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Isoflavone consumption and subsequent risk of hepatocellular carcinoma in a population-based prospective cohort of Japanese men and women

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The incidence of hepatocellular carcinoma (HCC) is much higher in men than in women. Several experiment and epidemiological studies have suggested that estrogen might play an inhibitory role in the development of HCC. Because isoflavones have a similar structure as 17β-estradiol and appear to have an anti-estrogenic effect in women and estrogenic effect in men, we hypothesized that the effect of isoflavones on HCC differs by sex. We investigated the association between isoflavones (genistein and daidzein) and soy products and HCC in Japan in a population-based prospective study in 19,998 Japanese (7,215 men and 12,783 women) aged 40–69 years. During 11.8 years of follow-up, 101 subjects (69 men and 32 women) were newly diagnosed with HCC. Case patients were grouped according to consumption of isoflavones and soy products and stratified by hepatitis virus infection. Hazard ratios (HRs) and 95% confidence intervals (CIs) for HCC were calculated by Cox proportional-hazards modeling. In women, genistein and daidzein were dose-dependently associated with an increased risk of HCC, with multivariable HRs for the highest versus lowest tertile of 3.19 (95% CI = 1.13–9.00, p_{trend} = 0.03) and 3.90 (95% CI = 1.30–11.69, p_{trend} = 0.01), respectively. No association between isoflavones and HCC was observed in men. These results persisted when analysis was restricted to subjects positive for either or both hepatitis C and B virus. In conclusion, isoflavone consumption may be associated with an increased risk of HCC in women. Women with hepatitis virus infection may be advised to abstain from isoflavone consumption. Further studies are warranted to confirm these findings.

Key words: isoflavone; hepatocellular carcinoma (HCC); hepatitis C virus (HCV); hepatitis B virus (HBV); JPHC study

Hepatocellular carcinoma (HCC) is an important disease worldwide. In Japan, HCC ranks as the third- and fourth-leading cause of death from cancer among men and women, respectively.[1] The most important risk factors for the development of HCC in humans are chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV).[2] However, despite a similar prevalence of chronic HCV or HBV infection in men and women,[3,4] the incidence of HCC is higher in men, with the International Agency for Research on Cancer (IARC) reporting a 2-fold or greater difference.[5] Although this may partly result from differences in exposure to environmental risk factors such as alcohol consumption and cigarette smoking, several human and nonhuman studies point to a possible role of hormonal factors. In laboratory experiments, ovariectomy in mice increased susceptibility to chemically induced hepatocarcinogenesis,[6,7] whereas administration of estrogens inhibited the development of HCC in male mice.[7] Additionally, Naugler *et al.*[8] showed that estrogen-mediated inhibition of interleukin-6 (IL-6) reduced HCC risk in female mice. In an epidemiological study, Yu *et al.* reported that natural menopause at a younger age and ovariectomy during premenopause were associated with an increased risk of HCC.[9] These various observations suggest that sex hormones, especially estrogen, may confer a protective effect against the development of HCC.

Isoflavones are structurally similar to 17β-estradiol and have the ability to bind to estrogen receptors (ERs),[10] suggesting that they may influence the development of HCC. However, to date this possibility has received relatively scant interest.[11–16] Isoflavones act as estrogen agonists and also as antagonists competing for estradiol at the receptor complex.[17] Because physiological levels of estradiol differ substantially between men and women,

Abbreviations: CI, confidence interval; ER, estrogen receptor; HBsAg, hepatitis B virus antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; IL, interleukin.

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we speculated that the effects of isoflavones on HCC might differ by sex. Long-term isoflavone consumption in typical daily life appears to have an anti-estrogenic effect in women and an estrogenic effect in men, although several studies have reported that short-term dietary soy showed a weak estrogenic response in the breast in women.[18–20] Indeed, in epidemiological studies, isoflavones have been inversely associated with breast cancer in women[10,21,22] and prostate cancer in men.[10,23,24] Additionally, the inverse association between isoflavones and breast cancer was more pronounced in women with high blood levels of estradiol.[25] On the basis of these, the effects of isoflavones may be dependent on endogenous levels of estradiol, and we hypothesized that their effects on HCC may differ by sex. However, previous epidemiological findings for isoflavones or soy food intake and HCC are inconsistent, and most studies did not analyze by sex,[11,13–16] nor consider HCV or HBV infection status.[11,12,14,15]

Here, we investigated the presence of an association between isoflavone consumption and HCC in Japanese men and women in a large-scale population-based cohort study in Japan, with due consideration for HCV and HBV infection status.

Material and methods

Study population

The Japan Public Health Center-based Prospective Study (JPHC study) Cohort II was initiated in 1993–1994. This cohort consisted of 6 PHC areas (Ibaraki, Niigata, Kochi, Nagasaki, Okinawa and Osaka) across Japan. The study design has been described in detail previously.[26] The study was approved by the Institutional Review Board of the National Cancer Center, Tokyo, Japan. The study population was defined as all residents aged 40–69 years at the start of the respective baseline survey. In the present analysis, we excluded some subjects from the Osaka area for whom different definitions were used. Initially, we defined a population-based cohort of 68,974 subjects (33,888 men and 35,086 women) after the exclusion of ineligible subjects ($n = 103$).

Baseline survey

At baseline, participants completed a self-administered questionnaire that assessed information on personal medical history, smoking and drinking habits, diet and other lifestyle factors. Completed questionnaires were received from 26,850 men (response rate, 79%) and 29,785 women (response rate, 85%). Subjects with a self-reported history of cancer at baseline were excluded from analysis ($n = 1,219$).

Blood collection

Subjects were asked to voluntarily provided 10 mL of blood during health checkups in 1993–1995. Samples were divided into plasma and buffy layers, and preserved at −80°C until analysis. Among respondents to the baseline questionnaire, a total of 20,406 subjects (36%) (7,442 men and 12,964 women) donated blood.

Food frequency questionnaire

The questionnaire asked about the usual consumption of 52 foods, including beverages, during the previous year. We then calculated the consumption of isoflavones (genistein and daidzein) and soy food. Soy food referred to the consumption of *tofu*, *miso* (soybean paste) and *natto* (fermented soybeans), for which the major ingredient is soybean. Standard portion sizes were specified for each food item in 3 amounts: small (50% smaller), medium (same as the standard) and large (50% larger). The frequency of soy food intake was divided into 5 categories: almost never, sometimes, 1 or 2 times per week, 3 or 4 times per week and almost daily. The total consumption of soy food (g/day) was calculated from these responses, whereas isoflavone consumption was calculated using values in a specially developed food composition table for isoflavones in Japanese foods.[27,28] Energy was calculated using the fifth revised edition of the Standard Tables of Food Composition in Japan.[29]

Validity was assessed in subsamples using 14- or 28-day dietary records. Spearman's correlation coefficients between energy-adjusted intake of soy food from the questionnaire and from dietary records for men and women were 0.47 and 0.44, respectively, whereas those for energy-adjusted intake of genistein and daidzein were 0.56 and 0.55 for men, and 0.51 and 0.49 for women, respectively (unpublished data).

Among the 20,406 subjects who responded to the questionnaire and provided a blood sample, 408 who reported extreme total energy intake (upper 1.0% or lower 1.0%) were excluded, leaving 19,998 subjects (7,215 men and 12,783 women) for analysis.

Follow-up and identification of HCC

Subjects were followed from the baseline survey until December 31, 2005. Changes in residence status, including survival, were identified annually through the residential registry in their public health center area. Among study subjects, 1,070 (5.4%) moved out of their study area and 49 (0.2%) were lost to follow-up during the study period.

Incidence data on HCC were identified by active patient notification from major local hospitals in the study area and data linkage with population-based cancer registries, with permission from the local governments responsible for the registries. Death certificates were used as a supplementary information source. In our cancer registry system, 5.9% of cases were based on death certificate only. Cases were coded using the International Classification of Diseases for Oncology, Third Edition (ICD-O-3; C22.0).[30] We identified 101 (69 for men, 32 for women) newly diagnosed cases of HCC during the study period among subjects who had returned the baseline questionnaire and provided blood samples.

Laboratory assays

Plasma samples were screened for anti-HCV using a third-generation immunoassay (Lumipulse II Ortho HCV, Ortho-Clinical Diagnostics K.K., Tokyo, Japan)[31] and for hepatitis B virus antigen (HBsAg) by reversed passive hemagglutination with a commercial kit (Institute of Immunology, Tokyo, Japan). The virus-positive group consisted of subjects positive for either or both anti-HCV and HBsAg.

Statistical analysis

Person-years of follow-up were calculated for each subject from the date of completion of the baseline questionnaire to the date of HCC diagnosis, date of emigration from the study area, or date of death, whichever occurred first; or if none of these occurred, follow-up was through to the end of the study period (December 31, 2005). Subjects who were lost to follow-up were censored at the last confirmed date of presence in the study area. Hazard ratios (HRs) of HCC were calculated by tertiles of isoflavones and soy food consumption, with the lowest consumption category as the reference. HRs and 95% confidence intervals (CIs) were calculated by the Cox proportional hazards model, adjusting for age at baseline survey (5-year age categories) and study area (6 PHC areas) according to the SAS PHREG procedure (Version 9.1; SAS Institute, Cary, NC). For further adjustment, additional possible confounders were incorporated into the model: smoking status (never, former, current); alcohol intake (non- and ex-drinkers, less than weekly, weekly or more [<150 g/week, 150-300 g/week or ≥300 g/week]); intake of coffee (almost never, 1–4 days/week, 1–4cups/day or 5 or more cups/day) and vegetables (continuous); and HCV or HBV infection status (positive or negative). In females, further adjustment was made for menopausal status (yes or no). These variables are either known or suspected risk factors for cancer or were previously associated with the risk of HCC.[32] When covariates were entered into the statistical model, isoflavones, soy food and vegetable intakes were adjusted for total energy intake using the residual method.[33] Vegetable intakes were

