Smoking and Women's Health

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Chapter 6

Effect of Gender and Smoking on Incidence of Cardiovascular Disease and Peptic Ulcer in A Japanese Population: The Radiation Effects Research Foundation Adult Health Study

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Abstract

Background: Studies on the effects of gender and smoking on cardiovascular and peptic ulcer disease have been reported in Western countries, but data from Asian countries are limited and inconsistent.

Methods: We examined the effects of gender and smoking on cardiovascular and peptic ulcer disease using the longitudinal data of the Adult Health Study collected during biennial health examinations from 1 July 1958 to 30 June 1998. The examinations included medical history, chest x-ray, ultrasonography, and fluoroscopy or endoscopy. Smoking histories were obtained from 5 questionnaires self-administered during different time periods. We estimated the relative risks for being female and for "ever" versus "never" smoking after adjusting for significant effects of age, city, birth cohort, calendar time, alcohol intake, and radiation dose. We also examined the interaction between gender and smoking.

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Results: Eight hundred and fifty four strokes, 215 aortic aneurysms, 1093 gastric ulcers, and 437 duodenal ulcers were detected between 1958 to 1998: and, from 1978 to 1998, 125 myocardial infarction were detected. The incidence of myocardial infarction, stroke, and gastric and duodenal ulcer was significantly higher in men than in women, but we found no gender difference for aortic aneurysm incidence after adjustment for smoking status. We detected positive associations of smoking with myocardial infarction (RR for ever smoked to never smoked, 1.96), stroke (RR, 1.26), aortic aneurysm (RR, 1.80), gastric ulcer (RR, 2.06), and duodenal ulcer (RR, 1.32). The interaction between gender and smoking status was not significant for any of the diseases.

Conclusions: Male gender and smoking were significant risk factors for cardiovascular and peptic ulcer disease in a Japanese population.

KeyWords: *Gender differences, smoking, myocardial infarction, stroke, aortic aneurysm, gastric ulcer, duodenal ulcer*

Introduction

Many epidemiological studies in Western populations have reported gender differences for, and smoking effects on, cardiovascular disease and peptic ulcers.[1-5] Studies regarding stroke and coronary heart disease from Asian populations are limited, however, and the results are inconsistent.[6-10] Incidence and risk factor studies on peptic ulcers and aortic aneurysm in Asia are also limited.

Previous investigations on the relationship between cardiovascular disease and smoking in Japan varied by design (cross-sectional, case-control, and prospective studies), study population (gender, age, general population, and outpatient), or endpoint (mortality and incidence). The 23-year follow-up of the Hisayama study (a long-term prospective study of rural Japanese subjects followed since 1961) showed that cigarette smoking was an independent and significant risk factor for coronary heart disease, but not for non-embolic cerebral infarction.[6] Other pre-1980 Japanese epidemiological studies found no association between smoking and stroke.[7, 11, 12] The 32-year follow-up of the Hisayama study reported that smoking was a risk factor for lacunar stroke, the most common type of cerebral infarction in their study.[8] Studies published after the 1980s showed that smoking raised the risk of stroke [9, 13] and myocardial infarction (MI).[14] Only the Hisayama study reported gender differences in the incidence of all types of cardiovascular disease[6] and the prevalence of coronary atherosclerosis in the Japanese population.[15]

The Honolulu heart program, a long-term prospective study that has been following Japanese-American men in Hawaii since 1965, provided evidence that smoking was a risk factor for stroke, coronary heart disease, aortic aneurysm, and peptic ulcer.[16-19]

Although many studies report gender-specific estimates of incidence and mortality rates and gender-specific smoking effects on cardiovascular disease and peptic ulcer, gender differences have not been examined formally. In this study, we examined the effects of gender and smoking on the incidence of MI, stroke, aortic aneurysm, gastric ulcer, and duodenal ulcer in the Radiation Effects Research Foundation (RERF) Adult Health Study

(AHS) cohort. The AHS has health data spanning from 1958 to1998 for one of the largest existing cohorts of middle-aged and elderly men and women,[20, 21] and it is still ongoing.

Subjects and Methods

Subjects

The AHS was begun in 1958 by the Atomic Bomb Casualty Commission and was succeeded in 1975 by the Radiation Effects Research Foundation (RERF). By providing biennial clinical examinations to atomic-bomb survivors and their controls in Hiroshima and Nagasaki, the AHS has tracked the long-term clinical effects of exposure to atomic-bomb radiation.[20, 21]

The subjects of the present analysis are the 11,982 who attended at least two AHS examinations between 1 July 1958 and 30 June 1998 (about half of the original AHS subjects had died by then). About 62% of the participants were women and 69% were Hiroshima residents (Table 1). A high participation rate (75% to 90%) has been maintained, and more than half of the study participants underwent 11 or more routine clinical examinations.

