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

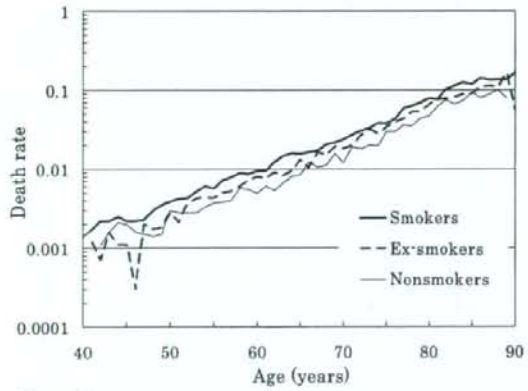

Figure 1

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

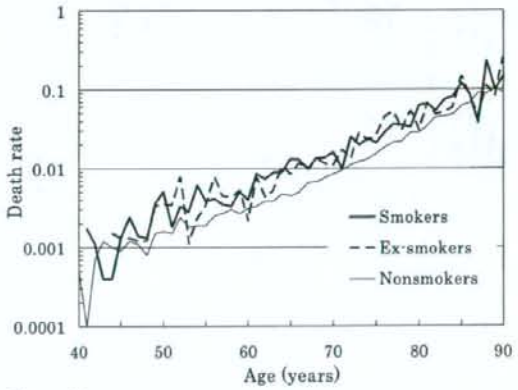

Figure 2

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

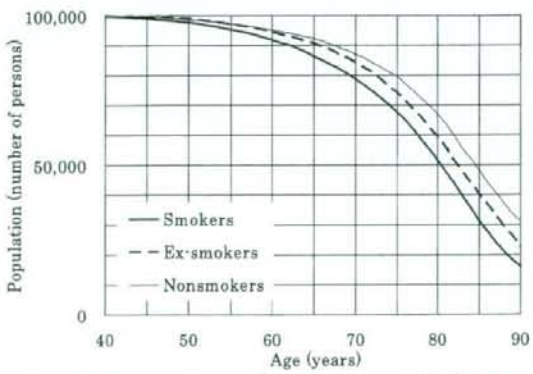

Figure 3. Survival curves for all males included in the study, starting from age 40 years, for a population of 100,000.

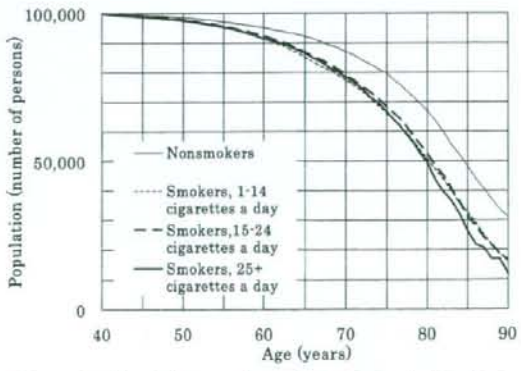

Figure 4. Survival curves for male smokers, starting from age 40 years, for a population of 100,000.

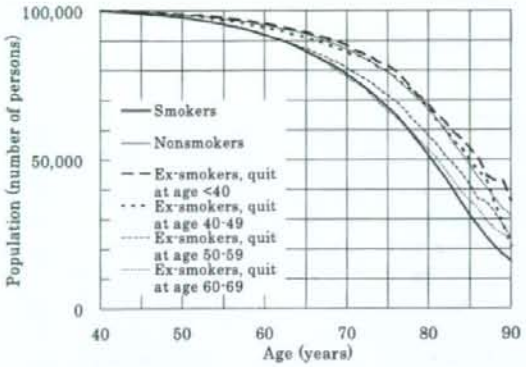

Figure 5. Survival curves for male ex-smokers, starting from age 40 years, for a population of 100,000.

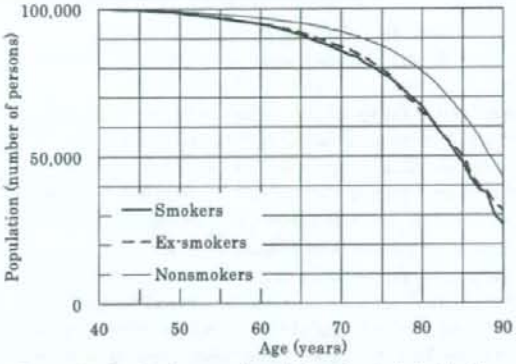

Figure 6. Survival curves for all females included in the study, from age 40 years, for a population of 100,000.