TABLE I – SUBJECT CHARACTERISTICS AT BASELINE ACCORDING TO GENISTEIN CONSUMPTION

	Men			Women		
	Genistein consumption			Genistein consumption		
	Low	Middle	High	Low	Middle	High
Age, years ± SD	56.6 ± 8.6	57.5 ± 8.2	59.0 ± 7.6	55.9 ± 8.5	56.2 ± 8.3	57.3 ± 7.9
Current smoker (%)	47.0	41.5	36.9	5.4	3.9	3.0
Regular drinker (yes, %)	64.6	63.6	59.3	12.1	9.0	7.2
Postmenopausal (%)	–	–	–	69.7	70.6	76.9
Coffee, daily (%)	46.6	36.3	31.6	42.4	34.7	27.3
Vegetables (g/day)	49.4 ± 67.1	59.3 ± 65.9	71.9 ± 68.9	55.2 ± 68.2	63.5 ± 68.5	69.6 ± 64.6
Soy food (g/day)	21.7 ± 10.2	49.5 ± 14.4	81.9 ± 18.8	23.1 ± 11.1	49.7 ± 15.5	76.1 ± 17.3
Genistein (mg/day)	6.0 ± 2.7	13.8 ± 3.5	24.2 ± 6.3	6.4 ± 2.9	13.9 ± 3.8	23.2 ± 6.3
Daidzein (mg/day)	3.6 ± 1.6	8.2 ± 2.1	14.5 ± 3.8	3.8 ± 1.7	8.4 ± 2.3	13.9 ± 3.8
Infection status						
HCV(−)/HBV(−)	89.43	90.89	90.61	92.65	93.24	93.22
HCV(−)/HBV(+)	3.29	2.83	2.99	2.00	1.92	2.06
HCV(+)/HBV(−)	7.20	6.24	6.28	5.19	4.76	4.62
HCV(+)/HBV(+)	0.08	0.04	0.12	0.16	0.07	0.09

Values are mean unless otherwise indicated. SD = Standard deviations, HCV = hepatitis C virus, HBV = hepatitis B virus.

TABLE II – HAZARD RATIO (HR) AND 95% CONFIDENCE INTERVAL (CI) FOR HEPATOCELLULAR CARCINOMA (HCC) ACCORDING TO ISOFLAVONE AND SOY FOOD CONSUMPTION AMONG JAPANESE MEN AND WOMEN

		No. of cases	Person-years of follow-up	HR (95%CI)[1]	HR (95%CI)[2]
Men (N = 7,215)					
Genistein (mg/day)					
Low	<12.0	26	27,304	1	1
Middle	12.0–19.9	16	27,793	0.66 (0.35–1.23)	0.78 (0.41–1.49)
High	≥20.0	27	27,863	1.07 (0.61–1.89)	1.13 (0.60–2.11)
P_{trend}				0.93	0.80
Daidzein (mg/day)					
Low	<8.0	26	27,310	1	1
Middle	8.0–12.7	17	27,781	0.69 (0.37–1.29)	0.81 (0.43–1.54)
High	≥12.8	26	27,869	1.03 (0.58–1.82)	1.09 (0.58–2.05)
P_{trend}				0.98	0.87
Soy food (g/day)					
Low	<37.6	26	27,318	1	1
Middle	37.6–64.9	16	27,738	0.65 (0.34–1.21)	0.77 (0.40–1.47)
High	≥65.0	27	27,904	1.05 (0.60–1.84)	1.10 (0.59–2.03)
P_{trend}				0.97	0.84
Women (N = 12,783)					
Genistein (mg/day)					
Low	<12.2	6	50,398	1	1
Middle	12.2–19.5	12	51,424	2.36 (0.88–6.32)	2.36 (0.85–6.51)
High	≥19.6	14	51,029	2.86 (1.07–7.64)	3.19 (1.13–9.00)
P_{trend}				0.03	0.03
Daidzein (mg/day)					
Low	<8.1	5	50,402	1	1
Middle	8.1–12.5	13	51,408	3.08 (1.09–8.70)	3.10 (1.07–8.99)
High	≥12.6	14	51,041	3.46 (1.21–9.83)	3.90 (1.30–11.69)
P_{trend}				0.02	0.01
Soy food (g/day)					
Low	<38.2	8	50,403	1	1
Middle	38.2–62.7	11	51,056	1.51 (0.60–3.78)	1.68 (0.65–4.35)
High	≥62.8	13	51,393	1.74 (0.71–4.28)	1.74 (0.67–4.52)
P_{trend}				0.22	0.25

[1]Adjusted for age and area.–[2]Adjusted for age, area, HCV, HBsAg, smoking status, alcohol consumption, and intake of coffee and vegetables. Further adjusted for menopausal status in women.

calculated from 6 items in the questionnaire. Testing of the proportional hazards assumption by Schoenfeld and scaled Schoenfeld residuals found no violation of proportionality. We additionally analyzed the association between isoflavone intake and HCC in subjects who were either or both anti-HCV- or HBsAg-positive.

Trends were assessed by assignment of the median value in each category. All p-values were 2-sided, and statistical significance was determined at the $p < 0.05$ level.

Results

During 235,811 person-years of follow-up (average follow-up, 11.8 years) for 19,998 subjects (7,215 men and 12,783 women), a total of 101 cases (69 for men, 32 for women) of HCC were newly diagnosed and included in the analyses.

Subject characteristics at baseline according to tertile of energy-adjusted isoflavone consumption are shown in Table I, with the results for genistein used as a surrogate for isoflavones owing to the high correlation among results for genistein and daidzein. Subjects with high genistein consumption were older, smoked and drank less, consumed less coffee, and consumed more vegetables, notwithstanding sex. The proportion of postmenopausal women increased as genistein intake increased. As expected, soy food and daidzein increased as genistein intake increased. The proportion of subjects positive for anti-HCV,

TABLE III – HAZARD RATIO (HR) AND 95% CONFIDENCE INTERVAL (CI) FOR HEPATOCELLULAR CARCINOMA (HCC) ACCORDING TO ISOFLAVONE AND SOY PRODUCT CONSUMPTION AMONG JAPANESE MEN AND WOMEN WHO WERE ANTI-HCV- OR HBSAG-POSITIVE

	No. of cases	Person-years of follow-up	HR (95%CI)[1]	HR (95%CI)[2]
Men (N = 699)				
Genistein				
Low	22	2,481	1	1
Middle	12	2,493	0.58 (0.29–1.20)	0.59 (0.28–1.24)
High	23	2,451	1.06 (0.56–2.00)	1.05 (0.52–2.12)
p_{trend}			0.99	0.96
Daidzein				
Low	22	2,481	1	1
Middle	13	2,483	0.63 (0.31–1.26)	0.63 (0.31–1.31)
High	22	2,460	1.00 (0.52–1.89)	0.97 (0.48–1.98)
p_{trend}			0.88	0.84
Soy food				
Low	22	2,483	1	1
Middle	12	2,482	0.61 (0.30–1.26)	0.61 (0.29–1.28)
High	23	2,459	1.10 (0.58–2.06)	1.10 (0.55–2.20)
p_{trend}			0.86	0.87
Women (N = 890)				
Genistein				
Low	4	3,426	1	1
Middle	11	3,504	3.28 (1.02–10.48)	3.11 (0.92–10.51)
High	10	3,507	3.07 (0.94–10.09)	3.30 (0.92–11.82)
p_{trend}			0.06	0.06
Daidzein				
Low	4	3,427	1	1
Middle	11	3,498	3.27 (1.02–10.47)	3.12 (0.92–10.56)
High	10	3,512	3.08 (0.94–10.13)	3.32 (0.93–11.88)
p_{trend}			0.06	0.06
Soy food				
Low	8	3,393	1	1
Middle	8	3,518	1.11 (0.41–3.05)	0.97 (0.34–2.77)
High	9	3,526	1.18 (0.44–3.12)	1.02 (0.36–2.94)
p_{trend}			0.74	0.98

[1]Adjusted for age and area.–[2]Adjusted for age, area, smoking status, alcohol consumption, and intake of coffee and vegetables. Further adjusted for menopausal status in women.

HBsAg or both among tertiles of genistein consumption were similar.

Table II shows minimally adjusted and multivariable HRs and 95% CIs for HCC by tertile of genistein, daidzein and soy food consumption in men and women. Consumption of genistein, daidzein and soy food showed no association with HCC in men, with respective multivariable HRs for the highest versus lowest tertile of 1.13 (95% CI = 0.60–2.11), 1.09 (95% CI = 0.58–2.05) and 1.10 (95% CI = 0.59–2.03). In women, in contrast, genistein and daidzein were dose-dependently associated with an increased risk of HCC, with multivariable HRs for the highest versus lowest tertile of 3.19 for genistein (95% CI = 1.13–9.00, p_{trend} = 0.03) and 3.90 for daidzein (95% CI = 1.30–11.69, p_{trend} = 0.01). Similarly, soy food consumption also tended to be associated with an increased risk of HCC in women, but without statistical significance (highest versus lowest: multivariable HR = 1.74, 95% CI = 0.67–4.25). Miso soup, natto and tofu consumption also showed no association with HCC in men (data not shown). In women, natto and tofu consumption was positively associated with HCC. Multivariable HRs for the highest *versus* lowest tertile of natto and tofu consumption was 3.71 (95% CI = 1.42–9.71) and 1.67 (95% CI = 0.65–4.28), respectively (data not shown).

These results remained essentially unchanged when analysis was restricted to subjects who were either or both anti-HCV- or HBsAg-positive (Table III); the positive association between genistein and daidzein and HCC in these women remained, albeit with attenuation of the test for linear trend (p_{trend} = 0.06 and 0.06 for genistein and daidzein, respectively). In contrast, soy food was not associated with HCC in women who were either or both HCV- and HBV-positive. No association between isoflavones and soy food and HCC was observed in men. Further, no association with individual soy foods was seen in men (data not shown). In women, the positive association between natto consumption and HCC remained, whereas tofu and miso soup consumption were not associated with HCC risk (data not shown).

Because the effects of isoflavones on HCC might differ between premenopausal and postmenopausal women due to difference in their estrogen levels, we also analyzed the association between soy foods and isoflavones and HCC in postmenopausal women. Results were similar to those for total women in Table II (data not shown). Hazard ratios among premenopausal women could not be calculated, because only one case occurred among them.