Table 1. Characteristics of study subjects

		Hiroshima		Nagasaki	
		Men	Women	Men	Women
Total		2984	5265	1561	2172
Age in 1945	Mean	31.0	30.0	25.5	23.6
S.D.		15.9	14.6	14.7	13.0
Age at examination	Range	13 – 92	13 – 98	14 – 98	14 – 97
Smoking	Never smoked	300 (10%)	3709 (70%)	205 (13%)	1658 (76%)
	Ever smoked	2366 (79%)	996 (19%)	1258 (80%)	364 (17%)
	Missing data	318 (11%)	560 (11%)	98 (6%)	150 (7%)
Drinking	Never drank	472 (16%)	3180 (60%)	272 (17%)	1530 (70%)
	Ever drank	2076 (70%)	1440 (27%)	1132 (73%)	464 (21%)
	Missing data	436 (15%)	645 (12%)	157 (10%)	178 (8%)
Number of cases	Total				
Myocardial infarction[a]	125	50	40	17	18
Stroke	854	291	312	142	109
Aortic aneurysm	215	60	88	31	36
Gastric ulcer	1093	394	394	182	123
Duodenal ulcer	438	169	115	94	59
Radiation dose	Dose=0	1003 (34%)	1746 (33%)	514 (33%)	691(32%)
	Mean (Sv)	0.38	0.33	0.41	0.40
	Missing	286 (10%)	388 (7%)	450 (29%)	519 (24%)

[a] for incidence during 1978-1998.

Parenthetical values represent %.

Clinical Procedures and Selection of Diseases for Study

All participants provided informed consent, and the study complied with institutional guidelines regarding research ethics and the welfare of human subjects. A detailed description of the clinical procedures is available elsewhere.[20, 21] Briefly, the biennial AHS examination includes a clinical history taking, a physical examination, blood pressure measurements, urinalysis, blood cell count, biochemical tests, a chest X-ray, an electrocardiogram, and ultrasonography. Diagnoses were encoded according to the International Classification of Diseases (ICD)[22] and entered into the AHS database. The first 3 digits of the ICD codes (up to 6 diagnoses per person) were stored until June 1986, and 4-digit codes (up to 12 per person) were stored thereafter (appendix). MI was determined by history of hospitalization or angiography with a diagnosis of MI, episode of chest pain, and development of ischemic change on electrocardiogram. Stroke was determined by history of hospitalization or CT/MRI examination with a diagnosis of stroke and episode of neurological deficit. MI was not ascertained prior to July 1978 because ICD codes for acute MI and old MI did not exist then. Aortic aneurysm (thoracic and abdominal aortic aneurysm and aortic dissection) was diagnosed by medical history, chest x-ray examination, and ultrasonography. Ultrasonography was used optionally from 1981 to 1990 in Hiroshima and from 1984 to 1990 in Nagasaki. Since 1991, it has been performed routinely. It should be noted that this study includes only survivors of MI, stroke, ruptured aortic aneurysm, and aortic dissection who underwent subsequent examinations, as death certificate data were not considered. About 5% of participants, however, underwent clinical examinations at home or in a nearby hospital or an institution where they were residing because of severe illness or advanced age. Peptic ulcer was diagnosed by medical history and fluoroscopy or endoscopy, which were conducted optionally for subjects whose stool occult blood test was positive in a routine examination.

Cigarette Smoking and Alcohol Consumption Data

We obtained cigarette smoking history from 5 questionnaires self-administered to men in 1965, to women in 1969-1970, and to both men and women in 1965-1966, 1979-1980, and 1991. The response rate was over 95% for all surveys. Due to differences in the questionnaires and the make-up of the survey participants, the subjects were classified simply as "never smoked" (i.e., indicated in all the surveys that they had never smoked), "ever smoked" (indicated in any survey that they had smoked some quantity of cigarettes), or "missing smoking data" (did not participate in any of the smoking surveys).

Alcohol intake information was obtained from 3 questionnaires self-administered to both sexes in 1965-1966, 1979-1980, and 1991. The same classifications were applied: never drank, ever drank, and missing data. Non-drinkers were subjects who did not drink any beer, whiskey, shochu (Japanese distilled liquor), wine (including sake), or other liquor.

