Table 2. Association of tobacco smoking with risk of death from all causes in selected study populations in Asia.

Population	Men			Women		
	Number of Participants	Number of Deaths	HR (95% CI)[a]	Number of Participants	Number of Deaths	HR (95% CI)[a]
All cohorts combined						
Never smoker	177,956	19,353	1.00	501,246	43,067	1.00
Ever smoker	332,305	54,822	1.44 (1.37, 1.51)	38,422	6,733	1.48 (1.38, 1.58)
India						
Never smoker	68,866	6,613	1.00	104,223	6,880	1.00
Ever smoker	49,530	6,554	1.31 (1.26, 1.36)	1,378	198	1.16 (0.98, 1.36)
Mainland China						
Never smoker	48,664	4,797	1.00	126,085	6,945	1.00
Ever smoker	91,519	9,036	1.30 (1.25, 1.35)	11,154	1,417	1.36 (1.28, 1.45)
Taiwan						
Never smoker	5,830	647	1.00	13,696	1,103	1.00
Ever smoker	7,463	1,344	1.44 (1.30, 1.58)	142	17	1.41 (0.85, 2.33)
Singapore						
Never smoker	10,875	1,357	1.00	29,645	2,786	1.00
Ever smoker	14,470	3,399	1.58 (1.48, 1.68)	2,724	692	1.75 (1.60, 1.92)
Republic of Korea						
Never smoker	4,153	220	1.00	7,567	330	1.00
Ever smoker	14,565	1,180	1.47 (1.26, 1.72)	841	105	1.36 (1.07, 1.73)
Japan						
Never smoker	39,108	5,700	1.00	218,448	24,997	1.00
Ever smoker	152,519	33,162	1.49 (1.42, 1.55)	21,892	4,290	1.50 (1.38, 1.63)
East Asians[b]						
Never smoker	108,630	12,721	1.00	395,441	36,161	1.00
Ever smoker	280,536	48,121	1.46 (1.39, 1.54)	36,753	6,521	1.50 (1.40, 1.61)
South Asians[c]						
Never smoker	69,326	6,632	1.00	105,805	6,906	1.00
Ever smoker	51,769	6,701	1.31 (1.26, 1.36)	1,669	212	1.18 (1.01, 1.38)

[a]Adjusted for age, education, rural/urban resident, marital status, and body mass index; data from participants with <1 y of follow-up are excluded. Analyses were conducted among those age 45 y or older.
[b]Including data from mainland China, Taiwan, Singapore, Republic of Korea, and Japan.
[c]Including data from India and Bangladesh.
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the association was statistically significant for coronary heart disease and chronic obstructive pulmonary disease but not for stroke. Smoking was associated with elevated risk of death due to tuberculosis in South Asians. However, no association between smoking and tuberculosis was found in East Asians.

Among men ≥45 y, approximately 15.8% (95% CI = 14.3%–17.2%) of deaths (1.34 million [95% CI = 1.21–1.46 million]) from all causes in 2004 were attributable to tobacco smoking in these seven countries/regions combined (Table 7). Smoking-associated PARs for all-cause mortality were higher in Japan (27.7%), Republic of Korea (26.9%), and Singapore (24.8%) than in mainland China (16.2%), India (11.5%), Taiwan (19.7%), and Bangladesh (14.3%). Among women ≥45 y, tobacco smoking accounted for ~3.3% (95% CI = 2.6%–4.0%) of total deaths (239,000 [95% CI = 188,300–289,700]) in the seven countries/regions combined in 2004.

Among men aged ≥45 y, ~11.4% (95% CI = 9.1%–13.8%), 30.5% (95% CI = 27.4%–33.6%), and 19.8% (95% CI = 14.8%–24.8%) of deaths due to CVD, cancer, and respiratory diseases, respectively, were attributable to tobacco smoking in 2004 (Table 8). Smoking-associated PARs for cause-specific mortality were also higher, in general, in Japan, Republic of Korea, and Singapore than in the other study populations. Overall, 60.5% (95% CI = 54.5%–66.4%) of lung cancer deaths in men were attributable to tobacco smoking. Data for women are presented for mainland China, Japan, and all East Asians combined, because of the small sample size for other groups. Smoking-associated PARs were much smaller in women than in men: 1.7% (95% CI = 0%–4.0%), 3.7% (95% CI = 2.4%–5.0%), and 4.6% (95% CI = 3.3%–5.8%) for deaths due to respiratory diseases, CVD, and cancer, respectively. Nevertheless, ~16.7% (95% CI = 13.3%–20.0%) of lung-cancer deaths in East Asian women ≥45 y were attributable to tobacco smoking in 2004.