Discussion

We found a dose-dependent increase in the risk of HCC with consumption of isoflavones in Japanese women, even after consideration of infection status of hepatitis virus. In contrast, no association between isoflavones and HCC was seen in men. To our knowledge, this is the first study to report a positive association between the consumption of isoflavones and HCC in women.

Previous epidemiological findings for isoflavone and soy food intake and HCC are inconsistent.[11–16] Two prospective[11,12] and one case-control study[13] reported an inverse association between frequency of miso soup intake and HCC mortality. Lei *et al.*[14] reported that genistein consumption was lower at first diagnosis in patients with HCC than in those with cirrhosis. In several case-control studies, in contrast, no association with HCC was seen for frequency of tofu[15] and pulses intake.[16] However, most of these studies did not control for the potentially important confounding effects of infection with either or both HCV and HBV.[11,12,14,15] Additionally, most of these previous studies did not analyze by sex,[11,13–16] notwithstanding that the effects of isoflavones on HCC may differ between men and women.[10]

Although the relation between estrogen and HCC remains obscure,[2,3,4] previous epidemiological studies have reported the

preventive effects of estrogen against HCC or the progression of liver fibrosis. Yu *et al.* reported that the use of hormone replacement therapy was associated with a lower risk of HCC, and that younger age at menopause and ovariectomy during premenopause were risk factors for HCC.[9] Tanaka *et al.* reported that elevated serum testosterone, together with decreased serum estrogens, may promote the development of HCC in patients with cirrhosis.[35] Additionally, menopause seems to play a role in accelerating the progression of fibrosis.[36] In animal experiments, the degree of fibrosis was increased in males and females with hypoestrogenemia compared with females with normal levels of estrogen.[37] Moreover, variant ERs were more frequently expressed in male HCC patients than female subjects, even in an early stage of chronic liver disease,[38,39] while expression of both ERβ and wild ERα was lower in patients with HCC than in those with chronic liver disease.[40] Taken together, these findings may indicate that a loss of estrogen responsiveness might lead to HCC, and suggest that estrogen and ER status may play a role in hepatic defense.

Several mechanisms may explain the association we found between isoflavone consumption and increased risk of HCC in women. First, because isoflavones compete for estradiol at the receptor complex, they may have an anti-estrogenic effect in women.[17] Indeed, a number of epidemiological studies reporting an association between isoflavone intake and decreased breast cancer risk have suggested that this finding is ascribable to the possibility of anti-estrogenic effects of isoflavone.[10,21,22] Second, serum estradiol concentration shows a significant inverse correlation with soy product intake in women.[41,42] These findings suggest that isoflavones inhibit the preventive effects of estrogen against HCC in women. Moreover, the anti-estrogenic effects of isoflavone in women might impede the preventive effects of estrogen-mediated inhibition of IL-6 on HCC, given that estrogen's inhibitory effect on IL-6 secretion reduced HCC risk in female mice,[8] and that an isoflavone-rich diet increased IL-6 levels in women.[43]

We attempted to specify which kinds of soy products contributed to the increased risk of HCC in women. Our results showed a stronger association for natto (fermented soybean) than other soyfoods. Given that natto is the greatest contributor to isoflavones intake in Japan,[44] this result is plausible. Additionally, the isoflavone aglycones in fermented foods may have greater bioavailability than their glucosides, because genistein and daidzein are absorbed as isoflavone aglycones following hydrolysis of the glycoside by beta-glucosidases present in not only human gut bacteria but also in foods.[45] These findings indicate the need for further study of risk and bioavailability using plasma data.

In this study, most women (97%) who developed HCC during the follow-up period were postmenopausal at baseline. Isoflavone may have not competed with estrogen in postmenopausal women due to their low estrogen levels. However, even when analysis was restricted to postmenopausal women, a positive association between isoflavones and HCC risk remained. This lack of change between premenopausal and postmenopausal women has also been reported for breast cancer.[21,22,46,47] Given the extended period required for carcinogenesis to occur, an anti-estrogenic effect of isoflavones in premenopausal women might remain in postmenopausal women. In contrast, given that isoflavones may have an estrogenic effect in men,[10,21,22] they might be expected to decrease the risk of HCC in men. Here, however, we saw no association between isoflavone consumption and HCC in men. The predominance of androgens in men may obfuscate any estrogenic impact of isoflavones, because testosterone level is positively associated with the risk of HCC in men.[35,48]

The strength of the present study is its prospective design and negligible proportion of loss to follow-up (0.2%). Information on isoflavones and soy food consumption was collected before the subsequent diagnosis of HCC, thereby diminishing the probability of the recall bias that is inherent to case–control studies. Another strength was that virus infection status was determined at baseline for the entire population, allowing us to clarify the association between isoflavones and HCC in a high-risk population.

Several limitations of the study also warrant mention. First, because we estimated consumption from self-reports and at a single point (at baseline), and that validity for isoflavones was moderate, some measurement error in the assessment of isoflavones and soyfoods consumption is inevitable. If present, however, this was probably nondifferential and would have lead to the underestimation of results. Second, it would have been preferable if we had been able to confirm the association between plasma isoflavone level and HCC. Further studies using plasma samples are needed. However, Spearman's correlation coefficients for daidzein and genistein between intakes from the questionnaire and from serum concentrations in a validation study using subsamples in the JPHC Study were 0.31 and 0.33, respectively.[44] Additionally, we previously reported similar results regarding the effects of isoflavone between studies using plasma isoflavone levels and using a FFQ in both breast[21,22] and prostate cancer.[23,24] On the basis of these findings, we expect that results using plasma samples would be similar to our present results. Third, we had no information on the clinical severity of hepatitis or on the treatment of subjects with hepatitis virus infection before and during the study period. If infected subjects had received treatment, the occurrence of HCC may have been decreased. However, this might have lead to the underestimation of HCC occurrence, which would also bias the results toward the null. Finally, any generalization of our results should be done with caution.[49] Our subjects were restricted to those who provided a blood sample and participated in the baseline health checkup survey (28% for men, 45% for women), and subjects already under care for hepatitis infection may have been less willing to provide blood samples.

In conclusion, we found that isoflavones have a relevant role in HCC risk in women. In particular, the unfavorable effect of isoflavones was independent of other major risk factors, namely HBV and HCV infection. It might be therefore necessary for women with hepatitis virus infection to abstain from isoflavone. Because our cases numbers were relatively small, confirmation of these findings in further studies is required.

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Short Communication

Vegetable, fruit and antioxidant nutrient consumption and subsequent risk of hepatocellular carcinoma: a prospective cohort study in Japan

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In a population-based prospective study of 19 998 Japanese individuals, consumption of vegetables, green–yellow and green leafy vegetables was inversely associated with the risk of hepatocellular carcinoma (101 cases), with multivariable hazard ratios for the highest *vs* lowest tertile of 0.61 (95% confidence interval (CI) = 0.36–1.03, $P_{trend} = 0.07$), 0.65 (95% CI = 0.39–1.08, $P_{trend} = 0.06$) and 0.59 (95% CI = 0.35–1.01, $P_{trend} = 0.04$), respectively.
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Keywords: hepatocellular carcinoma; vegetables; fruits; carotenoid; vitamin C; prospective study.

Although the potential roles of fruits and vegetables in cancer prevention have been demonstrated at various cancer sites (Vainio and Weiderpass, 2006), the association with hepatocellular carcinoma (HCC) remains unclear (World Cancer Research Fund/American Institute for Cancer Research, 2007). Fruits and vegetables are a rich source of antioxidants, such as retinol and carotenoids, and vitamin C, and they are thought to exert protective effects against cancer (Stanner *et al*, 2004). In an intervention study, however, not all antioxidant nutrients might be protective against HCC (Bjelakovic *et al*, 2004).

Here, we investigated the association between fruit and vegetable consumption and HCC in a large-scale population-based cohort study in Japan, with due consideration for hepatitis C virus (HCV) and hepatitis B virus (HBV) infection status.

MATERIALS AND METHODS

The Japan Public Health Center-based Prospective Study (JPHC study) Cohort II, initiated during 1993–1994, has been described earlier (Kurahashi *et al*, 2009). The study population was defined as all residents aged 40–69 years who lived in six PHC areas at the start of the baseline survey. We enrolled 56 635 men and women who provided valid responses to a self-administered questionnaire (82%) and excluded participants with a history of cancer ($n = 1219$). Among them, a total of 20 406 participants (36%) provided a blood sample. These plasma samples were screened for anti-HCV and for HBV antigen (HBsAg).

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[3]Study group members are listed in the Appendix.
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The self-administered food-frequency questionnaire (FFQ) consisted of 52 foods, including beverages. It asked about the usual consumption of six vegetable and three fruit items during the previous year. The vegetables included two pickled vegetables (green leafy vegetables and other vegetables), green leafy vegetables (spinach, Chinese chives, etc), carrot, tomato and 100% vegetable juice, whereas the fruit items included apple, citrus fruits and 100% fruit juice. The questionnaire contained five frequency categories for vegetable and fruit consumption ranging from 'never' to 'almost every day', except for juices. Standard portion sizes were specified for each food item, which were then used to determine the three choice amounts of small (50% smaller), medium (same as the standard) and large (50% larger). Six frequency choices for juice ranged from 'almost never' to '5 or more cups per day'. The consumption of total fruit and total vegetables ($g\,day^{-1}$) was calculated from these responses. We documented the validity of the FFQ in the assessment of vegetable and fruit consumption in subsamples using dietary records. Although validities for vegetables and fruits were relatively low (from 0.22 for vegetables to 0.31 for fruit), correlation coefficients for antioxidant nutrients were considered moderate (from 0.31 for vitamin C to 0.41 for β-carotene).

Among the 20 406 participants who responded to the questionnaire and provided a blood sample, 408 who reported extreme total energy intake (upper 1.0% or lower 1.0%) were excluded, leaving 19 998 participants for analysis, who were followed from the baseline survey until 31 December 2005. Of these, 5% moved out of a study area and 0.2% were lost to follow-up during the study period.