Statistical Methods

We applied Poisson regression methods for the longitudinal analysis of incidence data using AMFIT from the EPICURE program package.[23] We based person-year calculations on the subject's follow-up period, which began at the initial AHS visit and ended on the last disease-free visit or the date of disease onset, whichever came earlier. We estimated the disease onset date as the midpoint between the date of the initial AHS exam with a positive diagnosis and the date of the previous disease-free examination. For each disease, we excluded prevalent cases at the initial visit. We cross-tabulated person-years and case counts by stratifying the following covariates: city (Hiroshima, Nagasaki), sex (male, female), age at examination in years (0–39, 40–49, 50–59, 60–69, 70+), age at the time of the atomic bombings in years (0–9, 10–19, 20–29, 30–39, 40+), calendar time (1 July 1958 to 30 June 1978, 1 July 1978 to 30 June 1998), cigarette smoking (never smoked, ever smoked, missing data), alcohol consumption status (never drank, ever drank, missing data), and atomic-bomb radiation dose using the DS86 weighted stomach dose in Sv (missing, 0, 0.001–0.49, 0.5–1.49, 1.50+). Significant dose effects were not demonstrated in the previous AHS report for the diseases considered here.[20, 21] A detailed description of the dose estimation is available elsewhere.[21]

We modeled the disease incidence rates (γ) parametrically using the exponential function, $\gamma(x_1, \ldots, x_c) = \exp\{\sum_i \beta_i x_i\}$, where x_i is a covariable. We treated covariates as categorical except for age at the time of the bombings and age at examination, for which we used the cell-specific means. We included up to the third power of mean age at examination and at the time of the bombings in order to adjust for potential non-linear age effects. We allowed only the significant covariates in the model and considered first order interactions. We computed the relative risks (RRs) of a covariate using models that did not include its interactions with age at time of the bombings or age at examination. We calculated the RR based on indicator variables for the covariates in the models. We used the likelihood ratio method to test the significance of the coefficients of the covariates using Type I error rate of .05, in a forward step-wise algorithm, and to compute the 95% confidence intervals.

Results

Table 1 shows the characteristics of study subjects by gender and city. Overall among men, 11% never smoked, 80% ever smoked, and smoking data were missing for 9%; 16% never drank, 70% ever drank, and drinking data were missing for 13%. Overall among women, 72% never smoked, 18% ever smoked, and smoking data were missing for 10%; 63% never drank, 26% ever drank, and drinking data were missing for 11%. The distribution of smokers by atomic bomb radiation exposure did not vary significantly for men ($P = 0.14$), but there were significantly more smokers among the exposed women than among the non-exposed women (23% vs. 17%; $P < 0.0001$). The distribution of drinkers did not vary significantly by radiation exposure for either sex (data not shown).

Table 2 shows the number of incident cases and crude incidence rates for MI, stroke, aortic aneurysm, gastric ulcer, and duodenal ulcer by each variable and the multivariate adjusted RRs. Crude incidence rates were higher for men for all diseases, and RRs were significantly lower for women for all diseases, except aortic aneurysm. Risk for aortic aneurysm was same in males and females. Although the incidence of aortic aneurysm was significantly lower for women when smoking was not included in the model ($P = 0.008$), the gender difference was not significant when smoking status was included ($P = 0.42$).

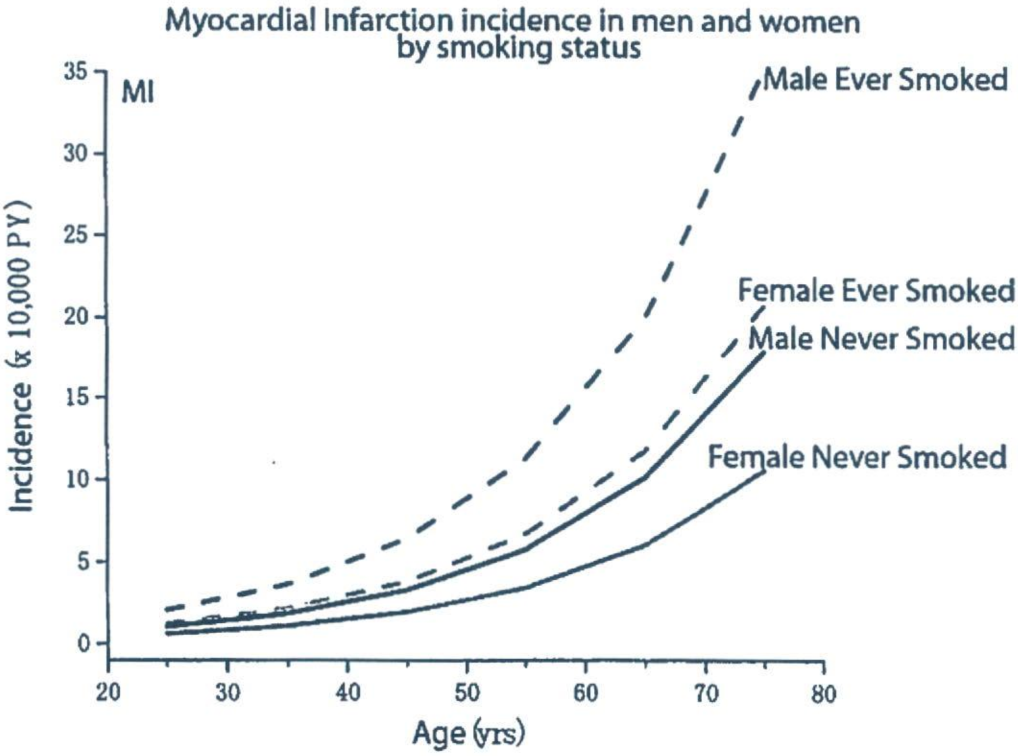
Table 2. Multivariate adjusted relative risks for myocardial infarction, stroke, aortic aneurysm, gastric ulcer, and duodenal ulcer

