		Case	Control					Case	Control			Case	Control		
Japanese living in Nagano, Japan															
Tertile 1	22.1	152	129	1.00		1.00		80	67	1.00		72	62	1.00	
Tertile 2	39.6	118	131	0.75	(0.53–1.07)	0.86	(0.59–1.27)	52	44	0.99	(0.58–1.71)	66	87	0.79	(0.48–1.29)
Tertile 3	69.1	120	130	0.75	(0.52–1.10)	0.83	(0.54–1.28)	46	26	1.35	(0.72–2.54)	74	104	0.62	(0.38–1.01)
P for trend				0.12		0.39				0.41				0.06	
Japanese Brazilians living in São Paulo, Brazil															
Tertile 1	4.7	41	26	1.00		1.00									
Tertile 2	13.4	25	28	0.51	(0.23–1.15)	0.48	(0.20–1.16)								
Tertile 3	42.8	15	27	**0.35**	**(0.15–0.80)**	**0.25**	**(0.09–0.68)**								
P for trend				**0.01**		**<0.01**									
Median 1	8.0	48	40	1.00		1.00		16	10	1.00		32	30	1.00	
Median 2	35.0	33	41	0.68	(0.37–1.26)	0.52	(0.26–1.06)	9	14	**0.17**	**(0.03–0.84)**	24	27	0.84	(0.37–1.92)
Non-Japanese Brazilians living in São Paulo, Brazil															
Non-consumers	0	343	318	1.00		1.00		147	124	1.00		196	194	1.00	
Consumers	15.0	36	61	**0.54**	**(0.34–0.84)**	**0.56**	**(0.35–0.90)**	14	21	0.54	(0.26–1.13)	22	40	0.58	(0.33–1.03)

[a] Crude intake (mg/day)

[b] Crude OR

[c] Conditional model adjusting for menopausal status (premenopausal women, postmenopausal women), number of births (0, 1, 2, 3, 4, 5+), family history of breast cancer (yes, no), smoking status (never, past, current smokers), moderate physical activity in the past 5 years (no, less than 3 days/month, 1–4 days/week, more than 5 days/week), and vitamin supplement use (yes, no)

[d] Unconditional model adjusting for matching factors (age and area for Japanese; age and hospital for Japanese Brazilians; age and ethnicity for non-Japanese Brazilians), number of births (0, 1, 2, 3, 4, 5+), family history of breast cancer (yes, no), smoking status (never, past, current smokers), moderate physical activity in the past 5 years (no, less than 3 days/month, 1–4 days/week, more than 5 days/week), and vitamin supplement use (yes, no)

Bold characters indicates statistically significant values

Table 3 Odds ratios (ORs) and 95% confidence intervals (CIs) of hormone receptor-defined breast cancer according to dietary isoflavone intakes

	No. of controls	ER+/PR+			ER+/PR−			ER−/PR−			Unknown		
		No. of cases	OR[a]	95% CI	No. of cases	OR[a]	95% CI	No. of cases	OR[a]	95% CI	No. of cases	OR[a]	95% CI
Japanese living in Nagano, Japan, all subjects													
Tertile 1	129	82	1.00		23	1.00		38	1.00				
Tertile 2	131	70	0.98	(0.64–1.51)	24	1.10	(0.58–2.08)	21	0.58	(0.32–1.07)			
Tertile 3	130	67	0.97	(0.62–1.51)	22	0.71	(0.36–1.43)	28	0.71	(0.40–1.28)			
P for trend			0.89			0.35			0.23				
Japanese living in Nagano, Japan, premenopausal women													
Tertile 1	67	46	1.00		8	1.00		18	1.00				
Tertile 2	44	40	1.35	(0.74–2.46)	4	0.80	(0.22–2.89)	6	0.47	(0.17–1.32)			
Tertile 3	26	27	1.51	(0.74–3.07)	7	1.64	(0.48–5.58)	10	0.94	(0.34–2.56)			
P for trend			0.22			0.52			0.65				
Japanese living in Nagano, Japan, postmenopausal women													
Tertile 1	62	36	1.00		15	1.00		20	1.00				
Tertile 2	87	30	0.68	(0.37–1.25)	20	1.25	(0.57–2.73)	15	0.65	(0.30–1.44)			
Tertile 3	104	40	0.68	(0.38–1.22)	15	0.53	(0.22–1.26)	18	0.57	(0.27–1.22)			
P for trend			0.21			0.14			0.15				
Japanese Brazilians living in São Paulo, Brazil, all subjects													
Median 1	40	24	1.00		7	1.00		7	1.00		9	1.00	
Median 2	41	16	0.63	(0.27–1.45)	2	0.22	(0.04–1.36)	4	0.34	(0.08–1.49)	11	1.24	(0.38–4.03)
Non-Japanese Brazilians living in São Paulo, Brazil, all subjects													
Non-consumers	318	97	1.00		41	1.00		76	1.00		108	1.00	
Consumers	61	8	0.46	(0.21–1.004)	9	1.10	(0.50–2.41)	10	0.67	(0.33–1.40)	7	**0.35**	**(0.16–0.80)**

[a] Unconditional model adjusting for matching factors (age and area for Japanese; age and hospital for Japanese Brazilians; age and ethnicity for non-Japanese Brazilians), menopausal status (premenopausal women, postmenopausal women), number of births (0, 1, 2, 3, 4, 5+), family history of breast cancer (yes, no), smoking status (never, past, current smokers), moderate physical activity in past 5 years (no, less than 3 days/month, 1–4 days/week, more than 5 days/week), and vitamin supplement use (yes, no)

Bold characters indicates statistically significant values

Table 4 Odds ratios (ORs) and 95% confidence intervals (CIs) of breast cancer according to dietary isoflavone intake based on combined individual study data from three populations

	Non-consumers and quintile category among consumers						*P* for trend
	0	1	2	3	4	5	
Median isoflavone intake (mg/day)[a]	0	8.7	23.1	33.8	45.7	71.3	
Japanese living in Nagano, Japan							
No. of cases/No. of controls	0/0	49/31	93/90	89/85	72/96	87/88	
Japanese Brazilians living in São Paulo, Brazil							
No. of cases/No. of controls	9/5	46/41	16/12	3/8	1/6	6/9	
Non-Japanese Brazilians living in São Paulo, Brazil							
No. of cases/No. of controls	343/318	27/33	5/3	2/13	2/3	0/9	
All subjects in three populations							
No. of cases/No. of controls	352/323	122/105	114/105	94/106	75/105	93/106	
OR	1.00	0.69	**0.54**	**0.45**	**0.34**	**0.43**	**<0.01**
(95% CI)[b]		(0.44–1.09)	**(0.31–0.94)**	**(0.26–0.77)**	**(0.19–0.62)**	**(0.24–0.76)**	
Premenopausal women in three populations							
No. of cases/No. of controls	150/127	48/37	58/52	49/37	23/30	36/23	
OR	1.00	0.68	0.44	0.54	**0.27**	0.62	0.27
(95% CI)[c]		(0.33–1.39)	(0.19–1.01)	(0.24–1.24)	**(0.10–0.69)**	(0.25–1.54)	
Postmenopausal women in three populations							
No. of cases/No. of controls	202/196	74/68	56/53	45/69	52/75	57/83	
OR	1.00	0.70	0.52	**0.31**	**0.34**	**0.33**	**<0.01**
(95% CI)[c]		(0.40–1.24)	(0.26–1.04)	**(0.15–0.64)**	**(0.17–0.71)**	**(0.16–0.66)**	