We used Cox regression to compute hazard ratios (HRs) and 95% confidence intervals (CIs) of HCC according to tertiles of consumption of the respective food items or nutrients with adjustment for potential confounders, including HCV or HBV infection status.

RESULTS

During 235 811 person-years of follow-up (11.8 years), a total of 101 new HCC cases were identified. The prevalence of chronic HCV and HBV infection in HCC cases was 70.3 and 12.9%, respectively.

We observed that participants with higher vegetable and fruit consumption tended to be older, smoke less, drink less alcohol, and consume less coffee and more genistein. Body mass index did not substantially differ according to consumption. The proportion of participants positive for anti-HCV, HBsAg or both among tertiles of vegetable and fruit consumption was similar. The prevalence of positive markers for HCV and HBV in this cohort was 5.3 and 2.5%, respectively.

Table 1 presents HRs in relation to vegetable and fruit consumption for HCC cases. Borderline inverse associations were seen between vegetables and green–yellow vegetables and HCC, with multivariable HRs for the highest *vs* lowest tertile of 0.61 (95% CI = 0.36–1.03, $P_{trend} = 0.07$) and 0.65 (95% CI = 0.39–1.08, $P_{trend} = 0.06$), respectively. In particular, green leafy vegetable consumption showed an inverse dose-dependent association with HCC (HR = 0.59, 95% CI = 0.35–1.01 for highest *vs* lowest tertile of consumption, $P_{trend} = 0.04$). Results for vegetables excluding pickled vegetables were similar to those for when they were included. In contrast, fruit consumption including fruit juice appeared to increase the risk of HCC, albeit without statistical significance (HR = 1.45, 95% CI = 0.85–2.48 for highest *vs* lowest tertile of consumption).

Table 2 shows the association between retinol, carotenoids (α-carotene and β-carotene) and vitamin C and HCC risk. A slightly negative association was seen between α- and β-carotene and HCC, with respective multivariable HRs for the highest *vs* lowest tertile of 0.69 (95% CI = 0.42–1.15) and 0.64 (95% CI = 0.38–1.08). Multivariable HR for vitamin C was somewhat increased in the highest category (HR = 1.38, 95% CI = 0.80–2.40).

When the analysis was restricted to participants who were either or both anti-HCV- or HBsAg-positive, these results were substantially unchanged. It is worth noting that our study showed that the preventive effects of α- and β-carotene on HCC strengthened, with respective multivariable HRs for the highest *vs* lowest tertile of 0.60 (95% CI = 0.34–1.08, $P_{trend} = 0.08$) and 0.61 (95% CI = 0.34–1.09, $P_{trend} = 0.08$) (data not shown).

After participants were stratified by smoking status, multivariable HRs for the highest *vs* lowest tertile among never smokers were 0.42 for vegetables (95% CI = 0.19–0.99, $P_{trend} = 0.03$), 0.30 for green–yellow vegetables (95% CI = 0.13–0.70, $P_{trend} < 0.01$) and 0.31 for green leafy vegetables (95% CI = 0.13–0.74, $P_{trend} < 0.01$). Regarding nutrients, β-carotene showed a significant

Table 1 Hazard ratio and 95% confidence intervals for hepatocellular carcinoma according to tertile of intake of vegetables and fruits, JPHC study ($n = 19\,998$)

	Lowest	Middle	Highest	P_{trend}
Total vegetables and fruits				
Median (g day^{-1})	55.3	120.3	200.9	
No. of cases/person-years of follow-up	32/79 057	22/78 938	47/77 816	
Age, area, sex-adjusted HR (95% CI)	1.00	0.71 (0.41–1.23)	1.23 (0.78–1.94)	0.38
Multivariate HR[a] (95% CI)	1.00	0.78 (0.45–1.38)	1.14 (0.70–1.86)	0.56
Vegetables				
Median (g day^{-1})	25.6	51.7	88.5	
No. of cases/person-years of follow-up	37/78 971	31/79 183	33/77 657	
Age, area, sex-adjusted HR (95% CI)	1.00	0.88 (0.55–1.43)	0.81 (0.50–1.29)	0.37
Multivariate HR[b] (95% CI)	1.00	0.79 (0.48–1.31)	0.61 (0.36–1.03)	0.07
Green–yellow vegetables				
Median (g day^{-1})	10.1	23.1	42.3	
No. of cases/person-years of follow-up	44/78 234	24/79 272	33/78 305	
Age, area, sex-adjusted HR (95% CI)	1.00	0.66 (0.40–1.09)	0.81 (0.51–1.28)	0.27
Multivariate HR[b] (95% CI)	1.00	0.55 (0.33–0.94)	0.65 (0.39–1.08)	0.06
Green leafy vegetables				
Median (g day^{-1})	7.1	17.0	32.3	
No. of cases/person-years of follow-up	42/78 473	31/79 018	28/78 320	
Age, area, sex-adjusted HR (95% CI)	1.00	0.82 (0.51–1.30)	0.72 (0.44–1.17)	0.17
Multivariate HR[b] (95% CI)	1.00	0.71 (0.44–1.17)	0.59 (0.35–1.01)	0.04
Fruit				
Median (g day^{-1})	13.4	68.0	120.3	
No. of cases/person-years of follow-up	29/78 795	25/78 872	47/78 144	
Age, area, sex-adjusted HR (95% CI)	1.00	0.91 (0.53–1.56)	1.30 (0.81–2.09)	0.32
Multivariate HR[c] (95% CI)	1.00	1.08 (0.61–1.91)	1.45 (0.85–2.48)	0.19
Fruit excluding 100% fruit juice				
Median (g day^{-1})	11.8	46.8	97.2	
No. of cases/person-years of follow-up	32/78 489	26/78 961	43/78 361	
Age, area, sex-adjusted HR (95% CI)	1.00	0.97 (0.58–1.65)	1.24 (0.77–1.99)	0.40
Multivariate HR[c] (95% CI)	1.00	0.79 (0.45–1.38)	1.08 (0.65–1.82)	0.81

CI = confidence interval; HBsAg = HBV antigen; HCV, hepatitis C virus; HR = hazard ratio. [a]Adjusted for age, area, sex, HCV, HBsAg, smoking status, alcohol consumption, body mass index, history of diabetes mellitus and intake of coffee, genistein. [b]Adjusted for age, area, sex, HCV, HBsAg, smoking status, alcohol consumption, body mass index, history of diabetes mellitus and intake of coffee, genistein and fruit. [c]Adjusted for age, area, sex, HCV, HBsAg, smoking status, alcohol consumption, body mass index, past history of diabetes mellitus and intake of coffee, genistein and vegetable.

Epidemiology

Table 2 Hazard ratio and 95% confidence intervals for hepatocellular carcinoma according to tertile of intake of nutrient, JPHC study ($n = 19\,998$)

	Lowest	Middle	Highest	P_{trend}
Retinol				
Median (mg day^{-1})	114.8	282.7	397.2	
No. of cases/person-years of follow-up	33/78 650	34/78 824	34/78 338	
Age, area, sex-adjusted HR (95% CI)	1.00	1.24 (0.75–2.03)	1.37 (0.84–2.23)	0.20
Multivariate HR[a] (95% CI)	1.00	1.26 (0.76–2.10)	1.07 (0.64–1.79)	0.65
α-carotene				
Median (mg day^{-1})	50.4	146.6	561.2	
No. of cases/person-years of follow-up	40/78 660	28/78 756	33/78 395	
Age, area, sex-adjusted RR (95% CI)	1.00	0.78 (0.48–1.27)	0.81 (0.51–1.29)	0.34
Multivariate HR[a] (95% CI)	1.00	0.73 (0.44–1.22)	0.69 (0.42–1.15)	0.14
β-carotene				
Median (mg day^{-1})	602.2	1355.7	2319.0	
No. of cases/person-years of follow-up	39/78 628	30/79 082	32/78 101	
Age, area, sex-adjusted HR (95% CI)	1.00	0.87 (0.54–1.41)	0.79 (0.49–1.26)	0.31
Multivariate HR[a] (95% CI)	1.00	0.82 (0.50–1.35)	0.64 (0.38–1.08)	0.10
Vitamin C				
Median (mg day^{-1})	36.4	67.8	93.9	
No. of cases/person-years of follow-up	23/78 495	34/78 964	44/78 352	
Age, area, sex-adjusted HR (95% CI)	1.00	1.41 (0.82–2.40)	1.33 (0.79–2.24)	0.39
Multivariate HR[a] (95% CI)	1.00	1.74 (0.996–3.06)	1.38 (0.80–2.40)	0.44

CI = confidence interval; HBsAg = HBV antigen; HCV, hepatitis C virus; HR = hazard ratio. [a]Adjusted for age, area, sex, HCV, HBsAg, smoking status, alcohol consumption, body mass index, history of diabetes mellitus and intake of coffee and genistein.

inverse association with risk among never smokers (highest *vs* lowest: HR = 0.31, 95% CI = 0.13–0.76). In contrast, vitamin C seemed to be positively associated with HCC risk among current smokers, with an increase in multivariable HR for HCC in the second and highest categories (HR = 3.58, 95% CI = 1.21–10.63 and HR = 2.69, 95% CI = 0.89–8.08, respectively) (data not shown).

DISCUSSION

Our study identified inverse associations between the consumption of vegetables, green–yellow and green leafy vegetables and HCC. Concomitantly, an inverse association between α- and β-carotene and HCC risk was shown. These results are plausible, given the abundance of these nutrients in vegetables, particularly green–yellow vegetables.

In an animal experiment, carotenoids were shown to suppress liver carcinogenesis (Murakoshi *et al*, 1992; Moreno *et al*, 2002), whereas in an intervention study in patients with viral hepatitis and cirrhosis, a greater than 50% decrease in HCC incidence was found in the group administered a carotenoid mixture in addition to conventional treatment compared with a group given conventional symptomatic treatment alone (placebo not used) (Nishino, 2007). These findings support our present findings. It is worth noting that our study showed that the preventive effects of α- and β-carotene on HCC were strengthened when participants were limited to those who were either or both HBV and HCV positive. Given that inflammation is accompanied by the excess production of free radicals and that carotenoids have antioxidant potential in the scavenging of free radicals (Krinsky, 1989), carotenoids appear to play an important role in the prevention of hepatitis virus infection-related liver carcinogenesis.