Discussion

Similar to studies conducted in Europe and North America [1–5,9,10], we found that tobacco smoking is associated with

Table 3. Association of tobacco smoking with risk of death from cardiovascular diseases, cancer, or respiratory diseases in selected study populations in Asia.

Population	CVD		Cancer		Respiratory Diseases	
	Number of Deaths[a]	HR (95% CI)[b]	Number of Deaths[a]	HR (95% CI)[b]	Number of Deaths[a]	HR (95% CI)[b]
Men						
All cohorts combined	15,381/6,526	1.35 (1.26, 1.45)	17,049/3,818	1.75 (1.67, 1.85)	5,671/1,764	1.53 (1.39, 1.69)
India	2,183/2,275	1.27 (1.18, 1.36)	663/379	1.84 (1.59, 2.13)	825/615	1.50 (1.33, 1.69)
Mainland China	3,378/2,055	1.17 (1.11, 1.25)	3,195/1,227	1.72 (1.60, 1.85)	619/326	1.36 (1.18, 1.57)
Taiwan	291/121	1.69 (1.36, 2.10)	488/208	1.63 (1.38, 1.93)	111/43	1.59 (1.09, 2.32)
Singapore	1,050/476	1.43 (1.28, 1.60)	1,313/451	1.85 (1.66, 2.07)	591/190	1.79 (1.51, 2.13)
Republic of Korea	200/43	1.27 (0.90, 1.80)	543/92	1.66 (1.32, 2.10)	72/11	1.67 (0.82, 3.40)
Japan	8,208/1,544	1.35 (1.27, 1.43)	10,825/1,460	1.77 (1.67, 1.88)	3,437/579	1.55 (1.41, 1.70)
East Asians[c]	13,127/4,239	1.38 (1.28, 1.49)	16,364/3,438	1.75 (1.66, 1.84)	4,830/1,149	1.54 (1.38, 1.72)
South Asians[d]	2,254/2,287	1.26 (1.18, 1.35)	685/380	1.85 (1.59, 2.17)	841/615	1.50 (1.33, 1.69)
Women						
All cohorts combined	2,552/13,837	1.54 (1.36, 1.73)	1,752/9,971	1.58 (1.44, 1.74)	655/3,760	1.40 (1.20, 1.63)
India	59/2,316	1.04 (0.77, 1.40)	13/587	1.18 (0.66, 2.10)	29/814	1.05 (0.68, 1.62)
Mainland China	666/2,687	1.48 (1.35, 1.62)	344/1,827	1.56 (1.37, 1.77)	63/323	1.18 (0.89, 1.58)
Taiwan	4/235	1.73 (0.64, 4.71)	12/399	2.94 (1.59, 5.42)	0/63	—[e]
Singapore	230/969	1.50 (1.28, 1.75)	262/992	2.19 (1.90, 2.54)	112/323	2.13 (1.70, 2.67)
Republic of Korea	35/113	1.24 (0.83, 1.88)	18/79	1.46 (0.83, 2.57)	8/22	1.34 (0.54, 3.31)
Japan	1,511/7,502	1.63 (1.37, 1.95)	1,102/6,083	1.49 (1.39, 1.59)	441/2,212	1.40 (1.26, 1.56)
East Asians[c]	2,486/11,506	1.59 (1.41, 1.79)	1,738/9,380	1.59 (1.45, 1.75)	624/2,943	1.44 (1.23, 1.69)
South Asians[d]	66/2,331	1.07 (0.81, 1.43)	14/591	1.16 (0.66, 2.04)	31/817	1.05 (0.69, 1.61)

[a]Number of deaths among ever-smokers/never-smokers are presented.
[b]Adjusted for age, education, rural/urban resident, marital status, and body mass index; data from participants with <1 y of follow-up are excluded. Analyses were conducted among those age 45 y or older.
[c]Including data from mainland China, Taiwan, Singapore, Republic of Korea, and Japan.
[d]Including data from India and Bangladesh.
[e]HR not estimated because of small sample size.
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substantially elevated risk of total and cause-specific mortality. This study analyzed individual-level data from seven Asian countries/regions, using a uniform analytic approach, which enabled comparisons of smoking-associated HRs and PARs across these countries/regions. This study provides strong evidence that tobacco smoking is a major cause of death in Asia and underscores the importance and urgency of implementing comprehensive tobacco control programs for disease prevention in this populous continent.