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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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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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 (One area†: 1990-1994)	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%)
						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 (One area‡: Dec. 1, 1990)	Jan. 31, 1993-Oct. 31, 1995 (One area‡: Feb. 28, 2000)	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%)
						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	42,528	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

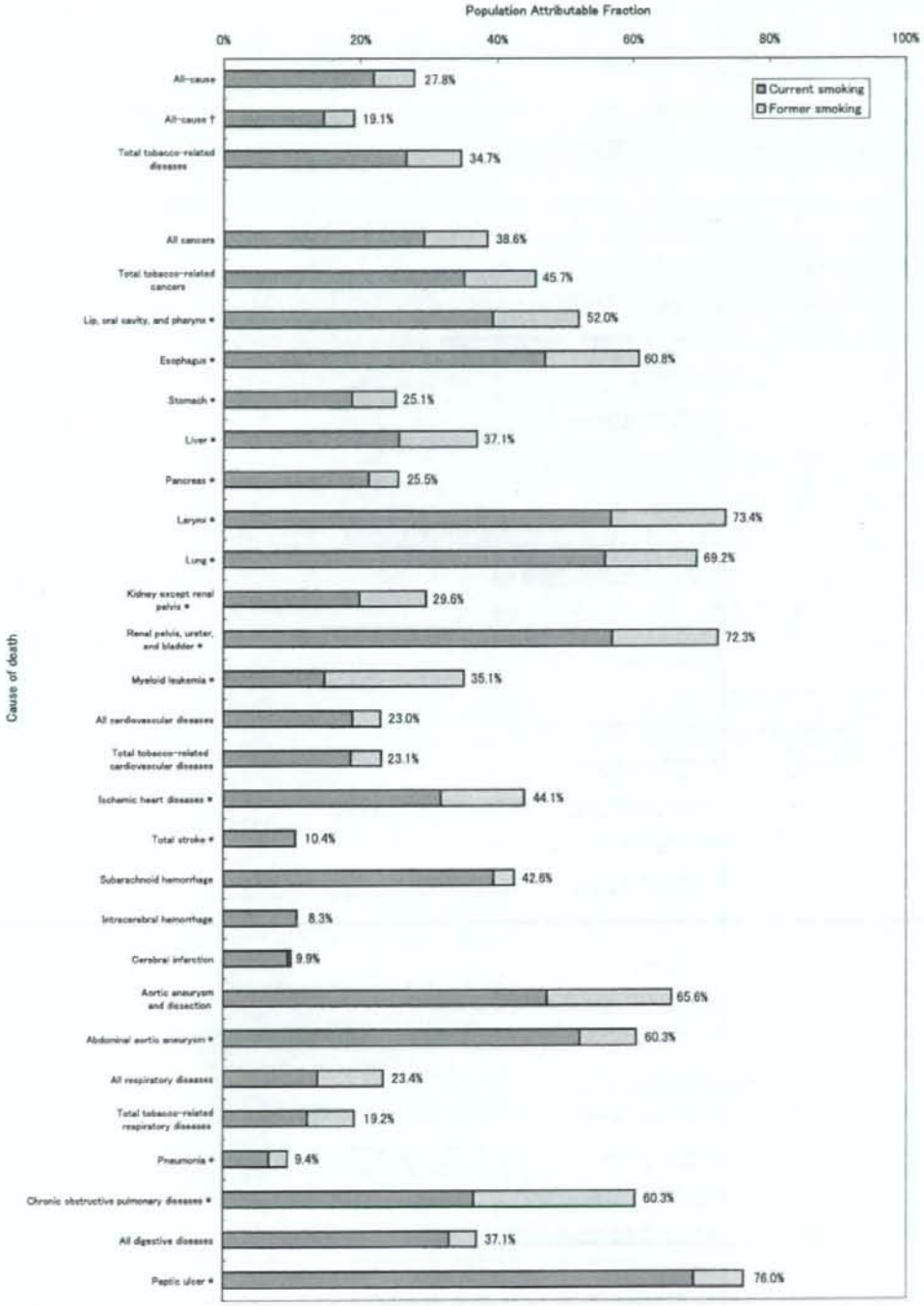

Figure 1. Population attributable fraction of disease-specific mortality due to smoking for males.

*: 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.