In contrast, vitamin C consumption appeared to be associated with an increased risk of HCC. These relations were strengthened among current smokers in our study (see Results). Although vitamin C has antioxidant potential, it also acts to stimulate the absorption of iron from food (Lynch, 1997), and iron overload is considered a risk factor for HCC (Kowdley, 2004). Dietary vitamin C is positively associated with ferritin, which was used as a measure of body iron stores in the study by Fleming *et al* (1998). Thus, a higher intake of vitamin C might be harmful to hepatic cells, especially among smokers.

Given that the prognosis for HCC is extremely poor, our results would, if confirmed, have important implications for public health. Greater consumption of vegetables that contain α- and β-carotene and restraint in those rich in vitamin C may modify the development of HCC in HBV- and/or HCV-infected participants.

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Appendix

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Original Article

Reduced Life Expectancy due to Smoking in Large-Scale Cohort Studies in Japan

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ABSTRACT

Background: To show the reduction in life expectancy due to smoking and the recovery of normal life expectancy by smoking cessation is useful for tobacco control health policy.

Methods: This study included 140,026 males and 156,810 females aged 40-79 years, who were participants of large-scale cohort studies in Japan (Japan Health Center-based Prospective Study [JPHC]-I, JPHC-II, Three-Prefecture Study, and Japan Collaborative Cohort [JACC] Study), which commenced around 1990. The mean follow-up period (±standard deviation) was 9.6 ± 2.3 years, during which 16,282 men and 9,418 women died. For persons aged 40-79 years grouped according to each defined smoking status in the baseline questionnaire, sex- and age-specific death rates at attained ages were calculated. The age-specific death rate was calculated by dividing the number of persons who died at the age by the number of persons who were followed-up at the attained age. From these death rates, current life tables were constructed according to the smoking status, and survival curves were plotted.

Results: The life expectancy of male smokers, ex-smokers, and never-smokers at age 40 years was 38.5, 40.8, and 42.4 years respectively. In women, the corresponding life expectancies were 42.4, 42.1, and 46.1 years. In both sexes, the age by which half of the current smokers had died was approximately 4 years younger than that for never-smokers. The life expectancies of male ex-smokers who quit smoking before ages 40, 50, 60, and 70 years were 4.8, 3.7, 1.6, and 0.5 years longer than those of smokers, respectively.

Conclusion: Smoking considerably reduced the life expectancy, and earlier smoking cessation resulted in a better survival than that seen with continued smoking.

Key words: Smoking, Life Expectancy, Cohort Studies

INTRODUCTION

Smoking is a major cause of cancers and cardiovascular and other diseases and consequently increases the risk of death.[1] Determining the reduced life expectancy due to smoking in addition to the increased risk of developing individual diseases should be effective in estimating the health burden associated with smoking. Survival curves derived from life tables have revealed a trend toward increased mortality with age. Several studies have used survival curves to investigate the reduction in life expectancy caused by smoking.[2-9] A previous Japanese study investigating circulatory diseases was based on a representative population in Japan but included a relatively small sample size.[10]

Several large-scale cohort studies based on the general population of Japan commenced in the early 1990s,[11-14] and around 300,000 middle-aged and elderly men and women were observed over approximately 10 years. In the present

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study, we sought to construct life tables to evaluate the reduction in life expectancy due to smoking and to assess whether normal life expectancy is regained by the cessation of smoking at different ages.

METHODS

The subjects of this study were derived from 3 cohort studies in Japan.[11-15] One of these was the Three-Prefecture Study, which was conducted in Miyagi, Aichi, and Osaka Prefectures in a total of 15 areas. The study population comprised all residents aged 40 years or older in the study areas. The subjects were followed up from February 1, 1983/December 1, 1990 through December 31, 1993/February 28, 2000 (different follow-up periods in different study areas).[11] The second study was the Japan Collaborative Cohort (JACC) Study, which was conducted in 45 areas in the 4 main islands of Japan, excluding Shikoku Island. The study population consisted of all residents aged 40 years or older in 22 areas, participants of health examinations conducted by the municipalities in 20 areas, and a combination of the above and atomic bomb survivors in the remaining areas. The subjects were followed up from 1988/1990 through December 31, 1999 (different starting periods in different areas).[12,13] The third study was the Japan Public Health Center-based Prospective (JPHC) Study.[14] The subjects of JPHC-I were recruited in 1990, and this study targeted registered inhabitants aged 40-59 years in 5 public health center areas in Iwate, Akita, Nagano, Okinawa, and Tokyo. They were followed up from January 1, 1990 to December 31, 2000.[15] JPHC-II subjects were recruited in 1993-1994, and this study targeted registered inhabitants aged 40-69 years in 6 public health center areas in Niigata, Ibaraki, Kochi, Nagasaki, Okinawa, and Osaka. They were followed up from January 1, 1993 through December 31, 2003.[15]

Smoking status was surveyed in the baseline questionnaire for each cohort study. The status was divided into 3 categories: smoking, ex-smoking, and nonsmoking. Among smokers and ex-smokers, the age at which smoking was started (and stopped in the case of ex-smokers) and the number of cigarettes consumed a day were recorded.[11-15] Follow up of the subjects was study specific, and the details are described elsewhere.[11-15] As a general rule, all deceased people in each study area and people who moved out of the study area were identified using the population registry in each municipality office. The cause of death for each person was obtained from the death certificate.

A total of 140,026 men and 156,810 women aged 40-79 years from the 3 cohorts were included in this study (Table 1). The mean follow-up period (±standard deviation) was 8.5 ± 2.7 years, 9.9 ± 2.2 years, 10.4 ± 1.6 years, and 10.2 ± 1.7 years for the Three-Prefecture Study, JACC Study, and JPHC-I and -II Studies, respectively. The prevalence of smokers in each cohort is shown in Table 1. The age-adjusted death rate by cohort, sex, and smoking status was separately calculated for the age groups of 40-69 years and 70 years or older and based on the sex- and 5-year age-specific death rates was classified according to the smoking status of each cohort. The standard population was constituted of age-specific numbers of persons who were followed-up at the attained age. The adjusted death rates in smokers and nonsmokers varied slightly between cohorts, and the rate ratios of smokers/nonsmokers were approximately 1.5-1.8 in men and 1.4-2.1 in women.

The characteristics of all the subjects are shown in Table 2. The mean age (±standard deviation) was 54.1 ± 9.7 years in men and 54.5 ± 9.8 years in women. The prevalence of male

Table 1. Characteristics of the cohorts.

	Cohort study	No.	Age at baseleine survey (years) (Mean±SD, ranege)	Prevalence of current smokers	Age-adjusted death rate at attained age groups ‡ (per 1,000)			
					40-69 years old		70 years or older	
					Smokers	Never-smoker	Smoker	Never-smokers
Male	Three-Prefecture	44,453	54.4 ± 10.2 (40-79)	57.8%	9.31	5.79	54.0	36.2
	JACC *	42,528	57.3 ± 10.2 (40-79)	53.0%	7.62	4.51	44.9	28.1
	JPHC †-I	23,478	49.0 ± 6.0 (40-59)	53.6%	8.24	5.28	NA	NA
	JPHC-II	29,567	53.2 ± 8.8 (40-69)	52.0%	9.32	4.96	41.4	24.1
	Total	140,026	54.1 ± 9.7 (40-79)	54.4%	8.59	5.01	48.2	30.9
Female	Three-Prefecture	43,704	55.2 ± 10.5 (40-79)	11.9%	6.21	3.62	33.8	25.0
	JACC	53,370	57.3 ± 10.1 (40-79)	5.6%	4.72	2.44	28.3	17.2
	JPHC-I	26,561	49.1 ± 5.9 (40-59)	7.9%	4.25	2.91	NA	NA
	JPHC-II	33,175	53.5 ± 8.9 (40-69)	7.3%	5.85	2.80	18.6	12.4
	Total	156,810	54.5 ± 9.8 (40-79)	8.1%	5.53	2.87	31.3	19.3

* JACC: Japan Collaborative Cohort
† JPHC: Japan Public Health Center-based prospective Study Cohort
‡ Adjusted for the standard population constituted of age-specific person years observed at the attained age.
NA: not available

Table 2. Characteristics at the baseline survey of subjects and observed person-years from all cohorts.