Most smoking-associated RR estimates in this study were 1.3–1.5 for all-cause mortality, comparable to most estimates from previous studies conducted in Asia [14–21]. These RRs, however, are substantially lower than those from studies conducted in Europe and North America, where >2-fold elevated risk for all-cause mortality is typically reported for current smokers [1–3,5,9,10]. Among specific causes of mortality evaluated in this study, lung cancer showed the strongest association with tobacco smoking, with estimated HRs of 3.0 to 4.0, approximately one-third of the risk observed in most studies conducted in Western countries [1–3,5,9,10]. The smaller effect of smoking on mortality in Asia compared with Western countries could be partly explained by the fact that widespread tobacco smoking in most Asian countries began several decades later than in Europe and North America, and thus many Asian countries are still in the early stages of a tobacco epidemic; many smokers in the population started smoking tobacco at a late age and smoke a small number of cigarettes daily [3,12]. In the British Doctors Study, a 1.6-fold elevated risk of all-cause mortality was observed among smokers in early years of follow-up (1951–1971) [26], close to the effect size estimated in this study. In later follow-up (1971–1991), the RR rose to 2.1. A recent Japanese study showed a clear birth-cohort effect: male smokers born before 1890 started smoking at a later age and smoked fewer cigarettes daily than those born in 1940–1945 [27]. As a result, the association of smoking with risk of all-cause mortality was weaker in the older cohort (RR = 1.24) than the younger cohort (RR = 1.92). Our study showed a clear dose–response relationship between pack-years of smoking and risk of all-cause and cause-specific mortality. It is likely that, with maturation of the tobacco epidemic in Asia and lack of effective tobacco control, more smokers will accumulate much higher pack-years of smoking, and, thus, smoking-associated RRs will rise, mirroring the trend in the US and Europe.

Several previous studies have estimated the burden of disease due to tobacco smoking in a specific Asian country/region [14,16,17,19,20] (Table S2). However, most previous estimates for smoking-associated RRs and PARs were derived from either a single cohort study [14,19] or a retrospective case–control study [16–18]. Not all previous studies had detailed demographic and risk-factor information to adequately adjust for potential confounders when estimating risks. Three previous studies conducted in mainland China and Taiwan provided somewhat lower

Table 4. Association of tobacco smoking with risk of death from all causes, cardiovascular diseases, cancer, or respiratory diseases in major Asian male populations.