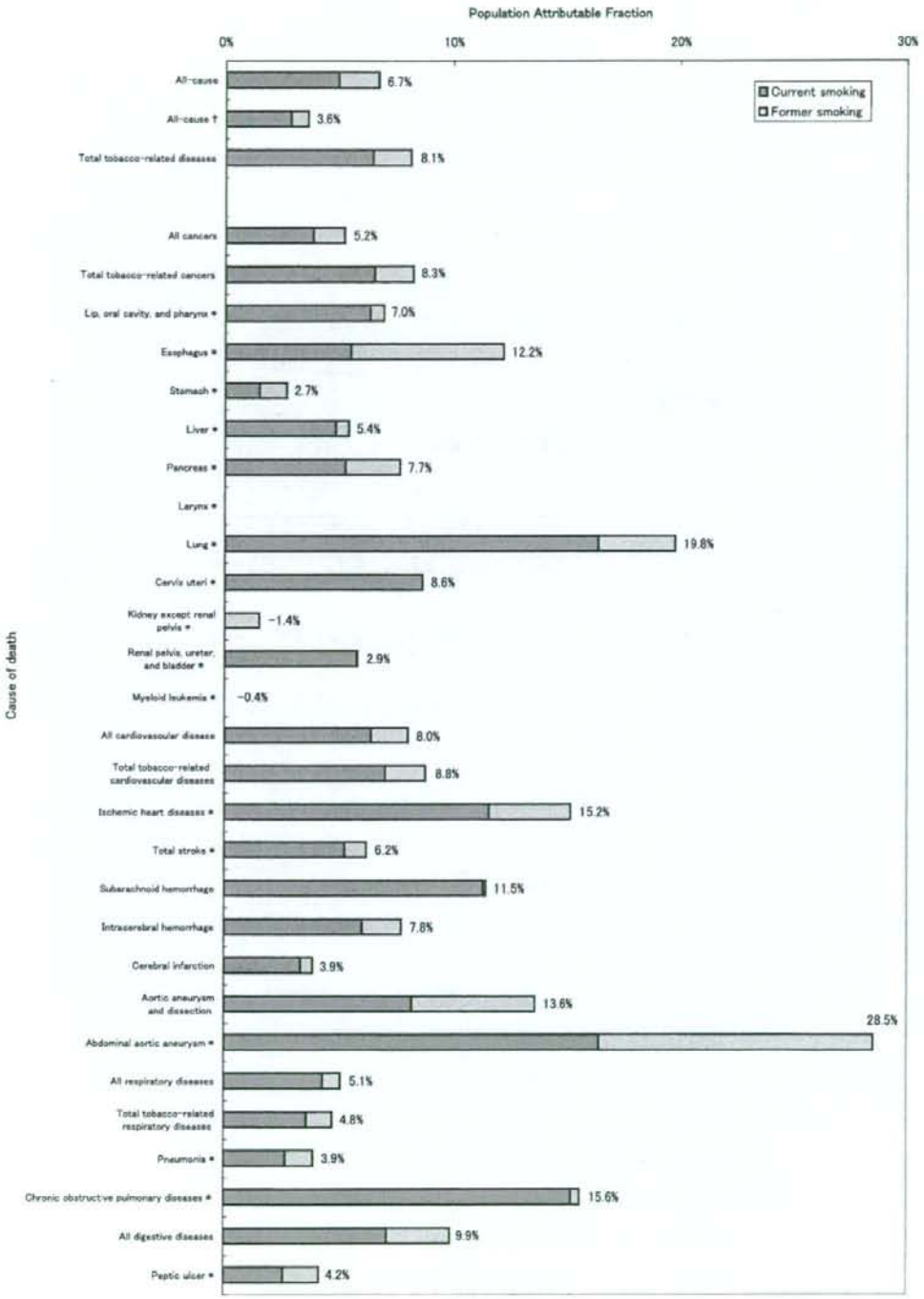

Figure 2. Population attributable fraction of disease-specific mortality due to smoking for females.

*: 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.

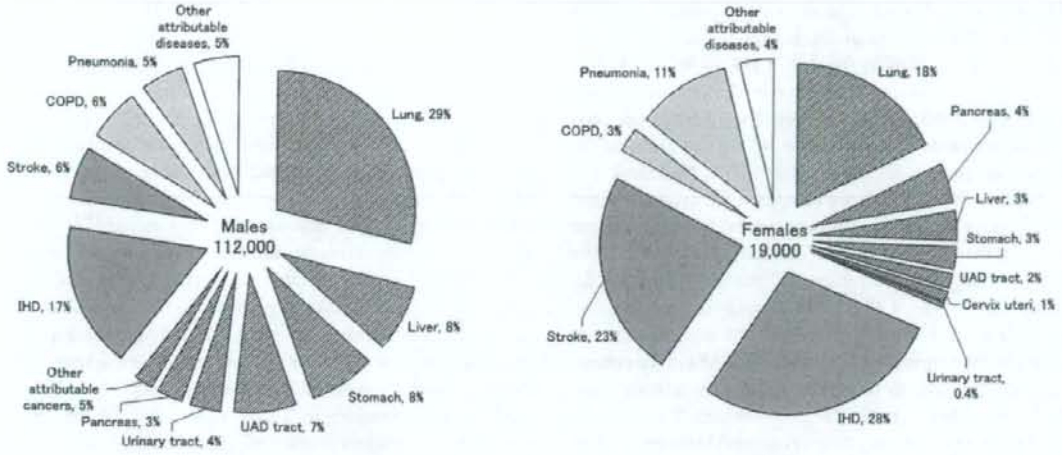

Figure 3. Estimated annual number of smoking-attributable deaths and disease distribution in Japan, for males and females.

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).