[a] Energy adjusted by residual method

[b] Conditional model adjusting for menopausal status (premenopausal women, postmenopausal women), number of births (0, 1, 2, 3, 4, 5+), family history of breast cancer (yes, no), smoking status (never, past, current smokers), moderate physical activity in the past 5 years (no, less than 3 days/month, 1–4 days/week, more than 5 days/week), and vitamin supplement use (yes, no)

[c] Unconditional model adjusting for age (continuous), study population (Japanese living in Nagano, Japan; Japanese Brazilians living in São Paulo, Brazil; non-Japanese Brazilians living in São Paulo, Brazil), number of births (0, 1, 2, 3, 4, 5+), family history of breast cancer (yes, no), smoking status (never, past, current smokers), moderate physical activity in the past 5 years (no, less than 3 days/month, 1–4 days/week, more than 5 days/week), and vitamin supplement use (yes, no)

Bold characters indicates statistically significant values

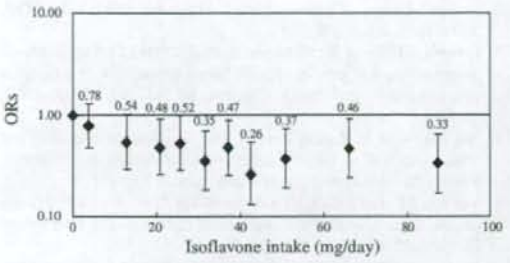

Fig. 1 Odds ratios (ORs) and 95% confidence intervals of breast cancer according to dietary isoflavone intake based on combined individual data from three populations. Subjects were categorized into 11 groups: non-consumers and deciles of isoflavone consumers based on the control distribution. ORs were estimated using matching pairs with adjustment for menopausal status (premenopausal women, postmenopausal women), number of births (0, 1, 2, 3, 4, 5+), family history of breast cancer (yes, no), smoking status (never, past, current smokers), moderate physical activity in the past 5 years (no, less than 3 days/month, 1–4 days/week, more than 5 days/week), and vitamin supplement use (yes, no)

presence of a ceiling effect and suggests that women may benefit from risk reduction if they consume at least a moderate amount of isoflavones. Alternatively, it might merely reflect differences in measurement errors due to the use of different FFQs, selection bias, and residual confounding among the three populations, notwithstanding that it clearly reflected the results of separate analyses. Specifically, consumers had lower risk than non-consumers in non-Japanese Brazilians, whose average intake of isoflavone was 4.4 mg/day among the control group; the risk of breast cancer decreased with increasing intake of isoflavone in Japanese Brazilians, whose average intake of isoflavone was 24.9 mg/day among the control group; while higher intake of isoflavone was not associated with further risk reduction in Japanese, whose average intake of isoflavone was 46.1 mg/day among the control group. Confirmation of this pattern would require further prospective cohort studies using blood or urine samples as an exposure assessment, because these could minimize the measurement errors and selection bias mentioned above.

Our stratified analysis by menopausal status using data from the three populations combined showed that an inverse association was more prominent among postmenopausal than premenopausal women. In addition, our separate analyses showed somewhat different patterns in the three populations: the inverse association was limited to postmenopausal women in Japanese; it was stronger in premenopausal than postmenopausal women in Japanese Brazilians; and no remarkable difference was found in non-Japanese Brazilians. These findings are inconsistent with a recent meta-analysis showing an inverse association regardless of menopausal status [11]. Moreover, findings to date on the association of isoflavone intake and the risk of breast cancer stratified by menopausal status have been inconsistent, with one prospective cohort study in Japan [4] and one case–control study in the United States [8] reporting that an inverse association was limited to postmenopausal women; one case–control study in Japan [5] showing it was limited to premenopausal women; and one prospective cohort study in the United States [16] and three case–control studies [6, 17, 18] finding no difference between the two strata.

Several mechanisms by which isoflavones may reduce the risk of breast cancer have been proposed [2, 3]. The most prominent and thoroughly investigated mechanisms are mediated via estrogen receptors, arising due to the similar chemical structure of isoflavones to the human estrogen hormone and their binding affinity to estrogen receptors [3, 29]. Given that the action of estrogen on breast cell proliferation appears to be mediated by estrogen receptors, therefore, any association between isoflavone intake and breast cancer risk might differ by hormone receptor-defined subtype. The present study did not support this hypothesis, however, showing no apparent difference in risk by subtype. Moreover, results for the few studies to date have been inconsistent [7, 16, 18, 19]. Although our findings might merely be explained by a lack of statistical power, they suggest that the anti-cancer effects of isoflavones might be evoked not only by mechanisms mediated by estrogen receptors but also by other mechanisms, such as the modulation of endogenous hormones via inhibition of the key enzyme involved in estrogen biosynthesis and metabolism; the arrest of cell cycle progression; induction of apoptosis; inhibition of tyrosine kinase activity, topoisomerase II activity, and angiogenesis; and antioxidant activity [2, 3].

Our study has several methodological advantages over previous studies of isoflavones and the risk of breast cancer. First, isoflavone intake differed considerably among the three populations, with median levels (interquartile rage) in the control group (mg/day) of 40.6 (25.9–61.2) among Japanese, 13.4 (8.1–35.0) among Japanese Brazilians, and 0 (0–0) among non-Japanese Brazilians. This range allowed the detailed evaluation of dose–response relations, ranging from zero to a relatively high level achievable from dietary intake only, and is unique to the present study. Second, the overall consistency of findings in the three populations allowed for the greater generalizability of results as compared to those from a single population.

Several limitations of this study warrant mention. First, dietary intake of isoflavone was assessed after the diagnosis of breast cancer and is therefore sensitive to recall bias. Second, although the substantially high participation rates among both eligible cases and controls minimized potential biases related to control selection, the use of controls from

medical checkup examinees and cancer-free patients, whose dietary habits may differ from the general population due to health consciousness or disease, might have lead to selection bias. Third, stratified analyses were performed based on a relatively small number of cases. The interpretability of our results might therefore be limited.

Allowing for these methodological issues, we found an inverse association between dietary isoflavone intake and the risk of breast cancer in case–control studies of Japanese, Japanese Brazilians, and non-Japanese Brazilians. Our findings suggest a risk-reducing rather than risk-enhancing effect of isoflavones on breast cancer within the range achievable from dietary intake alone. In addition, women may benefit from risk reduction if they consume at least moderate amounts of isoflavones.

Acknowledgments This study was supported by a Grant-in-Aid for Research on Risk of Chemical Substances from the Ministry of Health, Labour and Welfare of Japan, and Grants-in-Aid for Scientific Research on Priority Areas (17015049) and for Young Scientists (B) (17790378 and 19790415) from the Ministry of Education, Culture, Sports, Science, and Technology of Japan and the Japan Society for the Promotion of Science. We are grateful to the participants in the "São Paulo-Japan Breast Cancer Study Group": C. I. Yamaguchi, C. M. Kunieda, and S. S. Sugama (Nikkei Disease Prevention Center, São Paulo); C. K. Taniguchi and J. A. Marques (Departamento de Ginecologia, Hospital Pérola Byington, São Paulo); M. R. Eichhorn (Departamento de Nutrição, Hospital Pérola Byington, São Paulo); H. Iyeyasu, M. S. Maciel, S. M. T. Carvalho, J. B. D. Collins, and C. E. M. Fontes (Departamento de Mastologia, Hospital A.C. Camargo, São Paulo); L. P. Kowalski and J. M. F. Toyota (Departamento de Cirurgia de Cabeça e Pescoço e Otorrinolaringologia, A. C. Camargo Hospital, São Paulo); E. M. Barbosa (Departamento de Mastologia, Instituto Brasileiro de Controle ao Câncer, São Paulo); O. Ferraro (Departamento de Mastologia, Hospital do Servidor Público Estadual Francisco Morato de Oliveira, São Paulo); R. Anzai (Departamento de Mastologia, Hospital Santa Cruz); E. H. Hotta and D. A. Petti (Instituto de Ginecologia e Mastologia, Hospital Beneficencia Portuguesa); S. Mendes (Instituto Brasileiro de Mastologia e Ginecologia, Hospital Beneficencia Portuguesa).