Population	Tobacco Smoking	Number of Participants	Deaths from All Causes[a]		CVD Deaths[a]		Cancer Deaths[a]		Respiratory Disease Deaths[a]	
			Number of Deaths	HR (95% CI)[b]	Number of Deaths	HR (95% CI)[b]	Number of Deaths	HR (95% CI)[b]	Number of Deaths	HR (95% CI)[b]
Chinese and Koreans (n = 155,062)	**Never**	69,522	7,021	1	2,695	1	1,978	1	570	1
	Ever	85,540	9,904	1.48 (1.43, 1.53)	2,921	1.37 (1.29, 1.47)	3,998	1.77 (1.66, 1.88)	1,188	1.75 (1.57, 1.96)
	Former	20,256	2,583	1.27 (1.21, 1.34)	866	1.24 (1.14, 1.35)	839	1.27 (1.16, 1.39)	382	1.87 (1.62, 2.15)
	Current[c]	65,258	7,312	1.61 (1.55, 1.68)	2,053	1.47 (1.37, 1.58)	3,156	2.02 (1.89, 2.16)	806	1.71 (1.51, 1.94)
	0–9.9 pack-years	6,928	763	1.34 (1.23, 1.45)	229	1.29 (1.12, 1.49)	285	1.44 (1.26, 1.65)	75	1.41 (1.09, 1.82)
	10–19.9 pack-years	11,307	1,078	1.37 (1.28, 1.47)	309	1.30 (1.14, 1.49)	457	1.65 (1.48, 1.85)	82	1.20 (0.94, 1.55)
	20–29.9 pack-years	13,632	1,461	1.50 (1.41, 1.60)	401	1.37 (1.22, 1.54)	637	1.88 (1.70, 2.08)	167	1.69 (1.40, 2.04)
	≥30 pack-years	33,391	4,010	1.84 (1.75, 1.93)	1,114	1.64 (1.51, 1.79)	1,777	2.42 (2.24, 2.61)	482	2.00 (1.75, 2.30)
Japanese (n = 187,002)	**Never**	39,108	5,700	1	1,544	1	1,460	1	579	1
	Ever	147,894	32,214	1.48 (1.43, 1.52)	7,958	1.34 (1.26, 1.42)	10,466	1.76 (1.67, 1.87)	3,343	1.54 (1.41, 1.69)
	Former	43,248	8,207	1.24 (1.20, 1.28)	1,939	1.14 (1.06, 1.22)	2,423	1.39 (1.30, 1.49)	975	1.46 (1.31, 1.64)
	Current[c]	104,646	24,007	1.60 (1.55, 1.65)	6,019	1.45 (1.37, 1.54)	8,043	1.94 (1.83, 2.05)	2,368	1.57 (1.43, 1.73)
	0–9.9 pack-years	4,283	708	1.54 (1.42, 1.68)	183	1.58 (1.34, 1.86)	189	1.50 (1.28, 1.76)	63	1.93 (1.47, 2.54)
	10–19.9 pack-years	12,238	2,361	1.65 (1.57, 1.74)	679	1.69 (1.54, 1.86)	701	1.76 (1.60, 1.94)	207	1.55 (1.31, 1.83)
	20–29.9 pack-years	25,045	4,796	1.78 (1.71, 1.86)	1,263	1.77 (1.64, 1.92)	1,547	2.02 (1.88, 2.18)	413	1.73 (1.52, 1.98)
	≥30 pack-years	63,080	16,142	1.58 (1.53, 1.63)	3,894	1.35 (1.27, 1.44)	5,606	2.00 (1.88, 2.12)	1,685	1.55 (1.41, 1.72)
Indians and Bangladeshis (n = 101,278)	**Never**	69,326	6,632	1	2,287	1	380	1	615	1
	Ever	31,952	4,500	1.30 (1.23, 1.36)	1,657	1.31 (1.21, 1.43)	520	1.71 (1.44, 2.03)	825	1.46 (1.26, 1.69)
	Former	6,860	1,157	1.27 (1.18, 1.37)	399	1.16 (1.03, 1.31)	92	1.78 (1.35, 2.34)	144	1.70 (1.37, 2.10)
	Current[c]	25,092	3,343	1.30 (1.21, 1.39)	1,258	1.41 (1.27, 1.57)	428	1.62 (1.32, 1.99)	681	1.26 (1.05, 1.52)
	0–9.9 pack-years	6,654	597	1.17 (1.06, 1.30)	247	1.32 (1.12, 1.55)	62	1.17 (0.85, 1.62)	71	1.10 (0.81, 1.49)
	10–19.9 pack-years	6,623	704	1.22 (1.11, 1.35)	270	1.35 (1.15, 1.58)	95	1.69 (1.28, 2.24)	101	1.17 (0.89, 1.55)
	20–29.9 pack-years	4,466	610	1.35 (1.22, 1.49)	222	1.39 (1.17, 1.65)	89	1.82 (1.36, 2.46)	88	1.37 (1.05, 1.80)
	≥30 pack-years	7,349	1,432	1.39 (1.28, 1.50)	519	1.51 (1.32, 1.72)	182	1.76 (1.38, 2.25)	222	1.32 (1.06, 1.64)

[a]Excluding participants with less than 1 y of follow-up.
[b]Adjusted for age, education, rural/urban resident, marital status, and body mass index. Analyses were conducted among those age 45 y or older.
[c]Excluding current smokers with missing information on pack-years of smoking.
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Table 5. Association of tobacco smoking with risk of death from all causes, cardiovascular diseases, cancer, or respiratory diseases in major East Asian female populations.