	No.	Observed person-years	Age at baseleine survey (years) (Mean ± SD)	No. of cigarettes consumed a day (Mean ± SD)	Duration of smoking (years) (Mean ± SD)	Age at quitting (years) (Mean ± SD)	Duration after quitting smoking (years) (Mean ± SD)
Male							
Smokers	76,227	717,200	53.2 ± 9.4	22.3 ± 10.9	32.2 ± 9.6	NA	NA
Ex-smokers	35,079	328,883	56.4 ± 10.0	23.3 ± 13.6	24.7 ± 11.9	45.4 ± 12.0	10.8 ± 8.9
Never-smokers	28,720	278,921	53.7 ± 9.5	NA	NA	NA	NA
Total	140,026	1,325,004	54.1 ± 9.7	NA	NA	NA	NA
(subgroups)							
Smokers, 1-14 cigarettes a day	12,838	117,742	56.8 ± 10.3	8.9 ± 2.6	34.5 ± 11.3	NA	NA
Smokers, 15-24 cigarettes a day	37,845	357,916	53.9 ± 9.4	18.9 ± 2.0	33.0 ± 9.6	NA	NA
Smokers, 25+ cigarettes a day	24,374	230,170	50.2 ± 7.9	34.7 ± 9.4	30.0 ± 8.1	NA	NA
Ex-smokers, quit at age <40 years	10,384	100,155	49.0 ± 8.3	21.6 ± 13.6	11.8 ± 5.2	31.7 ± 5.0	17.2 ± 9.8
Ex-smokers, quit at age 40-49 years	10,122	97,328	53.5 ± 7.7	24.8 ± 14.1	22.9 ± 4.4	43.6 ± 2.9	9.9 ± 7.8
Ex-smokers, quit at age 50-59 years	7,917	74,227	61.1 ± 5.7	24.1 ± 13.4	32.5 ± 5.1	53.6 ± 2.9	7.5 ± 5.8
Ex-smokers, quit at age 60-69 years	3,962	34,117	68.0 ± 4.4	22.7 ± 12.6	41.1 ± 5.6	62.8 ± 2.6	5.1 ± 4.3
Female							
Smokers	12,717	117,172	53.4 ± 10.1	14.3 ± 8.6	23.3 ± 11.4	NA	NA
Ex-smokers	3,714	33,517	56.5 ± 11.1	12.1 ± 9.0	17.6 ± 11.9	46.6 ± 13.0	9.6 ± 8.4
Never-smokers	140,379	1,379,703	54.5 ± 9.7	NA	NA	NA	NA
Total	156,810	1,530,392	54.5 ± 9.8	NA	NA	NA	NA
(subgroups)							
Smokers, 1-14 cigarettes a day	6,296	58,029	54.4 ± 10.7	7.9 ± 2.9	22.3 ± 12.4	NA	NA
Smokers, 15-24 cigarettes a day	4,944	45,497	52.4 ± 9.5	18.2 ± 2.3	24.1 ±10.4	NA	NA
Smokers, 25+ cigarettes a day	1,061	9,570	50.7 ± 8.4	34.0 ± 8.9	25.4 ± 9.4	NA	NA
Ex-smokers, quit at age <40 years	956	8,923	46.2 ± 8.0	10.4 ± 7.8	8.1 ± 5.5	30.6 ± 5.5	15.5 ± 9.3
Ex-smokers, quit at age 40-49 years	879	8,027	52.7 ± 7.9	11.9 ± 9.1	15.4 ± 7.9	43.8 ± 3.0	8.9 ± 8.2
Ex-smokers, quit at age 50-59 years	869	7,966	60.7 ± 6.1	13.0 ± 9.0	20.6 ± 9.6	53.4 ± 3.0	7.3 ± 6.1
Ex-smokers, quit at age 60-69 years	469	3,966	68.2 ± 4.3	14.1 ± 10.3	29.2 ± 11.1	62.6 ± 2.6	5.5 ± 4.5

NA: not available, SD: standard deviation

smokers was 54.4% overall and 59.5%, 54.2%, 55.6%, and 42.5%, respectively, for the age groups of 40-49, 50-59, 60-69, and 70-79 years. There were 25.1% male ex-smokers and 20.5% male never-smokers. Amongst women, 8.1% were smokers (9.5%, 7.5%, 6.8%, and 8.5%, respectively, for the age groups mentioned above); 2.4% were ex-smokers; and 89.5% were never-smokers. The smokers were further classified according to the number of cigarettes consumed per day, and the ex-smokers were categorized by the age at which they stopped smoking.

Sex- and age-specific death rates were calculated based on the observed person-years at attaining ages and the number of deaths at that age. From these death rates, the complete current life tables were constructed using Chiang's method, for each smoking status.[16] Life expectancies at age 40 years were calculated, and survival curves beginning at age 40 years up to that at age 90 years, for a population of 100,000, were plotted. We estimated the 95% confidence interval (CI) for life expectancy by setting the age intervals less than 90 years as one year and the last interval as age 90 years or older.[16]

For the ex-smoker subgroup, the age group at which the subjects quit smoking was divided into 10-year intervals, i.e., 40-49 years, 50-59 years, and 60-69 years. For those who quit smoking at the age of 40-49 years, the death rates up to the age of 44 years were assumed to be equal to those of smokers, while those at ages 45 or older were considered to be equal to the death rates of ex-smokers. Death rates for those who quit smoking at the age 50-59 years or 60-69 years were derived in the same way.

RESULTS

The person-years by smoking status and the number of deaths among men and women are presented in Table 2. Most observations were distributed amongst subjects in their 50s and 60s. Sex- and age-specific death rates up to the age of 89 years are shown for men and women in Figures 1 and 2, respectively. In general, the rates increased in an exponential

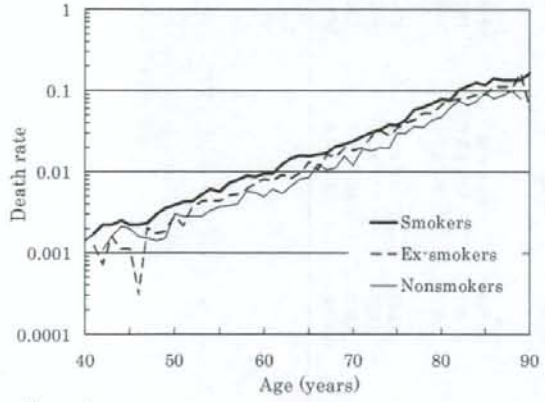

Figure 1

Age-specific death rates calculated at the attained ages (males).

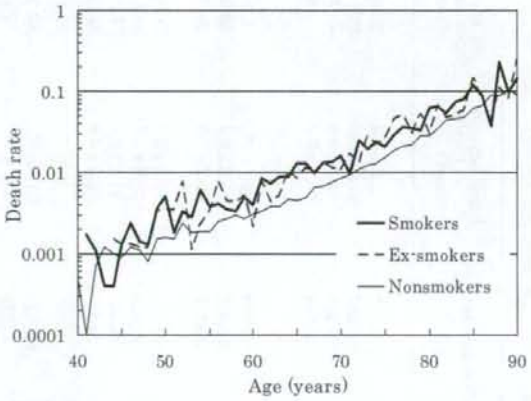

Figure 2

Age-specific death rates calculated at the attained ages (females).

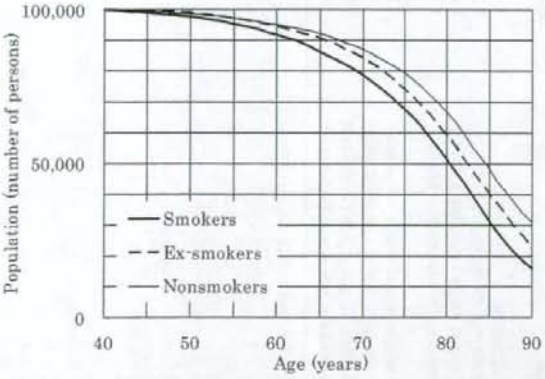

Figure 3. Survival curves for all males included in the study, starting from age 40 years, for a population of 100,000.

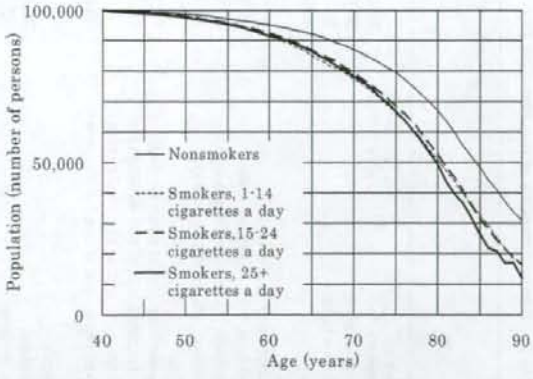

Figure 4. Survival curves for male smokers, starting from age 40 years, for a population of 100,000.

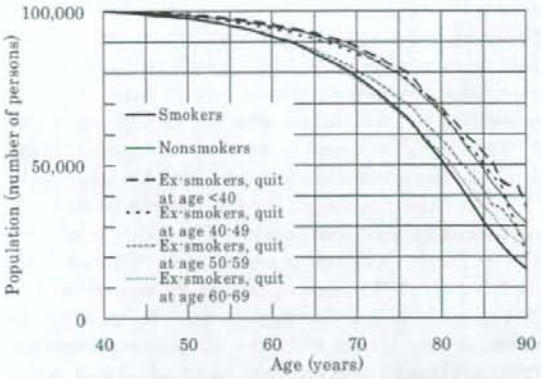

Figure 5. Survival curves for male ex-smokers, starting from age 40 years, for a population of 100,000.

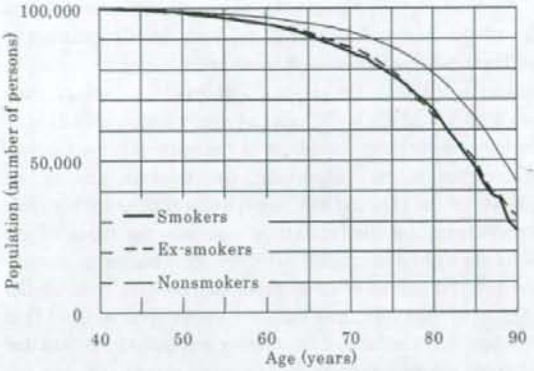

Figure 6. Survival curves for all females included in the study, from age 40 years, for a population of 100,000.

linear pattern in both sexes, regardless of the smoking status.

At age 40 years, the life expectancy was 38.5 years (95% CI: 38.3 and 38.7) for male smokers, 40.8 years (95% CI: 40.6 and 41.0) for ex-smokers, and 43.2 years (95% CI: 42.2 and 42.7) for never-smokers (Table 3). For women, the corresponding life expectancies at age 40 years were 42.4 (95% CI: 42.1 and 43.0), 43.1 (95% CI: 42.1 and 43.5), and 46.8 (95% CI: 46.0 and 46.3) years (Table 3). Both male and female heavy smokers had slightly shorter life expectancies than those of light smokers. Male ex-smokers who quit before age 40 years had a slightly longer life expectancy (43.3 years, 95% CI: 42.6 and 43.9) than that of never-smokers. Male ex-smokers who quit smoking at younger age had a longer life expectancy than that of ex-smokers who quit at older age.

Table3. Observations on follow up, and calculated survival rates and life expectancies.