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J Epidemiol 2008; 18(6) 251-264
doi:10.2188/jea.JE2007429

Original Article

Population Attributable Fraction of Mortality Associated with Tobacco Smoking in Japan: A Pooled Analysis of Three Large-scale Cohort Studies

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Received October 23, 2007; accepted April 23, 2008; released online December 9, 2008

ABSTRACT

Background: Quantitative measures of the burden of tobacco smoking in Asian countries are limited. We estimated the population attributable fraction (PAF) of mortality associated with smoking in Japan, using pooled data from three large-scale cohort studies.

Methods: In total, 296,836 participants (140,026 males and 156,810 females) aged 40-79 years underwent baseline surveys during the 1980s and early 1990s. The average follow-up period was 9.6 years. PAFs for all-cause mortality and individual tobacco-related diseases were estimated from smoking prevalence and relative risks.

Results: The prevalence of current and former smokers was 54.4% and 25.1% for males, and 8.1% and 2.4% for females. The PAF of all-cause mortality was 27.8% [95% confidence interval (CI): 25.2-30.4] for males and 6.7% (95% CI: 5.9-7.5) for females. The PAF of all-cause mortality calculated by summing the disease-specific PAFs was 19.1% (95% CI: 16.0-22.2) for males and 3.6% (95% CI: 3.0-4.2) for females. The estimated number of deaths attributable to smoking in Japan in 2005 was 163,000 for males and 33,000 for females based on the former set of PAFs, and 112,000 for males and 19,000 for females based on the latter set. The leading causes of smoking-attributable deaths were cancer (61% for males and 31% for females), ischemic heart diseases and stroke (23% for males and 51% for females), and chronic obstructive pulmonary diseases and pneumonia (11% for males and 13% for females).

Conclusion: The health burden due to smoking remains heavy among Japanese males. Considering the high prevalence of male current smokers and increasing prevalence of young female current smokers, effective tobacco controls and quantitative assessments of the health burden of smoking need to be continuously implemented in Japan.

Key words: Cohort Studies, Population, Risk, Smoking.

INTRODUCTION

Smoking is a major preventable cause of premature mortality. Estimating the mortality attributable to smoking is necessary in order to assess the health burden that it causes within a population, and such estimates have accordingly been performed in many countries and regions.[1-5] In Japan, recent studies have estimated the population impact of smoking on selected causes of death, including all causes,[6] all cancers,[7] lung cancer,[8] pancreatic cancer,[9] and cardiovascular diseases.[10] Since smoking causes many diseases, including numerous other types of cancer and cardiovascular, respiratory, and digestive diseases,[11,12] a comprehensive approach is needed to fully understand its health burden. Single cohort studies, however, do not include sufficiently large sample sizes to enable examination of the health effects

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of smoking on diseases with low mortality or incidence rates, particularly among populations with a low prevalence of smoking such as Japanese females. A historical large-scale cohort study in Japan, the Hirayama study, estimated the fraction of deaths attributable to smoking for many diseases among approximately 265,000 participants.[13] The baseline survey for the Hirayama study was conducted in 1965, and the follow-up was continued until the end of 1982. In the nearly 40 years since the Hirayama study began, the list of diseases known to be caused by smoking has been altered and expanded.[12] The purpose of the present study was, therefore, to estimate the population attributable fraction (PAF) of mortality caused by smoking in Japan in a comprehensive manner, based on the updated list of smoking-related diseases, and using data from nearly 300,000 participants of three large-scale Japanese cohort studies.

METHODS

Study Population

The present study used pooled data from three ongoing prospective studies in Japan: (1) the Japan Public Health Center-based Prospective Study (JPHC study),[14] which comprises two different cohorts (JPHC-I and JPHC-II) with different baseline survey years; (2) the Three-Prefecture Cohort Study (3-pref study);[15] and (3) the Japan Collaborative Cohort Study (JACC study).[16,17] For each cohort, we collected baseline and follow-up data from each of the participants aged 40-79 years at baseline (40-59 years for the JPHC-I cohort, 40-69 years for the JPHC-II cohort, and 40-79 years for the 3-pref and JACC cohorts). The numbers of participants in the original dataset collected from each cohort were 61,595 for the JPHC-I cohort, 78,825 for the JPHC-II cohort, 108,774 for the 3-pref cohort, and 110,792 for the JACC cohort. For participant selection, we applied the following exclusion criteria: (1) moving out of the study area before the beginning of the follow-up, (2) ineligible age (younger than 40 years or older than 80 years), and (3) unknown outcome. We applied the following additional exclusion criteria to the data from the JPHC-I and JPHC-II cohorts: (1) foreign nationality, (2) refusal to participate in the follow-up, (3) duplicate registration, and (4) unavailability of baseline questionnaire data. The number of participants in each cohort after the exclusion criteria had been applied was 50,217 for the JPHC-I, 63,189 for the JPHC-II, 104,876 for the 3-pref, and 110,792 for the JACC. From the combined 329,074 (148,929 males and 180,145 females) participants, we excluded 4,283 (1,719 males and 2,564 females) duplicates who were enrolled in both the 3-pref study and the JACC study, and 27,955 (7,184 males and 20,771 females) participants who had incomplete smoking data. As a result, 296,836 participants (140,026 males and 156,810 females) were included in the analysis, which covered 26 of Japan's 47 prefectures (55%). The characteristics of the participants included in the analysis are summarized in Table 1. This pooled study was approved by the institutional review board of the National Cancer Center, Japan.

Smoking Assessment

In each of the three studies, smoking habits were assessed by self-administered questionnaires. Although the style of the questions differed slightly,[18] all of the studies included questions concerning current smoking status, age at initiation of smoking, average number of cigarettes smoked per day, and age at cessation of smoking for former smokers. The smoking status at baseline was classified into three categories: never-smoker, current smoker, and former smoker. Current smokers included occasional smokers (JPHC-I and 3-pref studies).

Follow-up

The average follow-up period was 9.6 [standard deviation (SD): 2.3] years (Table 1). Residential status, including survival, date of death, and date of moving out of the study area, was confirmed through the residential registries kept in the municipalities of the study areas. Information on the cause of death was confirmed by vital statistics files obtained with official permission.

Causes of Death

The endpoint of the present study was defined as death during the observation period. We selected the causes of death from the diseases judged to be "causally related" to active smoking in the Surgeon General's report of 2004[12] or the International Agency for Research on Cancer (IARC) Monograph volume 83,[11] and grouped these into "tobacco-related diseases" (the ICD-9 and ICD-10 codes are listed in the Appendix). We also analyzed all-cause deaths and the following four major disease groups: all cancers, all cardiovascular diseases (CVDs), all respiratory system diseases, and all digestive system diseases.