Population	Tobacco Smoking	Number of Participants	Deaths from All Causes[a]		CVD Deaths[a]		Cancer Deaths[a]		Respiratory Disease Deaths[a]	
			Number of Deaths	HR (95% CI)[b]	Number of Deaths	HR (95% CI)[b]	Number of Deaths	HR (95% CI)[b]	Number of Deaths	HR (95% CI)[b]
Chinese and Koreans (*n*= 182,640)	**Never**	176,993	11,164	1	4,004	1	3,297	1	731	1
	Ever	5,647	1,028	1.65 (1.53, 1.77)	362	1.57 (1.39, 1.77)	356	1.98 (1.75, 2.24)	128	1.98 (1.61, 2.45)
	Former	1,609	305	1.38 (1.22, 1.56)	121	1.35 (1.11, 1.65)	86	1.62 (1.29, 2.04)	28	1.62 (1.08, 2.41)
	Current[c]	4,020	722	1.79 (1.65, 1.95)	241	1.73 (1.50, 2.00)	269	2.15 (1.88, 2.47)	100	2.37 (1.88, 3.00)
	0–9.9 pack-years	1,930	244	1.59 (1.39, 1.82)	79	1.56 (1.24, 1.98)	93	1.86 (1.50, 2.30)	31	2.16 (1.48, 3.16)
	10–19.9 pack-years	757	132	1.77 (1.48, 2.13)	38	1.52 (1.08, 2.14)	55	2.52 (1.90, 3.33)	14	1.91 (1.09, 3.37)
	≥20 pack-years	1,333	346	2.01 (1.79, 2.26)	124	2.01 (1.65, 2.43)	121	2.39 (1.96, 2.91)	55	2.87 (2.13, 3.86)
Japanese (*n*= 239,171)	**Never**	218,448	24,997	1	7,502	1	6,083	1	2,212	1
	Ever	20,723	4,053	1.42 (1.38, 1.48)	1,461	1.46 (1.37, 1.54)	1,043	1.49 (1.39, 1.60)	416	1.39 (1.25, 1.55)
	Former	3,957	788	1.24 (1.15, 1.34)	302	1.23 (1.09, 1.39)	203	1.43 (1.24, 1.65)	75	1.13 (0.89, 1.44)
	Current[c]	16,766	3,265	1.48 (1.42, 1.53)	1,159	1.53 (1.43, 1.63)	840	1.51 (1.40, 1.63)	341	1.48 (1.31, 1.66)
	0–9.9 pack-years	6,001	990	1.43 (1.34, 1.52)	339	1.48 (1.32, 1.65)	230	1.35 (1.18, 1.54)	99	1.46 (1.19, 1.79)
	10–19.9 pack-years	4,831	828	1.48 (1.38, 1.59)	296	1.57 (1.39, 1.78)	210	1.46 (1.27, 1.68)	96	1.76 (1.43, 2.18)
	≥20 pack-years	5,934	1,447	1.52 (1.43, 1.60)	524	1.56 (1.43, 1.71)	400	1.70 (1.53, 1.88)	146	1.45 (1.21, 1.72)

[a]Excluding participants with less than 1 y of follow-up.
[b]Adjusted for age, education, rural/urban resident, marital status, and body mass index.
Analyses were conducted among those age 45 y or older.
[c]Excluding current smokers with missing information on pack-years of smoking.
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Table 6. Association of tobacco smoking with risk of cause-specific death by study populations in Asia.