The prevalence of current smoking in the present study was lower than that reported in the Hirayama study,[13] [males: 54.4% vs. 74.5% (daily); females: 8.1% vs. 9.7% (daily)]. The prevalence of current smokers in the Hirayama study (carried out in 1965, when there were fewer former smokers) was comparable to the prevalence of ever-smokers in the present study (males: 79.5%; females: 10.5%, from the 1980s to the early 1990s). When we compared the estimate of the PAF of ever-smoking for all-cause mortality in the present study with the Hirayama results (current smoking only), the former was larger both for males (27.8% vs. 17.5%) and for females (6.7% vs. 4.4%). Considering the comparable prevalence of ever-smoking in the present study and current smoking in the Hirayama study, the larger PAFs in the present study would appear to be due to the higher relative risks. Indeed, the relative risks for ever-smokers for all-cause mortality in the present study (vs. never-smokers) were higher than the relative risks for current smokers in the Hirayama study (1.5 vs. 1.3 for males and 1.7 vs. 1.3 for females).

Compared with the annual smoking-attributable mortality in the US from 1997 to 2001,[1] our estimates of the male disease-specific PAFs of smoking were smaller for cancers of the lip/oral cavity/pharynx (52.0% vs. 74.1%) and the lung (69.2% vs. 87.9%), for pneumonia (9.4% vs. 22.5%), and for COPD (60.3% vs. over 80%), while our estimate was larger for IHD (44.1% vs. 20.8%). Note that the PAFs in the US were calculated from the numbers of deaths, excluding those from passive smoking. When we compared our estimated relative risks with the results of the CPS-II,[28] upon which the PAF for the US were based, the relative risks for male current smokers (vs. never-smokers) estimated in the present study were lower for all causes [1.6 vs. 2.3 (95% CI: 2.3-2.4)], lung cancer [4.8 vs. 23.2 (95% CI 19.3-27.9)], stroke [1.3 vs. 1.9 (95% CI: 1.6-2.2)], and COPD [3.1 vs. 11.7 (95% CI: 9.1-15.0)]. Given that the prevalence of current smokers among adult males is considerably higher in Japan than in the US (52.8% vs. 25.7%[29]), the smaller PAFs of smoking in the present study were considered to be due to these lower relative risks. In contrast, the relative risks for male current smokers for IHD were similar in the two studies [2.2 vs. 1.9 (1.8: 2.0)]. Thus, the larger male PAF of smoking for IHD recorded in the present study is considered to be due to the higher prevalence of smoking among Japanese males. For females, our estimate of the PAF of smoking was smaller than the US estimates[1] for many diseases, including lung cancer (19.8% vs. 70.9%), stroke (6.2% vs. 8.7%), and COPD (15.6% vs. over 70%). The relative risks for female current smokers were lower in the present study than in the CPS-II[28] for all causes [1.8 vs. 1.9 (95% CI: 1.9-2.0)], lung cancer [3.9 vs. 12.8 (95% CI 11.3-14.7)], and COPD [3.6 vs. 12.8 (95% CI 10.4-15.9)], whereas those for stroke were similar [1.8 vs. 1.8 (95% CI: 1.6-2.1)]. The prevalence of female current smokers is considerably lower in Japan than in the US (13.4% vs. 21.5%[29]). Thus, the lower PAFs of smoking in Japanese females for lung cancer and COPD are considered to be due to both the lower relative risks and the lower prevalence of smokers. In the case of stroke, the lower PAF was thought to be due to the lower smoking prevalence.

The lower relative risks associated with smoking for Japanese populations compared with those for Western populations have been well documented by previous studies for all causes,[6,30] total cancers,[7] and lung cancer.[15,31,32] A commonly proposed reason for this finding is the lower exposure level among Japanese smokers.[15,32] However, the difference in relative risks is reported to remain even after adjustment for duration of smoking and daily cigarette consumption,[15] or stratification by dose of exposure.[30,31] Other proposed reasons include the possibility of a higher level of passive smoking in Japan (i.e., a higher risk for non-smokers), the misclassification of former smokers as never-smokers (causing an apparent increase in the risk to non-smokers) and a lower genetic susceptibility to tobacco smoke among the Japanese. It is also possible that COPD tends to be underreported as a cause of death on death certificates.

There are several limitations to the present study that could have been potential sources of uncertainty in the estimation of the fraction and the number of smoking-attributable deaths. First, the smoking prevalence used for the estimation of the PAFs was obtained from our cohort data, the baseline survey for which was conducted from the 1980s to the early 1990s. The reason for using cohort data was the need to obtain the prevalence among those who died of a given cause of death.[20] There have been recent changes in the prevalence of smoking in Japan, and a decreasing trend for males is becoming evident. Although the pooled smoking prevalence in the present study was comparable to the national representative adult prevalence around the year 1990 (e.g., 53.1% for males and 9.7% for females in 1990),[33] recent corresponding values were lower for males and higher for females (43.3% for males and 12.0% for females in 2004).[34] On the basis of the national representative smoking prevalence data in 2004 and the relative risks for all-cause mortality in the present study, the PAF of ever-smoking was 25.2% for males and 11.0% for females. The corresponding value based on the prevalence data in the present study (i.e., the prevalence among all participants, not among those who died) was 29.1% for males and 7.2% for females. Thus, the PAFs of smoking in recent calendar years for the Japanese population are probably smaller for males and larger for females, as compared with our estimates.