Statistical Analysis

The person-years of follow-up were calculated from the date of the baseline questionnaire to whichever of the following events occurred first: the end of the follow-up for each study, the date of death, or the date of moving out of the study area. The hazard ratio (HR) and 95% confidence interval (CI) were used to describe the relative risk for current, former, and ever-smokers compared with never-smokers. The Cox proportional hazards model was used to adjust for age (continuous variable), using the SAS® PHREG procedure (version 8.02, The SAS Institute, USA).

In order to express the impact of tobacco smoking on the study population, the PAF (%) was estimated for all causes and specific causes of death. For each disease group, the PAF was calculated using the following equation:

Table 1. Characteristics of the pooled cohort studies and participants

Cohort	Area	Participants characteristics	Baseline year	End of follow-up	Average follow-up years (SD)	Sex	n	Age at baseline (year)			Smoking status at baseline (%)					
								Average	(SD)	Range	Current		Former		Never	
JPHC-I	5 public health center areas in Iwate, Akita, Nagano, Okinawa, and Tokyo prefectures	Residents in each public health center area in the first 4 prefectures; participants of a health checkup in Tokyo Prefecture	1990	December 31, 2000	10.4 (1.6)	Male	23,478	49.0	(6.0)	40-59	12,589	(53.6%)	5,428	(23.1%)	5,461	(23.3%)
			(One area†: 1990-1994)			Female	26,561	49.1	(5.9)	40-59	2,090	(7.9%)	656	(2.5%)	23,815	(89.7%)
JPHC-II	6 public health center areas in Ibaraki, Niigata, Kochi, Nagasaki, Okinawa, and Osaka prefectures	Residents in each public health center area in the first 5 prefectures; participants of a health checkup in Osaka Prefecture	1993-1994	December 31, 2003	10.2 (1.7)	Male	29,567	53.2	(8.8)	40-69	15,383	(52.0%)	7,246	(24.5%)	6,938	(23.5%)
						Female	33,175	53.5	(8.9)	40-69	2,435	(7.3%)	502	(1.5%)	30,238	(91.1%)
3-pref	10 cities, towns, or wards in Miyagi, Aichi, and Osaka prefectures	Residents in each area	Feb. 1, 1983-Nov 1, 1985	Jan. 31, 1993-Oct. 31, 1995	8.5 (2.7)	Male	44,453	54.4	(10.2)	40-79	25,699	(57.8%)	11,164	(25.1%)	7,590	(17.1%)
			(One area‡: Dec. 1, 1990)	(One area‡: Feb. 28, 2000)		Female	43,704	55.2	(10.5)	40-79	5,188	(11.9%)	1,631	(3.7%)	36,885	(84.4%)
JACC	45 cities, towns, or villages in 18 prefectures* throughout Japan, except Shikoku district	Residents in 22 areas; participants of a health checkup in 20 areas; combination of these two or atomic bomb survivors in the remaining 3 areas	1988-1990	December 31, 1999	9.9 (2.2)	Male	42,526	57.3	(10.2)	40-79	22,556	(53.0%)	11,241	(26.4%)	8,731	(20.5%)
						Female	53,370	57.3	(10.1)	40-79	3,004	(5.6%)	925	(1.7%)	49,441	(92.6%)
Pooled					9.6 (2.3)	Male	140,026	54.1	(9.7)	40-79§	76,227	(54.4%)	35,079	(25.1%)	28,720	(20.5%)
						Female	156,810	54.5	(9.8)	40-79§	12,717	(8.1%)	3,714	(2.4%)	140,379	(89.5%)

JPHC: Japan Public Health Center-based prospective study, 3-pref: Three-prefecture cohort study, JACC: Japan Collaborative Cohort Study
*: Hokkaido, Akita, Ibaraki, Tochigi, Chiba, Kanagawa, Niigata, Yamanashi, Nagano, Gifu, Shiga, Kyoto, Hyogo, Wakayama, Tottori, Hiroshima, Fukui, and Saga prefectures
†: Katsushika area in Tokyo Prefecture.
‡: Izumi-otsu in Osaka Prefecture.
§: The age distribution (40-49, 50-59, 60-69, and 70-79 years old) of the pooled data was as follows; 35.9%, 35.3%, 21.3%, and 7.5% for males; 34.2%, 35.5%, 22.3%, and 8.0% for females.
SD: standard deviation

$PAF = P_d (HR_a - 1)/HR_a$, (1)

where P_d is the proportion of exposed among those who died of a given cause of death, and HR_a is the age-adjusted HR for that cause of death.[19] The Greenland formula was used to calculate the 95% CI for the PAF.[20] For all-cause mortality, the PAF was calculated in two ways. The first was by equation (1) using the HR for all-cause mortality. The second was by calculating the weighted sum of the PAF for each disease as follows:

$PAF_{all\text{-}cause} = \Sigma (PAF_i \times D_i)/D_{all}$, (2)

where PAF_i and D_i indicate the PAF and the number of deaths, respectively, for each tobacco-related disease i, and D_{all} indicates the number of all-cause deaths. It should be noted that equation (2) assumes that the PAF for diseases other than tobacco-related diseases is zero. The PAF for "total tobacco-related diseases" was calculated by equation (1) using the HR for overall mortality from tobacco-related diseases.

The annual number of smoking-attributable deaths in Japan was calculated using the vital statistics data of 2005 using two methods: first, by multiplying the sex-specific total number of deaths in Japan by the PAF of ever-smoking for all-cause mortality calculated by equation (1); and, second, by summing the sex-specific number of deaths from each tobacco-related disease in Japan weighted by the corresponding PAF of ever-smoking. Since the number of deaths from abdominal aortic aneurysm was not available in the published data, the number of deaths and the PAF of aortic aneurysm and dissection were used instead.

RESULTS

The prevalence of current and former smoking at baseline among the pooled participants was 54.4% and 25.1% for males and 8.1% and 2.4% for females, respectively (Table 1).

During the 2,855,396 person-years of follow-up (1,325,004 males and 1,530,392 females) for 296,836 participants, a total of 25,700 deaths (male: 16,282, female: 9,418) were recorded. The numbers of deaths from major causes for males were 6,505 (40.0%) for cancer, 4,306 (26.4%) for CVD, 1,587 (9.7%) for respiratory system diseases, and 596 (3.7%) for

Table 2. Disease-specific, age-adjusted hazard ratio according to smoking status for males