Disease	Myocardial infarction[a]	Stroke	Aortic aneurysm	Gastric ulcer	Duodenal ulcer
Number of cases	125	854	215	1093	437
Males	67	433	91	576	263
Females	58	421	124	517	174
Person-years	111930	289629	293634	279650	287700
Males	36382	100183	102330	94738	98279
Female	75548	189446	191304	184912	189421
Crude incidence rate (10,000	11.2	29.5	7.3	39.1	15.2
PY) Males	18.4	43.2	8.9	60.8	26.8
Females	7.7	22.2	6.5	28.0	9.2
Relative risk					
Sex (Female to Male, age 50)	0.59	0.54	0.99	0.71	0.43
(95% confidence interval)	(0.37 – 0.94)	(0.46 – 0.64)	(0.70 – 1.39)	(0.61 – 0.83)	(0.33 – 0.56)
P-value	0.025	<0.001	0.97	<0.001	<0.001
Smoking (Ever to Never)	1.96	1.26	1.80	2.06	1.32
(95% confidence interval)	(1.20 – 3.16)	(1.05 - 1.51)	(1.37 – 2.37)	(1.75 - 2.42)	(1.01 - 1.72)
P-value	0.018	0.013	<0..001	<0.001	0.043
City (Nagasaki to Hiroshima)	0.75	1.04	1.14	0.76	0.95
P-value	0.14	0.62	0.38	<0.0001	0.62
Period (late to early[b])	-	1.11	0.92	0.92	0.95
P-value	-	0.15	0.57	0.60	0.84
Drinking (Ever to Never)	0.83	0.93	0.90	1.01	1.06
P-value	0.39	0.36	0.50	0.38	0.50
Age in 1945					
15	1.00	1.00	1.00	1.00	1.00
25	0.74	0.95	1.06	0.90	0.86
35	0.54	0.90	1.13	0.81	0.74
45	0.40	0.86	1.20	0.73	0.63
P-value	0.17	0.16	0.42	0.003	0.010
Age at examination					
45	1.00	1.00	1.00	1.00	1.00
55	1.76	3.71	2.91	1.19	0.91
65	3.10	10.57	8.51	1.25	0.66
75	5.46	18.21	16.88	1.17	0.39
P-value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

[a] Incidence, 1978-1998; [b] Early period, 7/58 – 6/78; late period, 7/78 – 6/98.

We detected a significantly increased RR for ever smokers compared with never smokers for all diseases, while the interaction between gender and smoking status was not significant for any of diseases (p-values=0.29, 0.81, 0.41, 0.16, and 0.44, respectively for MI, stroke, aortic aneurysm, gastric ulcer, and duodenal ulcer). Hiroshima residents showed a higher incidence of gastric ulcer. The younger birth cohort showed a higher incidence of gastric ulcer and duodenal ulcer. A higher incidence among older subjects was found for all diseases except duodenal ulcer, which displayed a convex risk curve (Figure 1).

Figure 1 shows the fitted age-specific incidence curves for MI, stroke, and gastric and duodenal ulcer by gender and smoking status. Because gender difference was significant for aortic aneurysm before, but not after adjustment for smoking status, age-specific incidence for aortic aneurysm by gender is shown unadjusted for smoking. The incidence curves by smoking status are also shown. The effects were significant, independent of gender. Adjusted for the significant covariates for each disease, we plotted the incidence of MI and duodenal ulcer in both cities, and of gastric ulcer for Hiroshima, for men and women aged 15 in 1945. Incidence of MI, stroke, aortic aneurysm, and gastric ulcer increased significantly with age. Incidence of duodenal ulcer peaked in the 4th and 5th decades of life and then declined. Incidence of duodenal ulcer peaked later in older cohorts.