The information on the smoking status of our participants was collected only at the baseline. Smoking cessation or initiation during the follow-up period might have led to an underestimation of the relative risks of current or former smokers and, conversely, smoking re-initiation during the follow-up period might have caused an overestimation of the relative risk of former smokers. A Japanese cohort study that

examined smoking status 5 years after the baseline survey demonstrated that the shift from current to former smokers was considerably more frequent than either the shift from never-smokers to current smokers or the shift from former to current smokers.[35] This suggests the possibility of underestimating the relative risks of current smokers. However, our relative risk estimate of male current smokers for lung cancer was similar to that obtained by pooling the data from Japanese case-control studies,[36] which implies that the possible change in smoking status had only a limited influence, at least on the lung cancer relative risks. It remains possible that the relative risks of current smokers were underestimated for diseases with a risk that decreases more rapidly after smoking cessation compared to lung cancer.

We excluded participants with unknown smoking status (5% of males and 12% of females). In our preliminary analysis, we calculated the lung cancer mortality rate among participants with unknown smoking status; the value was found to be similar to the mortality rate among current smokers for males, whereas for females it was between the mortality rates of former smokers and never-smokers. If the other risk factors of lung cancer were evenly distributed, it can be assumed that most of the males with unknown smoking status were actually smokers, whereas the females with unknown smoking status were not strongly biased toward smokers or never-smokers. Thus, the prevalence of male smokers could have been underestimated by the selective exclusion of smokers. However, the extent of this effect was considered to be small since the proportion of male participants with unknown smoking status was correspondingly small.

Since the relative risks estimated in the present study were adjusted only for age, other potential confounding factors might have influenced our results. One such possible confounding factor was cohort, although this might have been negligible because the HRs adjusted for age and cohort did not differ from those adjusted only for age [e.g., the age- and cohort-adjusted HR of lung cancer for current smokers was 4.8 (95% CI: 3.9-5.9) for males and 3.8 (95% CI: 3.0-4.9) for females]. Our relative risk and PAF estimates for a specific disease might have been overestimated if its risk factors were positively correlated with smoking (i.e., alcohol consumption for esophageal cancer). For several disease groups, the age-adjusted relative risks of current smokers (vs. never-smokers) have been reported to be slightly higher than the multivariate adjusted values (i.e., all causes,[6,30] stomach cancer,[37] and stroke[10,38]), suggesting the existence of risk factors associated with smoking. In contrast, it is possible that the list of tobacco-related diseases might overlook non-established smoking-attributable diseases or disease sub-categories. Thus, our PAF estimates of all-cause mortality calculated using the relative risk of all-cause mortality itself [i.e., equation (1) in the Methods section] might have included overestimates, whereas the PAF calculated by summing the disease-specific PAFs [i.e., equation (2)] might have included underestimates.

For diseases with a relatively long duration (i.e., a time lag from incidence to death), high HRs in former smokers could be due to the "ill-quitter" effect; that is, those individuals who developed these diseases might have quit smoking because of the illness. We analyzed our data excluding deaths within 5 years of follow-up and confirmed that there was no major change in the relative risks of former smokers.

The sample sizes were small for relatively rare diseases, particularly among females. We either could not estimate HRs, or the estimated HRs had a wide CI, for female mortality from cancers in the lip/oral cavity/pharynx, esophagus, larynx, and kidney (except renal pelvis), myeloid leukemia, abdominal aortic aneurysm, COPD, and peptic ulcer. However, since these causes of death accounted for a small proportion of the total number of deaths observed in the present study (2% of the total female deaths), we consider the instability of the HRs to have had only a weak influence on our estimates of the disease distribution of smoking-attributable deaths.

Regarding the generalizability of our PAF estimates, some of the participants in the present study were recruited not from the general population but rather from those undergoing health check-ups (Table 1). Health check-up examinees might have different relative risks to those of the general population to which they belong. For example, a previous study using the JPHC cohort examined the differences in relative risks between health check-up examinees and the entire cohort, and revealed that the relative risk of all-cause mortality for current smokers (vs. never-smokers) was 24% higher for health check-up examinees.[39] These types of difference might have influenced our relative risk estimates.

Another issue regarding generalizability is age. The age distribution of participants in the present study was slightly different to that of the Japanese population as a whole. Compared with the Japanese population aged 40-79 years in 1983-1994, the proportion of those aged 70-79 years was smaller among the participants in the present study (7.5% vs. 10.9% for males and 8.0% vs. 14.4% for females). Generally, the prevalence of current smokers was lower among the group aged 70-79 years than among the younger age groups. We used the age-pooled smoking prevalence to calculate the PAFs, which might have led to the inclusion of slight overestimations.