Cause of death	Age-adjusted hazard ratio (vs. never-smokers) (95% confidence interval)†					
	Current smokers		Former smokers		Ever-smokers	
All-cause	1.63	(1.56 - 1.70)	1.27	(1.21 - 1.33)	1.49	(1.43 - 1.55)
Total tobacco-related diseases	1.85	(1.74 - 1.97)	1.40	(1.30 - 1.50)	1.67	(1.57 - 1.78)
All cancers	1.97	(1.83 - 2.13)	1.50	(1.38 - 1.63)	1.79	(1.67 - 1.93)
Total tobacco-related cancers	2.32	(2.12 - 2.54)	1.64	(1.49 - 1.82)	2.06	(1.89 - 2.26)
Lip, oral cavity, and pharynx*	2.66	(1.48 - 4.77)	1.89	(1.00 - 3.58)	2.37	(1.34 - 4.20)
Esophagus*	3.39	(2.25 - 5.09)	2.22	(1.43 - 3.46)	2.96	(1.98 - 4.42)
Stomach*	1.51	(1.29 - 1.77)	1.28	(1.08 - 1.52)	1.42	(1.22 - 1.66)
Liver*	1.81	(1.49 - 2.20)	1.63	(1.32 - 2.01)	1.74	(1.44 - 2.11)
Pancreas*	1.58	(1.18 - 2.11)	1.19	(0.86 - 1.65)	1.43	(1.08 - 1.90)
Larynx*	5.47	(1.29 - 23.11)	3.03	(0.65 - 14.01)	4.50	(1.08 - 18.72)
Lung*	4.79	(3.88 - 5.92)	2.41	(1.91 - 3.03)	3.85	(3.12 - 4.74)
Kidney, except renal pelvis*	1.57	(0.81 - 3.06)	1.46	(0.71 - 3.00)	1.53	(0.81 - 2.90)
Renal pelvis, ureter, bladder*	5.35	(2.47 - 11.57)	2.76	(1.21 - 6.31)	4.30	(2.01 - 9.23)
Myeloid leukemia*	1.45	(0.74 - 2.82)	2.13	(1.07 - 4.25)	1.69	(0.89 - 3.18)
All cardiovascular diseases	1.52	(1.39 - 1.65)	1.17	(1.07 - 1.29)	1.38	(1.27 - 1.49)
Total tobacco-related cardiovascular diseases	1.51	(1.36 - 1.68)	1.19	(1.06 - 1.33)	1.38	(1.25 - 1.53)
Ischemic heart diseases*	2.18	(1.79 - 2.66)	1.71	(1.39 - 2.12)	2.00	(1.65 - 2.42)
Total stroke*	1.25	(1.10 - 1.42)	1.00	(0.87 - 1.14)	1.15	(1.02 - 1.29)
Subarachnoid hemorrhage	2.33	(1.50 - 3.64)	1.19	(0.71 - 2.02)	1.94	(1.25 - 3.00)
Intracerebral hemorrhage	1.24	(0.98 - 1.57)	0.91	(0.69 - 1.19)	1.11	(0.89 - 1.40)
Cerebral infarction	1.23	(1.02 - 1.50)	1.02	(0.82 - 1.26)	1.14	(0.95 - 1.37)
Aortic aneurysm and dissection	3.89	(2.02 - 7.49)	2.71	(1.35 - 5.42)	3.42	(1.80 - 6.51)
Abdominal aortic aneurysm*	3.89	(1.38 - 10.99)	1.64	(0.52 - 5.24)	2.94	(1.05 - 8.18)
All respiratory diseases	1.41	(1.22 - 1.62)	1.37	(1.18 - 1.59)	1.39	(1.22 - 1.59)
Total toabacco-related respiratory diseases	1.35	(1.15 - 1.59)	1.25	(1.05 - 1.48)	1.30	(1.12 - 1.52)
Pneumonia*	1.17	(0.98 - 1.39)	1.09	(0.91 - 1.31)	1.13	(0.96 - 1.33)
Chronic obstructive pulmonary diseases*	3.09	(1.90 - 5.03)	2.76	(1.68 - 4.55)	2.95	(1.84 - 4.72)
All digestive diseases	2.04	(1.60 - 2.60)	1.22	(0.92 - 1.62)	1.74	(1.37 - 2.21)
Peptic ulcer*	7.13	(1.71 - 29.78)	1.96	(0.40 - 9.72)	5.01	(1.21 - 20.77)

*: Tobacco-related diseases selected from the Surgeon General's Report of 2004 and IARC Monograph volume 83.
†: Cox proportional hazard model

digestive system diseases. The numbers of deaths from major causes for females were 3,475 (36.9%) for cancer, 2,904 (30.8%) for CVD, 681 (7.2%) for respiratory system diseases, and 320 (3.4%) for digestive system diseases.

Age-Adjusted HR According to Smoking Status

Table 2 shows the disease-specific, age-adjusted HRs for males according to smoking status. Current smokers had a nearly 1.5-fold higher age-adjusted rate of mortality from all causes, all CVDs, and all respiratory diseases, and a nearly 2.0-fold higher mortality from total tobacco-related diseases, all cancers, and all digestive diseases compared with never-smokers. Among the tobacco-related cancer sites, the larynx exhibited the highest HR point estimate, followed by the urinary tract (renal pelvis, ureter, and bladder), lung, esophagus, lip/oral cavity/pharynx, liver, pancreas, and stomach. Among CVDs, ischemic heart disease (IHD) had a higher HR than stroke. When divided into stroke subtypes, subarachnoid hemorrhage had the highest HR, followed by intracerebral hemorrhage and cerebral infarction. Abdominal aortic aneurysm had an even higher HR; however, this ratio had a wide CI. Chronic obstructive pulmonary diseases (COPD) and peptic ulcer had HRs of 3.0 or higher.

The excess risks for male former smokers were lower than those for male current smokers. The former smokers had lower HRs than the current smokers for the four major disease groups (cancer, CVD, respiratory, and digestive diseases), and also for the subgroups within each category, except myeloid leukemia.

Table 3 shows the disease-specific, age-adjusted HRs for females according to smoking status. The HRs of the current smokers (vs. never-smokers) were nearly 1.7 for all causes, all cancers, and all respiratory diseases, and nearly 2.0 for total tobacco-related diseases, all CVDs, and all digestive diseases. Among the tobacco-related cancer sites, the lung exhibited the highest HR for current smokers, followed by the cervix uteri, lip/oral cavity/pharynx, esophagus, urinary tract, pancreas, liver, and stomach, of which the lung, cervix uteri, pancreas, and liver were significant. As observed for males, IHD had a higher HR than stroke, and subarachnoid hemorrhage had the

Table 3. Disease-specific, age-adjusted hazard ratio according to smoking status for females.