Cause of Death	Men						Women			
	Chinese/Koreans		Japanese		South Asians		Chinese/Koreans		Japanese	
	Number of Deaths[a]	HR[b] (95% CI)	Number of Deaths[a]	HR[b] (95% CI)	Number of Deaths[a]	HR[b] (95% CI)	Number of Deaths[a]	HR[b] (95% CI)	Number of Deaths[a]	HR[b] (95% CI)
Cancer										
Mouth/pharynx/larynx	290/106	1.95 (1.51, 2.50)	286/36	1.89 (1.28, 2.79)	165/60	1.36 (0.94, 1.98)	16/97	1.99 (1.11, 3.59)	16/81	2.29 (1.28, 4.11)
Esophagus	360/123	1.54 (0.66, 3.57)	625/44	3.05 (2.21, 4.22)	52/9	3.13 (1.43, 6.86)	25/139	0.92 (0.54, 1.57)	21/82	2.62 (1.54, 4.46)
Stomach	855/352	1.43 (1.24, 1.64)	2,440/381	1.48 (1.32, 1.66)	43/16	1.40 (0.67, 2.94)	68/502	1.14 (1.08, 1.52)	191/1,150	1.32 (1.09, 1.59)
Colorectal	490/301	1.13 (0.93, 1.37)	1,123/222	1.22 (1.01, 1.47)	17/11	0.98 (0.40, 2.36)	76/541	1.40 (1.08, 1.83)	124/939	1.11 (0.89, 1.39)
Liver	1,019/460	1.35 (1.19, 1.53)	1,448/198	1.74 (1.48, 2.04)	40/20	1.00 (0.46, 2.16)	67/428	1.75 (1.05, 2.84)	135/621	1.83 (1.50, 2.24)
Pancreas	222/107	1.18 (0.75, 1.86)	658/100	1.60 (1.27, 2.01)	7/6	—[c]	31/200	1.65 (1.08, 2.53)	98/578	1.59 (1.21, 2.09)
Lung	2,124/374	3.56 (2.45, 5.16)	2,866/164	4.12 (3.49, 4.87)	108/20	3.16 (1.76, 5.69)	291/729	3.34 (2.29, 4.86)	253/714	3.15 (2.70, 3.68)
Bladder	80/30	1.97 (1.26, 3.09)	199/26	1.84 (1.07, 3.16)	12/2	—[c]	8/36	1.41 (0.56, 3.52)	17/86	1.63 (0.92, 2.90)
Breast							60/507	1.45 (1.05, 1.99)	74/467	1.40 (1.07, 1.84)
Cervix uteri							19/150	1.04 (0.58, 1.88)	28/122	2.09 (1.32, 3.30)
Other	855/432	1.22 (1.07, 1.40)	2,375/457	1.26 (1.12, 1.42)	131/76	1.11 (0.76, 1.62)	118/898	1.41 (1.13, 1.76)	283/1,945	1.17 (1.01, 1.36)
CVD										
CHD	1,828/903	1.52 (1.22, 1.90)	2,264/327	1.72 (1.52, 1.95)	1,159/553	1.57 (1.38, 1.78)	343/1,347	1.68 (1.47, 1.92)	391/1,579	1.89 (1.60, 2.23)
Stroke	2,733/1,613	1.19 (1.11, 1.28)	4,193/896	1.19 (1.10, 1.29)	411/261	1.09 (0.90, 1.32)	453/2,390	1.37 (1.16, 1.63)	787/4,075	1.62 (1.27, 2.07)
Other	1,491/877	1.36 (1.09, 1.70)	3,186/589	1.42 (1.26, 1.60)	115/35	1.01 (0.62, 1.64)	379/1,477	1.46 (1.29, 1.67)	636/3,201	1.42 (1.23, 1.64)
Respiratory disease										
COPD	820/224	2.05 (1.40, 3.01)	728/75	2.73 (1.93, 3.31)	522/208	1.28 (1.05, 1.57)	95/223	2.82 (1.18, 6.72)	95/262	2.10 (1.18, 3.72)
Other	755/457	1.09 (0.93, 1.29)	3,158/606	1.42 (1.29, 1.55)	77/45	1.07 (0.68, 1.68)	131/643	1.46 (1.13, 1.88)	405/2,246	1.38 (1.19, 1.60)
Tuberculosis	151/75	0.88 (0.64, 1.23)	56/14	0.66 (0.27, 1.60)	225/65	1.81 (1.21, 2.70)	12/76	0.90 (0.43, 1.85)	9/21	2.43 (0.92, 6.46)
All other known causes	3,369/1,956	1.11 (1.02, 1.20)	5,935/1,206	1.23 (1.13, 1.34)	1,342/818	1.09 (0.97, 1.21)	542/3,619	1.14 (1.00, 1.29)	943/5,307	1.35 (1.12, 1.62)

[a]Number of deaths among ever-smokers/never-smokers are presented.
[b]HRs estimated for ever-smokers compared with never-smokers and adjusted for age, education, rural/urban residence, marital status, and body mass index; data from participants with <1 y of follow-up are excluded. Analyses were conducted among those age 45 y or older.
[c]HR not estimated because of small sample size.
CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease.
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Table 7. Smoking prevalence, population attributable risk, and number of deaths due to tobacco smoking in selected Asian populations.