The reason for the small proportion of individuals aged 70-79 years among the participants in the present study was that this age group was only covered by the 3-pref and JACC cohorts. We analyzed the differences between the groups of cohorts with and without this age group (3-pref + JACC vs. JPHC-I + JPHC-II) in terms of the age-adjusted HR of the current smokers (vs. never-smokers) for all-cause mortality, limiting to the common baseline age groups (40-59 years old). The calculated HRs were similar [males: 1.8 (95% CI:

Appendix. Cause-specific, age-adjusted population attributable fraction according to smoking status, for males and females.

Cause of death	ICD-9	ICD-10	Males						Females					
			Current smokers		Former smokers		Ever-smokers		Current smokers		Former smokers		Ever-smokers	
All-cause	(All)	(All)	21.9%	(20.1% – 23.7%)	5.9%	(4.7% – 7.1%)	27.8%	(25.2% – 30.4%)	5.0%	(4.3% – 5.6%)	1.8%	(1.3% – 2.2%)	6.7%	(5.9% – 7.5%)
All-cause§	(All)	(All)	14.7%	(12.9% – 16.4%)	4.4%	(3.5% – 5.3%)	19.1%	(16.0% – 22.2%)	2.9%	(2.3% – 3.4%)	0.8%	(0.5% – 1.0%)	3.6%	(3.0% – 4.2%)
Total tobacco-related diseases			26.7%	(24.3% – 28.9%)	8.0%	(6.4% – 9.6%)	34.7%	(31.2% – 38.0%)	6.5%	(5.4% – 7.5%)	1.7%	(1.0% – 2.3%)	8.1%	(6.9% – 9.4%)
All cancers	140-208	C00-C97	29.3%	(26.5% – 31.9%)	9.3%	(7.5% – 11.1%)	38.6%	(34.5% – 42.3%)	3.8%	(2.7% – 4.9%)	1.4%	(0.7% – 2.0%)	5.2%	(3.9% – 6.5%)
All cancers§	140-208	C00-C97	26.0%	(22.5% – 29.5%)	7.8%	(6.2% – 9.5%)	33.8%	(27.5% – 40.2%)	3.5%	(2.6% – 4.5%)	1.0%	(0.5% – 1.5%)	4.4%	(3.3% – 5.5%)
Total tobacco-related cancers			35.2%	(32.1% – 38.1%)	10.5%	(8.5% – 12.5%)	45.7%	(41.2% – 49.8%)	6.5%	(4.9% – 8.2%)	1.7%	(0.8% – 2.6%)	8.3%	(6.3% – 10.1%)
Lip, oral cavity, and pharynx*	140-149	C00-C14	39.3%	(19.0% – 54.6%)	12.7%	(0.3% – 23.6%)	52.0%	(19.6% – 71.4%)	6.4%	(-7.2% – 18.2%)	0.6%	(-6.0% – 6.8%)	7.0%	(-6.6% – 20.3%)
Esophagus*	150	C15	47.0%	(35.3% – 56.5%)	13.8%	(6.7% – 20.4%)	60.8%	(43.4% – 72.9%)	5.5%	(-5.3% – 15.2%)	6.7%	(-2.7% – 15.2%)	12.2%	(-2.4% – 24.7%)
Stomach*	151	C16	18.8%	(12.1% – 24.9%)	6.4%	(2.0% – 10.6%)	25.1%	(15.0% – 34.1%)	1.5%	(-1.0% – 4.0%)	1.2%	(-0.4% – 2.8%)	2.7%	(-0.4% – 5.7%)
Liver*	155	C22	25.6%	(18.1% – 32.5%)	11.5%	(6.7% – 16.0%)	37.1%	(25.9% – 46.8%)	4.9%	(0.9% – 8.7%)	0.6%	(-1.5% – 2.6%)	5.4%	(0.9% – 9.8%)
Pancreas*	157	C25	21.2%	(8.3% – 32.3%)	4.4%	(-3.8% – 11.9%)	25.5%	(5.7% – 41.2%)	5.3%	(1.3% – 9.1%)	2.4%	(-0.1% – 4.9%)	7.7%	(2.9% – 12.2%)
Larynx*	161	C32	56.7%	(20.0% – 78.6%)	16.7%	(-4.8% – 33.9%)	73.4%	(-2.1% – 93.1%)	0.0%	– –	0.0%	– –	0.0%	– –
Lung*	162	C33-C34	55.8%	(51.2% – 60.0%)	13.4%	(10.3% – 16.4%)	69.2%	(62.6% – 74.7%)	16.4%	(12.0% – 20.5%)	3.4%	(1.2% – 5.6%)	19.8%	(14.9% – 24.4%)
Cervix uteri*	180	C53	–	– –	–	– –	–	– –	8.6%	(0.4% – 16.2%)	0.0%	(-3.1% – 3.0%)	8.6%	(-0.3% – 16.8%)
Kidney, except renal pelvis*	189.0	C64	19.9%	(-11.0% – 42.2%)	9.7%	(-8.6% – 25.8%)	29.6%	(-21.5% – 59.2%)	-2.9%	(-12.3% – 5.7%)	1.5%	(-7.4% – 9.8%)	-1.4%	(-15.0% – 10.7%)
Renal pelvis, ureter, bladder*	189.1, 189.2, 188	C65-C67	56.9%	(39.5% – 69.3%)	15.4%	(4.2% – 25.4%)	72.3%	(43.1% – 86.5%)	5.8%	(-4.0% – 14.7%)	0.0%	– –	2.9%	(-7.2% – 12.1%)
Renal pelvis	189.1	C65	74.6%	(-13.7% – 94.3%)	-2.6%	(-25.0% – 15.7%)	72.0%	(-87.7% – 95.8%)	0.0%	– –	0.0%	– –	0.0%	– –