	Person-years of follow up	No. of deaths	Age by which half of the population died from age of 40 years	Life expectancy at age of 40 years (95% confidence interval)
Male				
Smokers	717,200	9,240	80.4	38.5 (38.3, 38.7)
Ex-smokers	328,883	4,582	82.4	40.8 (40.6, 41.0)
Never-smokers	278,921	2,460	84.6	42.4 (42.2, 42.7)
Total	1,325,004	16,282	81.8	39.9 (39.8, 40.0)
(subgroups)				
Smokers, 1-14 cigarettes a day	117,742	2,224	80.1	38.3 (37.8, 38.7)
Smokers, 15-24 cigarettes a day	357,916	4,762	80.6	38.7 (38.4, 38.9)
Smokers, 25+ cigarettes a day	230,170	2,111	79.8	37.9 (37.4, 38.4)
Ex-smokers, quit at age <40 years	100,155	474	86.1	43.3 (42.6 43.9)
Ex-smokers, quit at age 40-49 years	97,328	739	84.9	42.2 (41.7, 42.7)
Ex-smokers, quit at age 50-59 years	74,227	1,300	82.4	40.1 (39.6, 40.6)
Ex-smokers, quit at age 60-69 years	34,117	1,201	81.1	39.0 (38.3, 39.6)
Female				
Smokers	117,172	1,085	84.4	42.5 (42.1, 43.0)
Ex-smokers	33,517	409	85.0	42.8 (42.1, 43.5)
Never-smokers	1,379,703	7,924	88.4	46.1 (46.0, 46.3)
Total	1,530,392	9,418	88.0	45.7 (45.6, 45.9)
(subgroups)				
Smokers, 1-14 cigarettes a day	58,029	609	84.5	42.5 (41.9, 43.2)
Smokers, 15-24 cigarettes a day	45,497	366	84.0	42.3 (41.5, 43.0)
Smokers, 25+ cigarettes a day	9,570	79	81.9	40.4 (38.3, 42.4)
Ex-smokers, quit at age <40 years	8,923	28	85.0	43.5 (41.2, 45.9)
Ex-smokers, quit at age 40-49 years	8,027	52	89.0	43.9 (41.7, 46.0)
Ex-smokers, quit at age 50-59 years	7,966	94	86.5	43.9 (42.6, 45.3)
Ex-smokers, quit at age 60-69 years	3,966	106	84.9	42.0 (41.0, 43.0)

Survival curves (commencing at age 40 years) were plotted for all the men and women in the study for a population of 100,000 and were classified according to smoking status, as shown in Figures 3-6. Figure 3 shows that 21% of male smokers would die by 70 years of age, whereas only 13% of male never-smokers would die by the same age. For women, the corresponding proportions for smokers and never-smokers were 14% and 8%, respectively (Figure 6). For male ex-smokers, the survival curve was between those of the smokers and never-smokers (Figure 3), whereas in women, the survival curves of ex-smokers and smokers were similar (Figure 6). Amongst male smokers, the survival curve of light smokers was similar to that of heavy smokers rather than that of never-smokers (Figure 4). The survival curve of male ex-smokers who quit before age 40 was better than that of never-smokers (Figure 5). Male ex-smokers who quit at age 40-49 showed similar survival to that of never-smokers. Those quitting at ages 50-59 and 60-69 showed intermediate survival, i.e., between those of smokers and never-smokers. Survival curves for female ex-smokers quitting at various ages were between those of smokers and never-smokers, most of whom were aged < 85 years.

The age by which half of the study population had died is shown in Table 3. In males, this age was 4.2 years lower in smokers than in never-smokers, whereas the difference was 4.0 years for female smokers compared with female never-smokers. For male ex-smokers, the age at death was 2.2 years younger than that for never-smokers and the age at death for women ex-smokers compared with that for never-smokers was 3.4 years lower.

DISCUSSION

In this study, life expectancy for male smokers aged 40 years was 3.9 years shorter than that for male never-smokers and 1.6 years shorter than that for ex-smokers. For women, the corresponding differences were 3.6 and 3.3 years. The respective life expectancies of male ex-smokers who quit smoking before ages 40, 50, 60, and 70 years were 4.8, 3.7, 1.6, and 0.5 years longer than those of smokers. Although smoking cessation at any age led to a certain recovery of life expectancy, the earlier the cessation, the larger was the recovery, and never smoking is the best way to live out our natural lives.

This study was based on data from cohort studies, but a current life table was constructed from the age-specific death rates calculated from the cross-sectional summation of observed person-years and the number of deaths at each age. Cohort subjects in age ranges 40-59, 40-69, and 40-79 years were followed up during the 1990s over approximately 10 years. We compared the life expectancy in this study with the life table to Japan in 1995, which was constructed at around the mid-point of the follow-up period of our examined cohorts.[17] Life expectancy at age 40 years for the entire population in this study was 40.2 years for men and 46.3 years for women, whereas in the 1995 life table for Japan, the life expectancies for men and women were 37.9 and 43.9 years respectively.[17] These figures were not directly comparable because the methods used to calculate them were different. The difference between smoking status should be considered.

The difference in median survival between smokers and never-smokers was approximately 4 years in both sexes (Tables 2 and 3). This was in contrast to the difference in the median survival (7.5 years) of smokers and nonsmokers in a 40-year study of male British physicians.[2] In this study, the difference was 5 years in the first 20 years of observation (1951-1971) and 8 years in the second half of the study period (1971-1991). In a subsequent study of male British physicians who were born in 1900-1930 and followed up over 50 years, the difference in the median survival between smokers and nonsmokers increased to 10 years.[3] The authors suggested that the difference between the observed median survivals calculated for the time periods 1951-1971 and 1971-1991 was because most of the deaths in nonsmokers occurred in the second half of the study.[3] The greater difference reported in 2004 was based on direct longitudinal observation over half a century.[3] This was because nonsmokers actually survived longer than their predicted life expectancy calculated from cross-sectional data. The median survival difference of 4 years observed in the present study, which was based on an approximately 1-decade follow-up period, is similar to that seen in the 1951-1971 part of the study on British physicians.[2] With a longer follow-up period and decreasing prevalence of smokers, we would have observed a greater difference in the median survival time.

In our study, the difference in the survival curves for light and heavy male smokers was small. This finding is consistent with the results of Hirayama's cohort study, which found that the relative risks of all causes of death were similar in smokers who consumed 1-9, 10-19, and 20+ cigarettes a day (relative risk: 1.35, 1.25, and 1.29, respectively); however, most individual diseases associated with smoking, such as lung cancer, showed dose-dependency.[18]

When considering the survival of ex-smokers, several points should be kept in mind. The reasons for cessation of smoking are many and varied; some smokers may quit because of illness, whereas others quit not because they are ill, but in order to avoid the known, long-term effects of smoking. In the former, the mortality rate of ex-smokers may be raised just after quitting, while in the latter, the mortality rate may be decreased for some time after quitting smoking.

Male ex-smokers who quit smoking before the age of 40 years (mean age 31 years) demonstrated an improved survival over never-smokers. These ex-smokers might have been health conscious and consequently healthier, in general, than never-smokers because they quit smoking when they were young, i.e., before the early 1990s, when the adverse effects of

smoking were less well known in Japan. Some of the smokers in this category may have quit because of illness, but their proportion appeared to be small because of the longer survival of ex-smokers who quit early. In the longitudinal study of British physicians, a similar result was demonstrated for ex-smokers who quit before the age of 35.[3] In our study, the survival of ex-smokers who quit smoking at 40-49 years of age was similar to that of never-smokers. In contrast, British physicians who quit smoking at ages 35-44 and 45-55 demonstrated reduced survival.[3]

An explanation for this difference may be that never-smokers in our Japanese study might have been less healthy, because smoking was very common in Japanese men, and the smoking rate was very high (approximately 80%) in the 1970s and 1980s.[19] Consequently, Japanese never-smokers might have had health problems that compelled them to avoid smoking. In British physicians, although the prevalences of smokers, ex-smokers, and never-smokers were 62%, 13%, and 25%, respectively in 1951, the corresponding figures in the 1990-91 survey were 18%, 60%, and 22%, respectively.[2] In addition, among young physicians aged 20-24 and 25-29 years in 1951, the prevalence of never-smokers was 43% and 30%, respectively.[20] Thus, British physicians quit smoking or chose to never smoke a very long time ago.

In a previous Japanese study (NIPPON DATA 80), the difference in the life expectancies of smokers and never-smokers was 3.5 years in males and 2.2 years in females.[10] These life expectancies are 0.4 and 1.4 years shorter than the comparable figures in our study. The baseline survey for the previous Japanese study was conducted in 1980, approximately 10 years earlier than our own, at a time when smoking was more common in Japan.[19] Therefore, the nonsmoking group was thought to include people with conditions that compelled them to avoid smoking, and the difference in their life expectancy and that of smokers might be considered small. In addition, passive smoking, being more common in that era, could have contributed to the small survival difference by increasing the death rate of never-smokers.

There were some limitations in our study. Misclassification of smokers and never-smokers may have occurred. For example, those classified as smokers at the time of baseline survey, who subsequently quit smoking, could have contributed to a lower mortality rate in the smoker group because of improved health. This misclassification may be largely because of contemporaneous tobacco-free promotions. Such misclassification may also have occurred in our study. To reduce this possibility, it would be useful to collect data regarding changed smoking status during follow up. In women, the small number of observations in smokers and ex-smokers may have decreased the reliability of their results although the survival of heavy smokers was shorter than that of light smokers, and the survival of ex-smokers was between those of never-smokers and smokers.

Reduced life expectancy due to smoking has been shown in previous studies. In the United States, the life expectancy of smokers of both sexes was reported to be approximately 7 years less than that of nonsmokers, as determined from data sets including smoking status just prior to death.[4] In Australia, in the mid-1980s, the difference in the life expectancies of 15-year-old males who had never smoked and those who were heavy smokers was estimated as 5.6 years. However, this estimate was based on a projection using age-specific mortality and an etiological fraction for smoking determined by the indirect method.[5] Based on population studies in Copenhagen, the reduction in the life expectancy of heavy smokers was 9.2 years in men and 9.4 years in women; this difference is large compared with other studies and may be because data regarding changed smoking status was repeatedly collected during follow up.[6] In a Danish National Cohort Study, the life expectancy at age 20 was 7 years less for heavy smokers than for subjects who had never smoked, and that at age 65 years was 5 years less in both men and women smokers. This was determined by estimating smoking-attributable mortality rates and using them for constructing a life table.[7] In the Chicago Heart Association Detection Project in Industry Study, the life expectancies of male current smokers were 5.3 and 5.7 years shorter than those of never-smokers in the 2 groups with lower cholesterol levels; the life expectancies were estimated using absolute risk and absolute excess risk.[8] In the Framingham Heart Study, the difference in the life expectancy at age 50 between subjects who had never smoked and those classified as always smokers was reported as 8.66 years in men and 7.59 years in women; in this study, the smoking status was determined in biennial exams during follow up.[9]

In conclusion, the life expectancy of the population included in Japanese large-scale cohort studies was reduced by slightly less than 4 years in smokers as compared with never-smokers in both men and women. Smoking cessation at any age led to a certain recovery of life expectancy, and the earlier the cessation, the larger was the recovery. Further, never smoking is the best way to live out our natural lives. The 4-year reduction in life expectancy may be an underestimation because in this study, the smoking status was determined only at the time of the baseline surveys for the cohort studies. In addition, in Japan around 1990, the never-smoker subset may have included people with conditions that compelled them to avoid smoking.