Cause of death	Age-adjusted hazard ratio (vs. never-smokers) (95% confidence interval)†					
	Current smokers		Former smokers		Ever-smokers	
All-cause	1.76	(1.65 - 1.87)	1.68	(1.52 - 1.86)	1.73	(1.64 - 1.83)
Total tobacco-related diseases	2.00	(1.83 - 2.19)	1.65	(1.42 - 1.91)	1.90	(1.75 - 2.06)
All cancers	1.57	(1.41 - 1.75)	1.57	(1.32 - 1.87)	1.57	(1.43 - 1.73)
Total tobacco-related cancers	2.01	(1.76 - 2.30)	1.70	(1.35 - 2.14)	1.93	(1.71 - 2.17)
Lip, oral cavity, and pharynx*	1.97	(0.69 - 5.65)	1.23	(0.17 - 9.12)	1.76	(0.68 - 4.59)
Esophagus*	1.90	(0.74 - 4.86)	3.59	(1.27 - 10.16)	2.40	(1.15 - 5.02)
Stomach*	1.22	(0.90 - 1.64)	1.47	(0.95 - 2.27)	1.29	(1.00 - 1.66)
Liver*	1.73	(1.21 - 2.48)	1.23	(0.63 - 2.39)	1.59	(1.15 - 2.20)
Pancreas*	1.81	(1.28 - 2.57)	1.96	(1.16 - 3.30)	1.85	(1.37 - 2.50)
Larynx*	0.00	- -	0.00	- -	0.00	- -
Lung*	3.88	(3.07 - 4.90)	2.63	(1.72 - 4.03)	3.55	(2.86 - 4.40)
Cervix uteri*	2.32	(1.31 - 4.10)	1.00	(0.25 - 4.09)	1.99	(1.16 - 3.41)
Kidney, except renal pelvis*	0.60	(0.08 - 4.47)	1.55	(0.21 - 11.52)	0.86	(0.20 - 3.69)
Renal pelvis, ureter, bladder*	1.86	(0.84 - 4.11)	0.00	- -	1.30	(0.59 - 2.88)
Myeloid leukemia*	0.96	(0.30 - 3.10)	0.96	(0.13 - 7.01)	0.96	(0.34 - 2.68)
All cardiovascular diseases	1.98	(1.78 - 2.21)	1.60	(1.34 - 1.91)	1.87	(1.70 - 2.06)
Total tobacco-related cardiovascular diseases	2.09	(1.83 - 2.39)	1.66	(1.33 - 2.07)	1.97	(1.75 - 2.21)
Ischemic heart diseases*	2.95	(2.33 - 3.73)	2.48	(1.71 - 3.60)	2.81	(2.28 - 3.46)
Total stroke*	1.80	(1.52 - 2.12)	1.35	(1.01 - 1.79)	1.66	(1.44 - 1.93)
Subarachnoid hemorrhage	2.79	(2.06 - 3.78)	1.05	(0.50 - 2.24)	2.33	(1.75 - 3.11)
Intracerebral hemorrhage	1.92	(1.39 - 2.67)	1.69	(0.99 - 2.89)	1.86	(1.39 - 2.48)
Cerebral infarction	1.48	(1.10 - 2.00)	1.17	(0.72 - 1.91)	1.39	(1.07 - 1.80)
Aortic aneurysm and dissection	2.35	(1.16 - 4.79)	3.16	(1.25 - 7.95)	2.59	(1.43 - 4.69)
Abdominal aortic aneurysm*	4.30	(1.16 - 15.96)	6.51	(1.39 - 30.39)	4.98	(1.66 - 14.94)
All respiratory diseases	1.65	(1.29 - 2.09)	1.27	(0.85 - 1.89)	1.53	(1.24 - 1.90)
Total toabacco-related respiratory diseases	1.53	(1.13 - 2.07)	1.39	(0.88 - 2.21)	1.49	(1.15 - 1.93)
Pneumonia*	1.39	(1.00 - 1.93)	1.40	(0.87 - 2.26)	1.40	(1.06 - 1.84)
Chronic obstructive pulmonary diseases*	3.55	(1.53 - 8.21)	1.16	(0.16 - 8.54)	2.82	(1.27 - 6.26)
All digestive diseases	2.13	(1.54 - 2.94)	2.10	(1.28 - 3.43)	2.12	(1.60 - 2.81)
Peptic ulcer*	1.37	(0.32 - 5.94)	1.50	(0.20 - 11.31)	1.42	(0.42 - 4.82)

*: Tobacco-related diseases selected from the Surgeon General's Report of 2004 and IARC Monograph volume 83.
†: Cox proportional hazard model

highest HR among the stroke subtypes, followed by intracerebral hemorrhage and cerebral infarction. A tendency toward a higher HR for abdominal aortic aneurysm was also observed among females. COPD had the highest HR among respiratory and digestive diseases. For total tobacco-related diseases and all CVDs, the HRs of former smokers were smaller than those of current smokers. The HRs of former smokers (vs. never-smokers) were similar to, or higher than, those of current smokers for many other diseases and all-cause mortality.

PAF of Disease-specific Mortality Due to Smoking

Figure 1 shows the male age-adjusted, disease-specific PAFs of current, former, and ever-smoking. After age-adjustment, 28% of the all-cause mortality was attributable to ever-smoking among males. For all cancers, the corresponding PAF was up to 40%. When divided into tobacco-related cancer sites, the larynx, urinary tract, and lung had PAFs of nearly 70%. The PAFs for the esophagus and the lip/oral cavity/pharynx were also greater than 50%, whereas those for the other sites ranged from 25% to 40%. The PAF for all CVDs was approximately 20%, which was smaller than that for all cancers. Among the CVDs, IHD, subarachnoid hemorrhage, and aortic aneurysm had PAFs of over 40%, whereas total stroke and its subtypes other than subarachnoid hemorrhage had PAFs of approximately 10%. The PAFs for all respiratory diseases and all digestive system diseases were approximately 20% and 40%, respectively. COPD and peptic ulcer had PAFs of over 60%.

Figure 2 shows the female age-adjusted, disease-specific PAFs of current, former, and ever-smoking. After age-adjustment, 7% of the all-cause mortality was attributable to ever-smoking among females, which was a considerably smaller proportion than that for males. For all cancers, the corresponding PAF was also approximately 5%. When divided into tobacco-related cancer sites, the lung had a relatively large PAF (20%), whereas the PAFs for the other sites were approximately 10% or less. The PAF for all CVDs was slightly larger than that for all cancers, but was less than 10%. As was the case among males, IHD, subarachnoid hemorrhage, and aortic aneurysm in females had relatively large PAFs (10-30%). The PAFs for all respiratory diseases and all digestive system diseases were 5% and 10%, respectively. COPD had a relatively large PAF of approximately 15%.

The PAF of ever-smoking for all-cause mortality, calculated by summing the disease-specific PAFs for tobacco-related diseases, was 19% for males and 4% for females. These values were smaller than those directly calculated from the relative risk of all-cause mortality (28% for males and 7% for females; Appendix).

Smoking-attributable Deaths and Diseases in Japan

Of the 1,083,796 total deaths in Japan in 2005 (584,970 males and 498,826 females),[21] 163,000 (95% CI: 147,000-178,000) male deaths and 33,000 (95% CI: 29,000-38,000) female deaths were estimated to have been caused by smoking, based on the PAF estimates calculated from the relative risk of all-cause mortality. In contrast, summing the disease-specific smoking-attributable deaths yielded smaller estimates; approximately 112,000 (95% CI: 93,000-130,000) male deaths and 19,000 (95% CI: 15,000-21,000) female deaths annually were estimated to have been caused by smoking.

Figure 3 shows the disease distribution of the latter set of estimates for smoking-attributable deaths. For males, cancer accounted for approximately 60% of the total smoking-attributable deaths, which was more than double the sum of deaths due to IHD and stroke. Lung cancer accounted for the largest percentage of male smoking-attributable deaths, followed by IHD, liver cancer, stomach cancer, upper aerodigestive (lip, oral cavity, pharynx, or esophagus) cancer, stroke, and COPD. In contrast, for females, IHD and stroke were the leading causes of smoking-attributable deaths, accounting for approximately 50%, whereas cancer accounted for approximately 30%. Lung cancer was the third leading cause, followed by pneumonia, pancreatic cancer, liver cancer, and stomach cancer.