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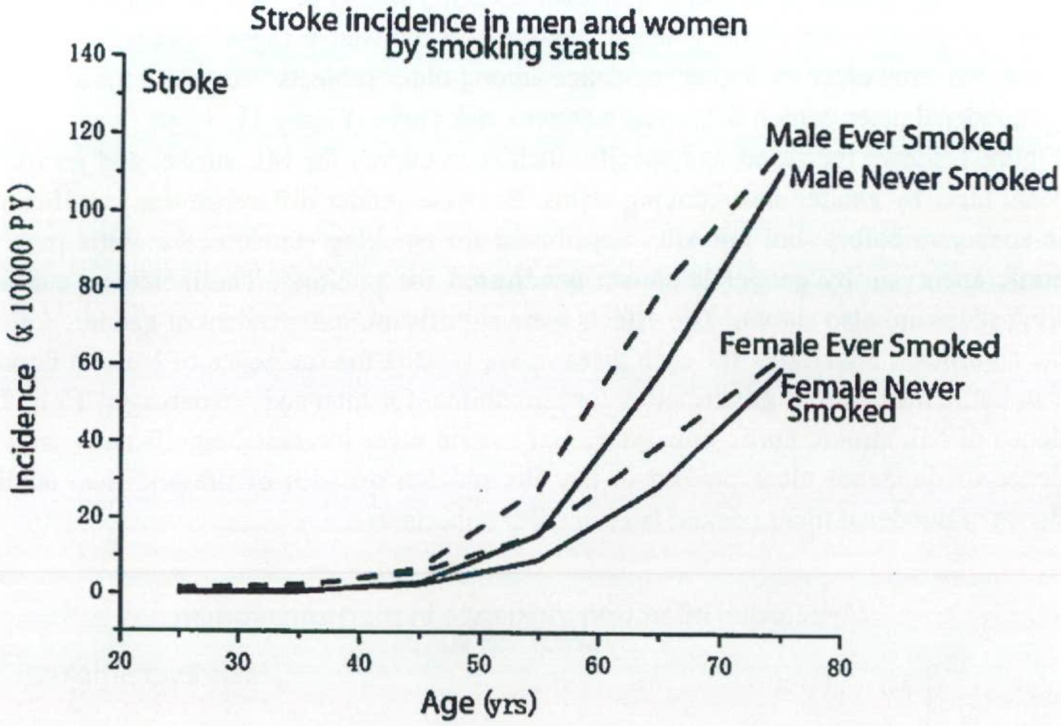