Ureter	189.2	C66	33.0%	(-59.1% – 71.8%)	0.3%	(-46.1% – 31.9%)	33.2%	(-141.3% – 81.5%)	19.1%	(-20.7% – 45.8%)	0.0%	– –	16.9%	(-23.9% – 44.3%)
Bladder	188	C67	57.4%	(38.4% – 70.5%)	21.3%	(8.2% – 32.5%)	78.6%	(44.3% – 91.8%)	4.5%	(-6.1% – 14.1%)	0.0%	– –	1.6%	(-9.5% – 11.4%)
Myeloid leukemia*	205	C92	14.8%	(-13.7% – 36.2%)	20.3%	(1.9% – 35.3%)	35.1%	(-12.6% – 62.8%)	-0.3%	(-8.9% – 7.6%)	-0.1%	(-4.8% – 4.4%)	-0.4%	(-10.5% – 8.8%)
All cardiovascular diseases	390-459	I01-I99	18.8%	(15.3% – 22.2%)	4.2%	(1.7% – 6.6%)	23.0%	(17.5% – 28.0%)	6.4%	(5.1% – 7.7%)	1.6%	(0.8% – 2.4%)	8.0%	(6.5% – 9.6%)
All cardiovascular diseases§	390-459	I01-I99	12.4%	(8.9% – 15.9%)	2.9%	(0.9% – 5.0%)	15.3%	(9.6% – 21.0%)	4.5%	(3.3% – 5.6%)	1.1%	(0.5% – 1.7%)	5.6%	(4.2% – 7.0%)
Total tobacco-related cardiovascular diseases			18.7%	(14.3% – 22.8%)	4.5%	(1.5% – 7.4%)	23.1%	(16.4% – 29.3%)	7.0%	(5.3% – 8.7%)	1.8%	(0.8% – 2.7%)	8.8%	(6.8% – 10.7%)
Ischemic heart diseases*	410-414	I20-I25	31.8%	(24.9% – 37.9%)	12.3%	(7.7% – 16.8%)	44.1%	(33.7% – 52.8%)	11.6%	(7.9% – 15.1%)	3.6%	(1.4% – 5.8%)	15.2%	(10.9% – 19.3%)
Total stroke*	430-438	I60-I69	10.6%	(4.8% – 16.0%)	-0.1%	(-4.1% – 3.8%)	10.4%	(1.4% – 18.6%)	5.3%	(3.4% – 7.1%)	1.0%	(-0.1% – 2.0%)	6.2%	(4.1% – 8.4%)
Subarachnoid hemorrhage	430	I60	39.5%	(21.3% – 53.5%)	3.1%	(-6.3% – 11.6%)	42.6%	(15.8% – 60.9%)	11.3%	(6.5% – 15.9%)	0.1%	(-1.7% – 1.9%)	11.5%	(6.2% – 16.4%)
Intracerebral hemorrhage	431	I61	10.8%	(-1.5% – 21.5%)	-2.5%	(-9.8% – 4.3%)	8.3%	(-10.2% – 23.7%)	6.0%	(2.1% – 9.8%)	1.7%	(-0.5% – 4.0%)	7.8%	(3.2% – 12.2%)
Cerebral infarction	433-434	I63	9.5%	(0.6% – 17.5%)	0.5%	(-6.1% – 6.7%)	9.9%	(-4.5% – 22.3%)	3.3%	(0.3% – 6.3%)	0.5%	(-1.2% – 2.3%)	3.9%	(0.3% – 7.3%)
Aortic aneurysm and dissection	441	I71	47.4%	(30.3% – 60.3%)	18.3%	(6.8% – 28.4%)	65.6%	(37.6% – 81.1%)	8.2%	(-1.5% – 17.0%)	5.4%	(-1.7% – 12.0%)	13.6%	(1.4% – 24.3%)
Abdominal aortic aneurysm*	441.3, 441.4	I71.3, I71.4	52.2%	(18.0% – 72.1%)	8.3%	(-11.8% – 24.8%)	60.3%	(-1.3% – 84.5%)	16.5%	(-9.9% – 36.5%)	12.1%	(-8.9% – 29.0%)	28.5%	(-5.6% – 51.6%)
All respiratory diseases	460-519	J00-J99	13.9%	(8.4% – 19.0%)	5.5%	(5.2% – 13.7%)	23.4%	(14.5% – 31.4%)	4.3%	(1.8% – 6.8%)	0.8%	(-0.7% – 2.2%)	5.1%	(2.1% – 8.0%)
All respiratory diseases§	460-519	J00-J99	8.8%	(3.7% – 13.9%)	4.9%	(1.0% – 8.8%)	13.7%	(4.2% – 23.2%)	2.4%	(0.3% – 4.5%)	0.8%	(-0.5% – 2.1%)	3.2%	(0.6% – 5.7%)
Total tobacco-related respiratory diseases			12.4%	(5.6% – 18.5%)	6.9%	(1.5% – 11.8%)	19.2%	(8.4% – 28.7%)	3.6%	(0.5% – 6.6%)	1.2%	(-0.7% – 3.1%)	4.8%	(1.1% – 8.3%)
Pneumonia*	480-486	J12-J18	6.6%	(-0.9% – 13.6%)	2.8%	(-3.2% – 8.5%)	9.4%	(-3.1% – 20.5%)	2.7%	(-0.4% – 5.7%)	1.2%	(-0.8% – 3.2%)	3.9%	(0.2% – 7.5%)
Chronic obstructive pulmonary diseases*	491-492, 496	J41-J44	38.5%	(23.8% – 47.1%)	23.8%	(13.5% – 32.9%)	60.3%	(39.0% – 74.2%)	15.2%	(-1.2% – 29.0%)	0.4%	(-5.8% – 6.3%)	15.6%	(-2.3% – 30.5%)
All digestive diseases	520-579	K00-K93	33.0%	(23.1% – 41.6%)	4.1%	(-1.6% – 9.4%)	37.1%	(22.6% – 48.8%)	7.1%	(3.0% – 11.0%)	2.8%	(0.2% – 5.3%)	9.9%	(5.0% – 14.5%)
All digestive diseases§	520-579	K00-K93	4.6%	(-0.5% – 9.7%)	0.5%	(-0.7% – 1.6%)	5.1%	(-4.0% – 14.2%)	0.2%	(-0.7% – 1.1%)	0.1%	(-0.5% – 0.7%)	0.3%	(-0.9% – 1.4%)
Peptic ulcer*	531-533	K25-K27	68.8%	(33.5% – 85.3%)	7.4%	(-9.9% – 21.9%)	76.0%	(7.5% – 93.8%)	2.6%	(-11.9% – 15.2%)	1.6%	(-8.3% – 10.6%)	4.2%	(-14.1% – 19.6%)