DISCUSSION

The present study analyzed pooled data from three large-scale prospective cohort studies in Japan and estimated the all-cause and disease-specific mortality attributable to smoking. Compared with the results of the historical Hirayama large-scale cohort study,[13] the estimated age-adjusted relative risks (current smokers vs. never-smokers) in the present study were higher for all-cause mortality [1.6 vs. 1.3 (90% CI: 1.3-1.3) for males, and 1.8 vs. 1.3 (90% CI: 1.3-1.4) for females], for all cancers [2.0 vs. 1.7 (90% CI: 1.6-1.8) for males, and 1.6 vs. 1.3 (90% CI: 1.2-1.4) for females], for IHD [2.2 vs. 1.7 (90% CI: 1.6-1.9) for males, and 3.0 vs. 1.9 (90% CI: 1.7-2.1) for females], for stroke [1.3 vs. 1.1 (90% CI: 1.0-1.1) for males, and 1.8 vs. 1.2 (90% CI: 1.1-1.3) for females]. A possible explanation for the higher relative risks observed in the present study is the increase in exposure levels that has occurred subsequent to the Hirayama study (the baseline survey was carried out in 1965 for the Hirayama study and around 1990 for the present study). The proportion of current smokers who smoked 20 cigarettes per day or more was larger in the present study than in the Hirayama study (71.5% vs. 41.6% for males and 34.3% vs. 8.4% for females, calculated on a person-year basis). Conversely, the proportion who smoked less than 10 cigarettes per day was smaller in the present study than in the Hirayama study (4.7% vs. 10.6% for males and 22.2% vs. 50.6% for females, calculated on a person-year basis). When we compared age at smoking initiation, the proportion of current smokers who started smoking at 19 years of age or earlier was larger in the present

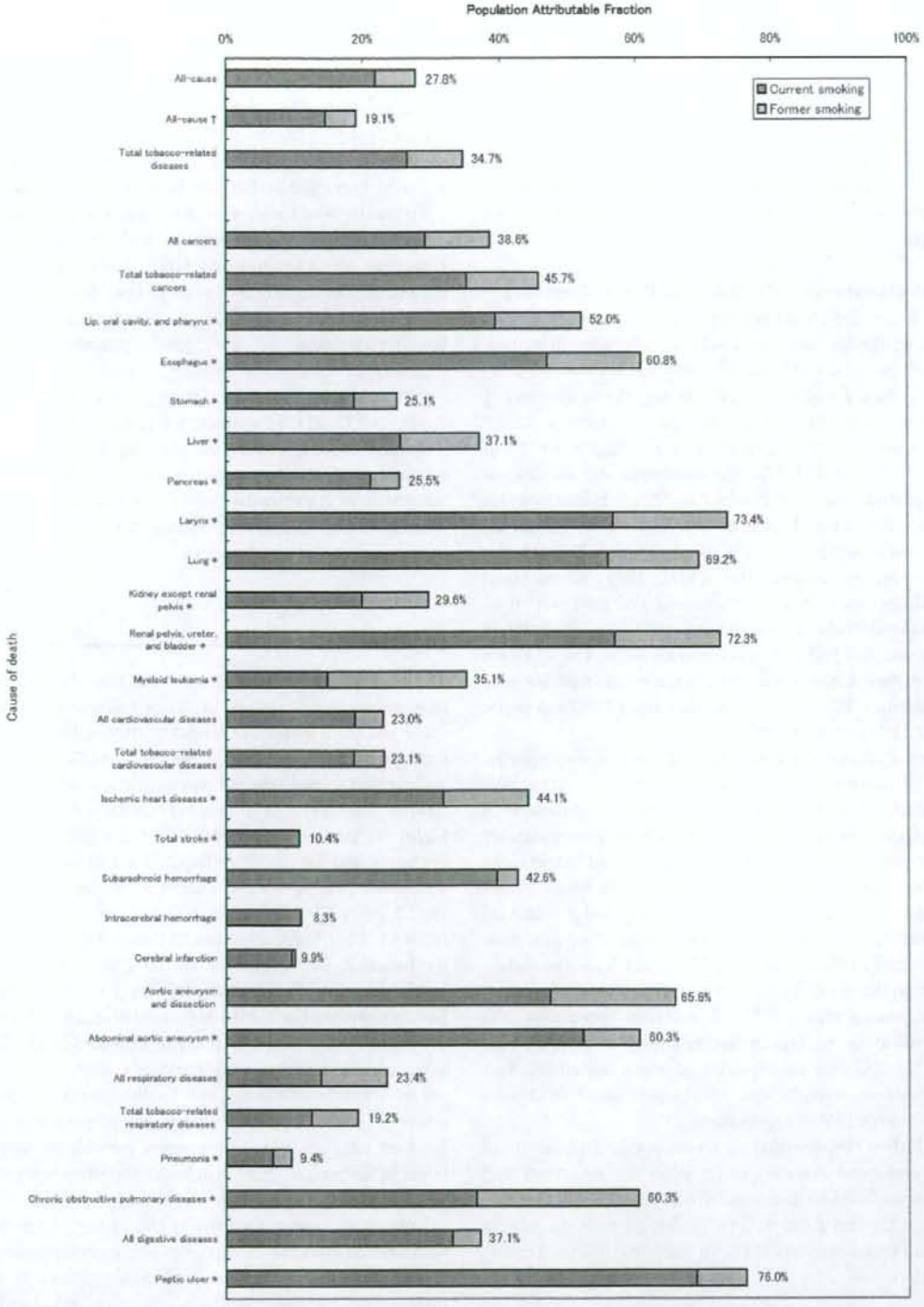

Figure 1. Population attributable fraction of disease-specific mortality due to smoking for males.

*: Tobacco-related diseases selected from the Surgeon General's Report of 2004 and the IARC Monograph volume 83.
†: The population attributable fraction was calculated by summing the attributable fractions estimated for each tobacco-related disease (*).
The percentage shown at the right-hand end of each bar is the population attributable fraction of ever-smoking.
See Appendix for the values of the point estimates and confidence intervals.