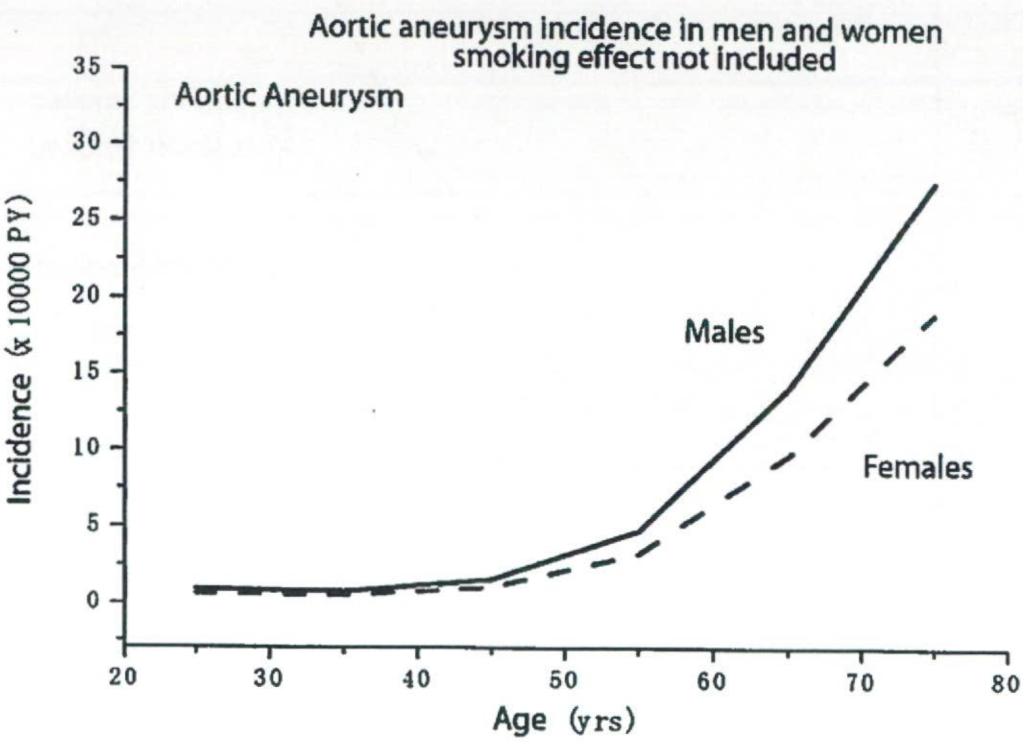

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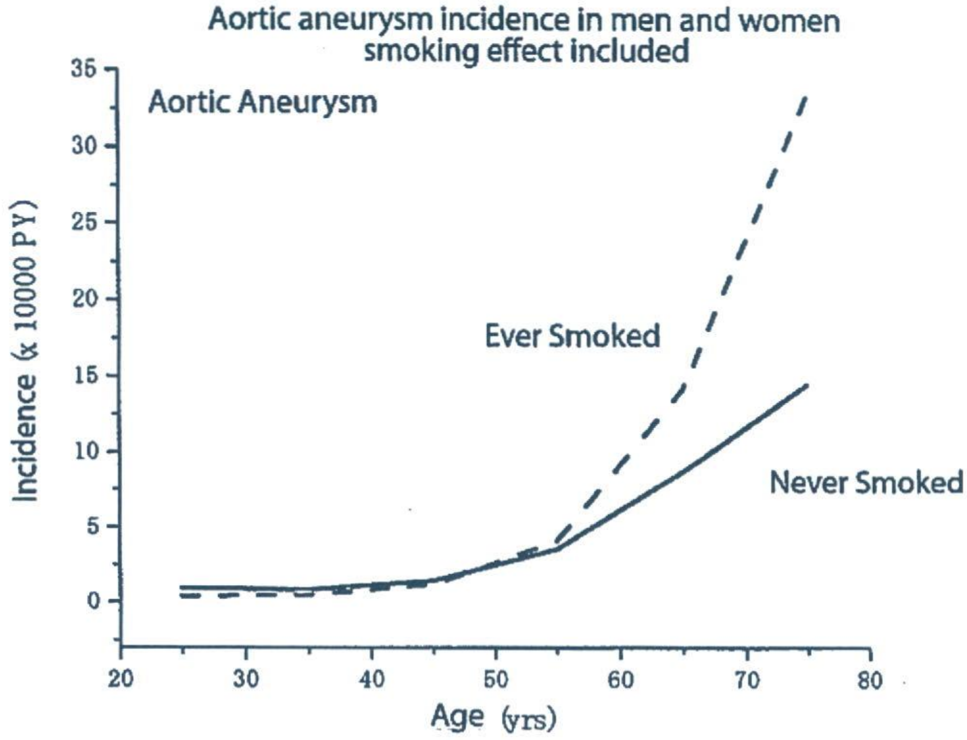