*: Tobacco-related diseases selected from the Surgeon General's Report of 2004 and IARC Monograph volume 83.
§: Population attributable fraction was calculated by summing up attributable fractions estimated for each tobacco-related disease, assuming that the fraction of diseases other than tobacco-related diseases was zero.

1.6-2.0) for 3-pref + JACC, 1.8 (95% CI: 1.6-2.0) for JPHC-I + JPHC-II; females: 1.9 (95% CI: 1.6-2.2) for 3-pref + JACC, 1.8 (95% CI: 1.5-2.1) for JPHC-I + JPHC-II]. The prevalence of current smokers in the two groups of cohorts was not widely different (males: 58.8% for 3-pref + JACC, 54.5% for JPHC-I + JPHC-II; females: 8.8% for 3-pref + JACC, 8.2% for JPHC-I + JPHC-II). Therefore, the influence of using partial data for the group aged 70-79 years was considered to be small.

The generalizability of our PAF estimates to the age groups that were not covered by the present study (i.e., those under 40 or over 79 years old) is limited. We estimated the number of deaths attributable to smoking using the all-age number of deaths in Japan. In this calculation, the influence of the group aged under 40 years was negligible because it accounted for only a small part of the all-age mortality in Japan (2.6% in 2005). The group aged over 79 years was partly covered by the present study in terms of attained age since the follow-up period was on average 10 years. According to a previous study that used the same dataset employed in the present study, the all-cause mortality rate ratios of current smokers vs. never-smokers were similar for the groups aged 40-69 years and 70 years or older (calculated using the attained age).[40] The smoking prevalence among those aged 70-79 years in the present study was not notably different to the national data for those aged 70 years or older (42.5% vs. 38.8% for males and 8.5% vs. 7.2% for females).[33] Thus, we believe that approximating the number of smoking-attributable deaths for all ages based on our PAF estimates is a valid approach.

In conclusion, we used the pooled data from three large-scale cohort studies in Japan to demonstrate that the estimated smoking-attributable fraction of all-cause mortality among individuals aged 40-79 years was 27.8% for males and 6.7% for females. The corresponding values calculated by summing the disease-specific smoking-attributable fractions were 19.1% for males and 3.6% for females. These results confirmed that the health burden of smoking is still large among Japanese males. Considering the high prevalence of male current smokers and the increasing prevalence of young female current smokers, effective tobacco controls and quantitative assessments of the health burden of smoking should be continuously implemented in Japan.

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