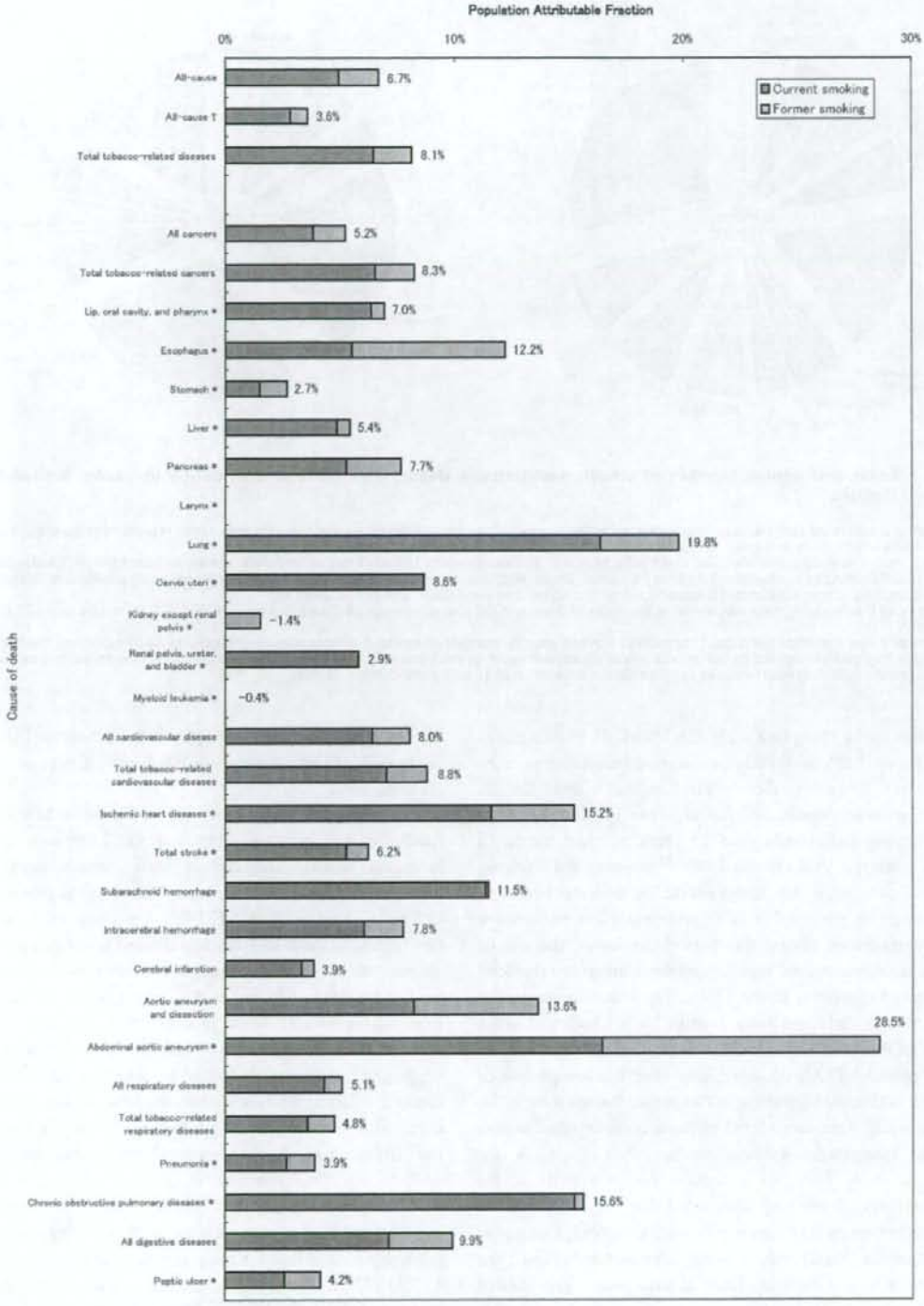

Figure 2. Population attributable fraction of disease-specific mortality due to smoking for females.

*: Tobacco-related diseases selected from the Surgeon General's Report of 2004 and the IARC Monograph volume 83.
†: The population attributable fraction was calculated by summing the attributable fractions estimated for each tobacco-related disease (*). The percentage shown at the right-hand end of each bar is the population attributable fraction of ever-smoking.
See Appendix for the values of the point estimates and confidence intervals.

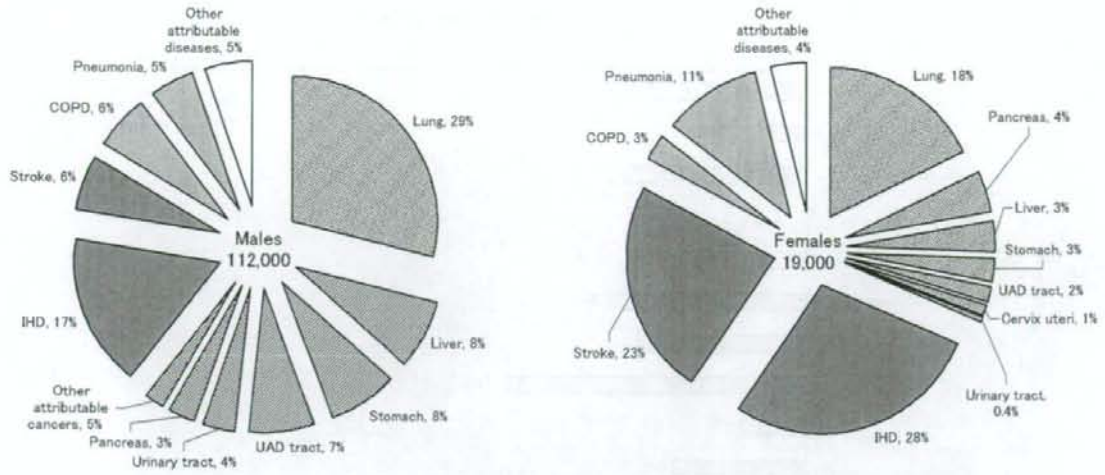

Figure 3. Estimated annual number of smoking-attributable deaths and disease distribution in Japan, for males and females.

The shaded areas represent cancers, the dark gray areas represent cardiovascular diseases, the light gray areas represent respiratory diseases, and the white areas represent other attributable diseases.
UAD tract: upper aerodigestive tract (lip, oral cavity, pharynx, and esophagus). Urinary tract: renal pelvis, ureter, and bladder. IHD: ischemic heart disease. COPD: chronic obstructive pulmonary disease. Other attributable cancers: cancers of the kidney (except renal pelvis) and larynx, and myeloid leukemia. Other attributable diseases: aortic aneurysm and dissection, and peptic ulcer.
The source of the mortality data was the Vital Statistics of Japan, 2005 (the number of all-cause deaths was 584,970 for males and 498,826 for females).
The number in the center of each chart represents the sex-specific number of smoking-attributable deaths calculated by summing the number of cause-specific deaths weighted by the population attributable fraction of ever-smoking (negative values for the fraction were treated as zero).
The percentage following each disease represents the proportion of smoking-attributable deaths.

study than in the Hirayama study (26.1% vs. 11.9% for males and 7.0% vs. 3.6% for females, calculated based on a person-year basis). Regarding the smoking exposure level for the whole Japanese population, the cigarette consumption per capita among individuals aged 15 years or older increased rapidly from the 1950s to the 1980s,[22] whereas the smoking prevalence among males decreased during the same period,[23] suggesting that the number of cigarettes smoked per smoker per day increased during this period. In Japan, the use of filtered cigarettes spread rapidly, and these cigarettes replaced non-filtered cigarettes in the 1960s. The baseline survey for the Hirayama study was carried out in 1965, which was in the middle of this period of change, whereas our baseline survey period (around 1990) occurred long after the completion of the shift to filtered cigarettes. In this sense, the smokers in the present study were considered to have been exposed to less harmful mainstream tobacco smoke than those in the Hirayama study. Previous systematic review reports on the health effects of smoking concluded that there was only a small reduction in lung cancer risk associated with changes in cigarette type,[11] and only a weak relationship between the cigarette type and coronary heart disease risk.[12] The HRs of these diseases in the present study were similar to or higher than those in the Hirayama study, and the HRs for the major disease groups, such as all causes, all cancers, and all CVDs, were also higher in the present study. Thus, the shift to filtered cigarettes does not appear to have been influential as far as each of these diseases or the disease groups as a whole are concerned.

One exception regarding the differences between the results of the present study and the Hirayama study is laryngeal cancer. The HR of male current smokers for laryngeal cancer was considerably lower in the present study [5.5 vs. 32.5 (90% CI: 8.7-121.9)]. A possible explanation for this finding is the shift from non-filtered to filtered cigarettes, as mentioned above. Although evidence is lacking, case-control studies conducted in the United States and in several European countries have reported that the use of filters reduced the laryngeal cancer risk by 50%.[24-26] One study suggested that the risk reduction produced by filter usage was larger for laryngeal cancer than for lung cancer,[26] which is consistent with the marked difference between our results and the Hirayama results for laryngeal cancer, but not for lung cancer. An improvement in the prognosis is another possibility. According to a report based on data from a population-based cancer registry in Osaka, Japan, the 5-year relative survival rate for male laryngeal cancer diagnosed in 1975-1977 was 62.1% compared with 80.0% for that diagnosed in 1987-1989.[27] However, an improvement in survival is common to the cancers of many other sites (e.g., 23.5% to 35.2% for all sites, 22.4% to 38.2% for the pharynx, and 6.0% to 11.7% for the lung).