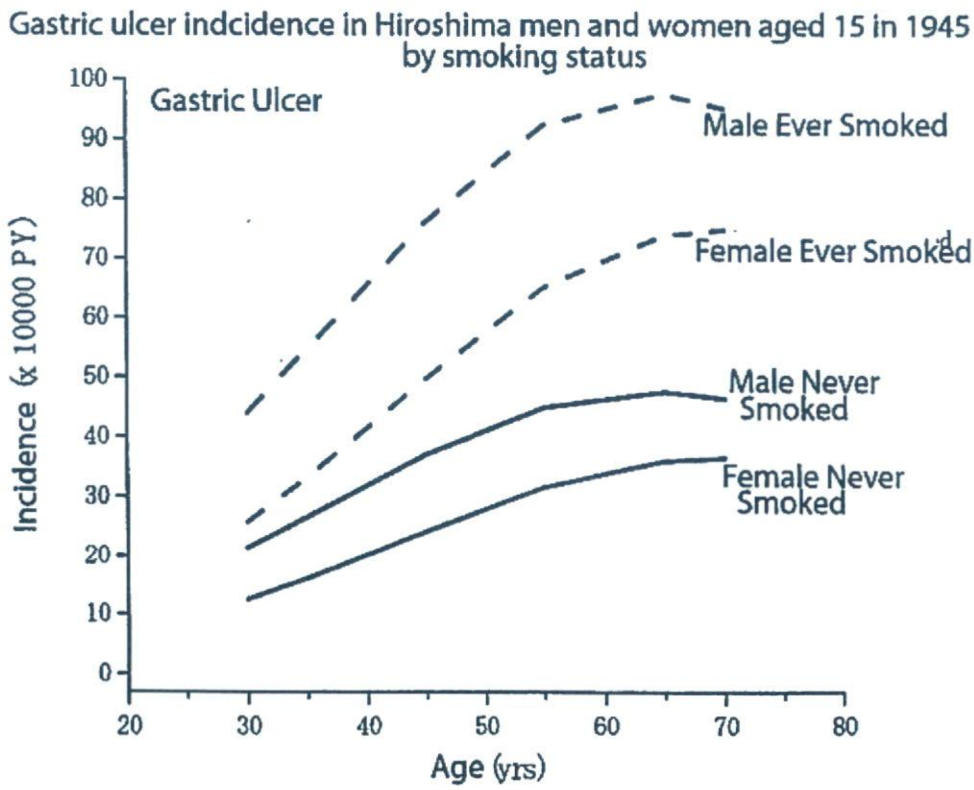

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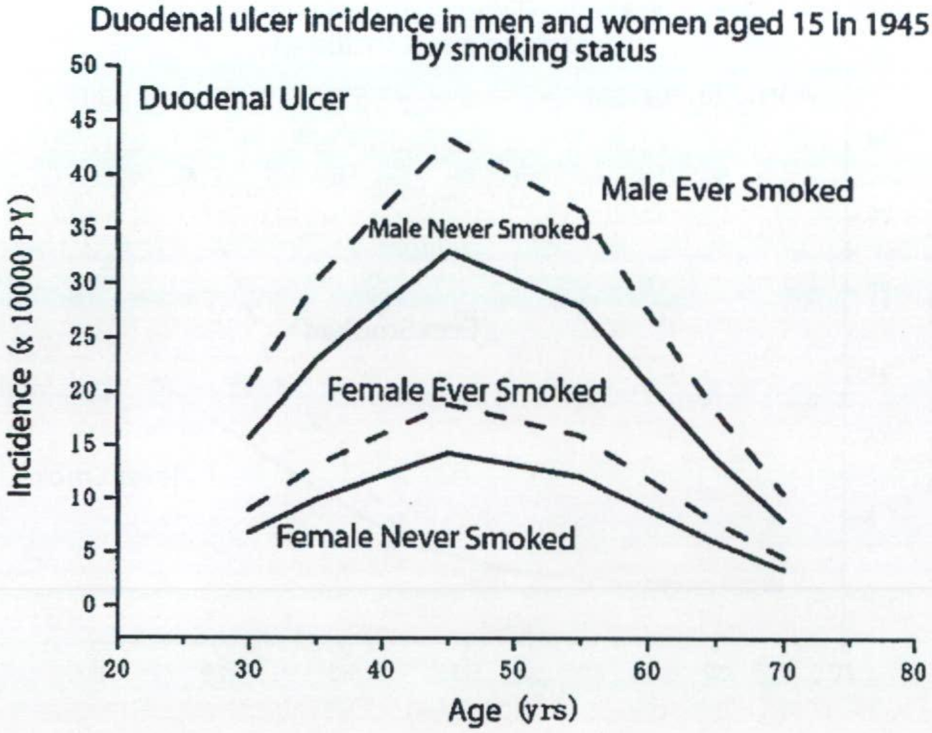

Figure 1. Gender-age specific incidence for myocardial infarction, stroke, aortic aneurysm, gastric ulcer, and duodenal ulcer.

Discussion

In this prospective study of a large Japanese cohort, the crude incidence rates for MI, stroke, and aortic aneurysm were higher for men than for women, but the RR was higher only for MI and stroke after adjustment for smoking status. Similar RRs for stroke were reported previously in Japan [6, 24] and Europe, [25, 26] and a smaller RR was reported in the US.[27] Although the gender difference in MI morbidity tended to diminish after menopausal age in the Framingham study, [28] we found no such tendency. A limitation in our study, however, was that some cases of silent MI, and all cases of fatal MI and stroke, were not included because some medical charts were not validated and death certificate data were not considered. The MI incidence in the AHS in 1958 and 1984 was calculated using a stringent set of criteria, including a review of medical history, electrocardiogram results, death certificate data, and autopsy information, was 1.6 times higher in men than in women.[29] In another AHS study that used similar criteria, the incidence of stroke and coronary heart disease, including asymptomatic and fatal cases, was twice as high in men as in women.[30] The risk of abdominal aortic aneurysm was about two times higher for men than for women in the Chicago Heart Association cohort.[31] The mortality rate of aortic aneurysm in Japan and its incidence rate (based on ultrasound scanning) in Malaysia were also more than twice as high in men.[32, 33] To clarify the disparity in the gender effect on aortic aneurysm that depended on smoking adjustment in this study, we examined the gender-specific crude incidence rates in the never smoked and the ever smoked groups. Whereas the crude incidence rate was higher for male never smokers than for female never smokers (7.97 vs. 5.32 per 10,000 py), it was lower for male ever smokers than for female ever smokers (8.96 vs. 11.36). A plausible explanation for our not detecting a gender difference in aortic aneurysm incidence after adjustment for smoking is that the proportion of fatal cases might have been higher among male smokers than among female smokers. The explanation is supported by the observation that male smokers have an increased risk of aneurysm rupture and poorer long-term survival.[34, 35] A future analysis that includes fatal cases should serve to clarify gender differences in cardiovascular disease within this cohort.

We found the incidence of peptic ulcer to be higher among men than among women, which is consistent with previous studies of Japanese and Koreans in Japan.[36, 37] Although more pronounced risks were seen in men in Western societies before the 1970s, [38] recent studies in Europe and in the US show a more equal distribution of peptic ulcer incidence between the sexes.[39, 40]

The smoking information we used in this study was obtained from multiple questionnaires administered over some time and could reflect changing habits. The lack of detailed temporal information necessitated our lumping current and past smokers into an "ever smoked" category. However, it is possible that the never smoked group may have contained a few subjects who started smoking after the last questionnaire was administered and that the ever smoked group included subjects who quit smoking over 5 years previously. Moreover, since the number of cigarettes smoked was not available in this study, we could not perform dose-response analyses.