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Letter to the editor

Smoking behavior and attitudes toward smoking cessation among members of the Japanese Cancer Association in 2004 and 2006

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We analyzed the postal surveys conducted by Japanese Cancer Association (JCA) in 2004 and 2006. This survey aimed to assess JCA members' behavior and their attitudes toward patients who are smokers, smoking cessation, and their responsibilities. In the 2006 version, questions were added about hope for various approaches related to smoking and health and the attitudes as medical experts when treating patients. JCA members' smoking rate was 5.9% in 2004 and 9.0% in 2006. Current smokers were significantly more likely than never or former smokers to disagree or have no opinion with most activities about smoking control such as 'raising the price of tobacco' and 'labeling health warnings describing the harmful effects of tobacco in large letters with clarity for easier reading', while most members including smokers agree to ban smoking while walking, to educate general people about tobacco and health, to provide an environment where children cannot get tobacco and the information about tobacco and health. Smoking rate among JCA members were less than that of general populations, and most of them are in favor of promoting tobacco control activities. (*Cancer Sci* 2008; 99: 824–827)

Smoking represents the single largest preventable cause of disease and death in the world today. Exposure can cause cancer of the lip, oral cavity, pharynx, esophagus, stomach, liver, pancreas, larynx, lung, cervix uteri, kidney, and bladder, and myeloid leukemia,[1,2] and recent research in Japan indicates that 29% of male cancers and 3% of female cancers are preventable in the Japanese middle-aged population if they avoid tobacco smoking.[3] The members of the Japanese Cancer Association (JCA) can play a leading role in helping people to live tobacco free through political action and by counseling people to quit smoking. The aim of the present study was to assess past and current smoking behavior and JCA members' attitudes toward patients who smoke, smoking cessation, and their responsibilities as JCA members.

The JCA conducted a postal survey in 2004 and 2006. In the 2004 survey, all members classified as honorary members, councilors, and general members were identified and 179, 360, and 607 members, respectively, whose last two-digit membership numbers were 21, 41, 71, or 91, were approached. In the 2006 survey, among all of the members identified through the membership database of JCA, those whose last-digit membership number was 5 were selected ($n = 1547$). After exclusion of members with incorrect addresses ($n = 24$), 923 were approached. The questions for the questionnaire were developed after a review of the literature with acceptable face validity and discussion with the Committee for Control of Tobacco Use. A nationally recognized expert with extensive experience in the areas of smoking cessation and survey research provided input to establish content validity. Changes suggested (e.g. adding or deleting questions, wording changes) were adopted to create the final questionnaires. The majority of questions had a closed-ended format, with multiple choices, or yes or no answers, with coverage of medical specialty, sex, age, and smoking behavior included.

After the first mailing, 144 honorary members, 249 councilors, and 269 general members in 2004 and 676 members in 2006 responded to the survey giving response rates of 57.8 and 44.5%, respectively. After a single reminder in 2006, the total rose to 923, a response rate of 60.6%. Participants that did not respond to the questions about smoking in the 2006 survey ($n = 3$) were deleted from the analysis.

The majority of the responders in both the 2004 and 2006 surveys were men (82.5% in 2004 and 78.2% in 2006) in their 50s (28.9%) in 2004 and in their 40s (35.0%) in 2006, and people who specialized in clinical fields (39.4% in 2004, 43.3% in 2006). In 2004, 40.6% were general members, 37.6% were councilors, and 21.8% were honorary members.

Overall, 5.9 and 9.0% were current smokers and 41.8 and 29.7% were former smokers in 2004 and 2006, respectively (Table 1). The prevalence of current smokers was higher in the younger age group whereas that of former smokers was lower in the younger age group in both surveys. In the 2004 survey, the prevalence of current smokers was higher and that of former smokers was lower in general members than in honorary members and councilors combined. For women, there were 31 and 116 responders in 2004 and 2006, respectively, and their smoking prevalence was much lower than in men. Current and former smokers accounted for 0 and 6.5% in 2004 and 0.9 and 7.8% in 2006, respectively.

Current smokers were also asked to respond to questions about smoking cessation behavior and concern about smoking cessation. A behavioral theoretical model was used to assess the position of smokers on the change continuum. The stages of the change model were based on the model of Prochaska and DiClemente,[4] and were developed by Nakamura.[5] Smokers who were not interested in quitting smoking and were not considering quitting in the next 6 months were defined as 'immotivators', whereas those who were interested in smoking cessation but not considering cessation in the next 6 months were defined as 'precontemplators'. Those who were seriously thinking of stopping within the next 6 months were defined as 'contemplators'.

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Table 1. Smoking prevalence according to background characteristics among study responders

Characteristic	2004				2006			
	Current smoker (%)	Former smoker (%)	Never smoker (%)	Total	Current smoker (%)	Former smoker (%)	Never smoker (%)	Total
Age (years)[†]								
20–59	6.5	37.8	55.7	418	10.1	26.8	63.1	794
≥60	4.9	49.0	46.1	243	2.5	46.7	50.8	122
Major[‡]								
Clinical	6.1	40.6	53.3	261	8.5	30.9	60.6	398
Not clinical	5.8	42.6	51.5	394	10.2	25.6	64.2	324
Position[§]								
Honorary members	4.9	50.0	45.1	144	–	–	–	–
Councilors	4.8	47.8	47.4	249	–	–	–	–
General members	7.4	32.0	60.6	269	–	–	–	–
Total	5.9	41.8	52.3	662	9.0	29.7	61.3	920

[†]One subject in 2004 and four subjects in 2006 were deleted due to unknown status.
[‡]Seven subjects in 2004 and 198 subjects in 2006 were deleted due to unknown status.
[§]In the 2006 survey, information regarding members' positions were not asked.

Table 2. Distribution of 'stage of change' according to cessation experience within the last year among current smokers

Stage	2004			2006[†]		
	Smoking cessation experience (%) $n = 13$	No smoking cessation experience (%) $n = 26$	Total (%) $n = 39$	Smoking cessation experience (%) $n = 54$	No smoking cessation experience (%) $n = 28$	Total (%) $n = 82$
Immotive	0.0	50.0	33.3	14.8	32.1	20.7
Precontemplation	53.8	42.3	46.2	51.9	50.0	51.2
Contemplation	38.5	3.8	15.4	27.8	14.3	23.2
Preparation	7.7	3.8	5.1	5.6	3.6	4.9

[†]One subject in 2006 was deleted because the experience of smoking cessation was unknown.
Smokers were classified into four groups according to the strength of feeling to quit smoking.
Immotive, smokers who were not interested in quitting smoking and not considering about quitting in the next 6 months.
Precontemplation, smokers who were interested in smoking cessation but not considering cessation in the next 6 months.
Contemplation, smokers who were seriously thinking of stopping within the next 6 months.
Preparation, smokers who were planning smoking cessation within the following 1 month.

Smokers planning smoking cessation within the following 1 month were considered to be in the 'preparation' stage. Current smokers were asked whether or not they made at least one quit attempt at least 1 day during the last year or not.

Table 2 presents the 'stage of change' profile of current smokers. The majority were either in the immotive or precontemplation stage and only 5.1% in 2004 and 4.9% in 2006 indicated they were in the preparation stage and ready to quit within the next month. In both surveys, smokers reporting past smoking-cessation experiences within the last year were less frequent in the immotive stage and more frequent in the preparation stage than those with no previous cessation experience. For former smokers, they were asked about the elapsed years since smoking cessation and the number of quit attempts in the 2004 version.

In both the 2004 and 2006 surveys, approximately 60% of former smokers reported that they succeeded in stopping smoking with only one attempt and the remaining 40% succeeded after multiple attempts.

In the 2006 version, questions were added about hope for various approaches related to smoking and health and their attitudes as medical experts when treating patients. Responders were asked to assess three different statements dealing with beliefs about smoking control, stop-smoking treatment, and staff or patient smoking. We presented responders with a series of items relating to control or actions about smoking, with the responses being 'agree', 'no opinion', or 'disagree'. Furthermore, for the medical doctors who responded that they push cessation for patients who smoke, we asked questions about barriers to stop-smoking treatments.

Comparisons of the views of current smokers, former smokers, and never smokers were made using the χ^2-test. Responders that indicated that they were not medical staff ($n = 132$) nor working in a clinical capacity ($n = 180$) were deleted from the analysis.

As a result, current smokers were significantly more likely than never or former smokers to disagree or have no opinion with most items about smoking control. Figure 1 shows the items that had significant differences among smoking status with P-values less than 0.0001. Compared with never or former smokers, there was especially low agreement of current smokers with 'raising the price of tobacco' (24.1%), 'labeling health warnings describing the harmful effects of tobacco in large letters with clarity for easier reading' (28.9%), 'prevention of obtaining tobacco easily (regulation of tobacco vending machines)' (41.0%), and 'no smoking in public spaces such as stations or hospitals' (65.1%). Also, more current smokers tended to disagree with 'no smoking while walking', 'no smoking in the office except for designated smoking areas', 'campaigns or events about smoking and health by government', 'providing more opportunities for persons wishing to quit smoking to consult and be guided freely', 'educating more about the relationship between tobacco and