The disease incidences for the ever smoked in this study were significantly higher than that for the never smoked, although the RR estimates (Table 2) were lower than those for current smoker versus nonsmoker reported in other studies.[3, 13, 14, 18, 19, 36, 41] Since smoking cessation and fewer smoking years are important for reducing the risk of cardiovascular disease and peptic ulcer,[4, 42-46] the lower RRs seen in this study may be due to the ever smoked category containing some current smokers.

Case ascertainment in this study was limited to participants whose illness was not fatal or too severe to preclude study participation. This may have led to an underestimation of smoker risk since illnesses in smokers tend to be of greater severity.[15, 47, 48] Although we did not consider in this analysis hypertension and diabetes, both well-known risk factors for cardiovascular disease, higher blood pressure among smokers has been observed in our cohort,[49] and smoking is associated with an increased risk of type 2 diabetes among middle-aged and elderly Japanese men and women.[50] Thus the smoking effects estimated in this study included both direct effects and indirect effects of confounding risk factors. Despite those limitations, we believe that our data clearly show that smoking negatively impacts the health of the cohort through the onset of these diseases.

Lederle's systematic review [51] of studies that examined smoking effects on aortic aneurysm and other smoking-related diseases showed that association of aortic aneurysm with smoking was greater than for MI or stroke. The RR estimate for aortic aneurysm in the present study was much lower than in previous studies based on both mortality and incidence. Further, there was no pronounced effect of smoking on aortic aneurysm.

The RR for individuals in the ever smoked category, relative to the never smoked category was higher for gastric ulcer than for duodenal ulcer, which is consistent with findings from other studies of Japanese [36, 37] and Japanese-Americans in Hawaii.[19] On the other hand, the RR was slightly greater for duodenal ulcer than for gastric ulcer among European countries.[52, 53] Our finding that the crude incidence rate was higher for gastric ulcer than for duodenal ulcer was consistent with reports from other Japanese populations [36, 37] and Japanese-Americans,[19] but not those from European countries.[53, 54] The US National Health Interview Survey [40] reported that duodenal ulcer was more common in whites than non-whites, while gastric ulcer was more common in non-whites. *Helicobacter pylori* infection, a major risk for peptic ulcer, [53] may be an important factor for interpreting apparent racial differences, since the prevalence of *H. pylori* infection is much higher in Japan and Asia than in Europe.[55] In Japan, the prevalence of *H. pylori* infection was high for those born before 1950 and decreased in later birth cohorts as Japan became more Westernized.[56, 57] Our study participants were all born in, or before 1945,. In this cohort, the prevalence of a positive IgG antibody response to *H. pylori* was about 60% in 2000 and 2002.[58] Since early acquisition of *H. pylori* increases the risk for developing gastric but not duodenal ulcer,[59] the higher prevalence of early *H. pylori* infection in Japan might have led to an increase in gastric ulcer incidence. Further analysis is required to fully elucidate the difference in incidence patterns and smoking effects on gastric and duodenal ulcer.

Although we found a greater incidence rate for MI, stroke, and peptic ulcer in men, the effects of smoking were comparable in both sexes. The incidence of MI, and its associated mortality, increased similarly among male and female smokers of European countries, as well as Japan.[5, 60] Other studies, by contract, showed a higher RR of MI for female smokers[26] and male smokers.[61] Many prospective studies in Europe and the US provided similar, strong evidence of an excess risk of stroke among male and female smokers,[3, 62-64] but data from Japanese populations are limited and results are not consistent.[6, 8, 9, 13] Many epidemiological and clinical studies of men[2, 19] and some of women [65] in Europe and the US demonstrate a similar increased risk of peptic ulcer in men and women who smoke.[66] However, there have been few Japanese and Asian prospective studies that have examined gender differences on the effects of smoking on peptic ulcer incidence. Our study was unusual in that we examined gender differences on the effects of smoking on several cardiovascular diseases, as well as peptic ulcer disease.

Participants in the present study--atomic bomb survivors and their controls--may not be representative of the general Japanese population, but we believe that the results might be extrapolated to the general population, due to the fact that one third of the participants were minimally exposed (estimated radiation dose, zero), and that the radiation exposure effects were fully accounted for by including radiation dose as a covariate in the analysis. The agreement of our findings on the effects of demographic variables such as age and gender with the findings of others [6, 37] further supports for the validity of our results.

The proportion of men who are current smokers is higher in Japan than in Western countries [9, 44] while the reverse is true for women, although a rise in smoking frequency among young to middle-aged Japanese women since 1990 has been reported.[67] The present results provide further support for smoking cessation as a way to prevent cardiovascular disease and peptic ulcer in Japan.

Appendix

International Classification of Diseases Codes			
		ICD edition	
Disease	7th	8th	9th
Myocardial infarction	-	410	410,412
Stroke	330-332,334	430,431,433,434,436	430,431,433,434,436
Aortic aneurysm	451	441	441
Gastric ulcer	540	531	531
Duodenal ulcer	541	532	532

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