Population	Men			Women		
	Smoking Prevalence (Percent)	PAR (Percent)	Number of Deaths (in Thousands)	Smoking Prevalence (Percent)	PAR (Percent)	Number of Deaths (in Thousands)
Bangladesh	53.8[a]	14.3 (12.2, 16.4)[b]	46.4 (39.6, 53.3)	3.0[a]	0.5 (0.0, 1.1)[b]	1.5 (0, 3.4)
India	41.8	11.5 (9.8, 13.2)	378.8 (322.8, 434.8)	1.3	0.2 (0.0, 0.4)	6.9 (0, 11.0)
Mainland China	65.3	16.2 (14.0, 18.5)	675.7 (583.9, 771.6)	8.1	2.9 (2.2, 3.5	104.6 (79.4, 126.3)
Taiwan[c]	56.1	19.7 (14.6, 24.7)	18.4 (13.6, 23.0)	4.2[a]	1.7 (0.0, 4.6)	1.0 (0, 2.7)
Singapore	57.1	24.8 (21.4, 28.1)	2.5 (2.1, 2.8)	8.4	6.0 (4.8, 7.1)	0.5 (0.4, 0.6)
Republic of Korea	77.8	26.9 (17.6, 36.3)	37.8 (24.8, 51.1)	6.1[a]	2.1 (0.2, 4.0)	2.4 (0.2, 4.5)
Japan	79.6	27.7 (25.9, 29.5)	143.7 (134.3, 153.0)	9.1	3.7 (3.3, 4.2)	16.8 (15.0, 19.1)
East Asians[d]	67.3	18.0 (15.9, 20.1)	869.4 (768.0, 970.9)	8.1	2.9 (2.0, 3.9)	122.8 (84.7, 165.1)
South Asians[d]	42.8	11.7 (10.0, 13.4)	424.6 (362.9, 486.3)	1.6	0.3 (0.0, 0.6)	9.2 (0, 18.4)
All populations[d]	58.6	15.8 (14.3, 17.2)	1,336.5 (1,209.7, 1,455.0)	5.8	3.3 (2.6, 4.0)	239.0 (188.3, 289.7)

Estimates are provided for populations age 45 y or older.
[a]Because of the small sample size in the current study for these populations, data for smoking prevalence rates were obtained from other sources: Bangladeshi men and women: [12], Taiwanese women: [19], and Korean women: [34].
[b]PARs were estimated using HRs derived from all South Asian cohorts combined because of unstable HR estimates using Bangladeshi data alone.
[c]Mortality data for Taiwan were obtained from http://www.mohw.gov.tw/CHT/Ministry/Index.aspx.
[d]PARs were estimated using weighted HRs and smoking prevalence of the study populations.
Thus, the number of deaths attributable to smoking in these populations may not be equal to the sum of the numbers of deaths from the countries in the population areas. East Asia: mainland China, Taiwan, Singapore, Republic of Korea, and Japan. South Asia: Bangladesh and India. All populations: all seven countries/regions listed above.
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estimates of total male deaths due to smoking than our estimates, perhaps because these studies were conducted during even earlier stages of the tobacco epidemic in these populations, resulting in smaller PARs [14,16,19]. For India, however, the estimate of male deaths attributable to tobacco smoking from a previous study (20% of total male deaths) [17] was substantially higher than the estimate from our study (11.5% of total male deaths). To our knowledge, no study has been previously conducted in Bangladesh, the Republic of Korea, or Singapore; thus, our study provides, for the first time, direct estimates of deaths due to tobacco smoking in these countries. Despite methodological differences between this and previous studies, all studies conducted to date have shown that an alarming proportion of deaths are caused by tobacco smoking.

In this study, some estimates among women are unstable because of very low smoking prevalence. Although not all participating cohorts are representative of the general population, smoking-associated RRs estimated in this study, are, in general, comparable to those from previous studies. Furthermore, smoking-associated RRs estimated in multiple cohorts within the same country are, in general, comparable. It is difficult to find national survey data consistent with the definitions, time period, and age groups of our study for all seven countries/regions in our analysis. Many national surveys used a smaller sample than our study, providing unstable smoking prevalence estimates. Therefore, we chose to use smoking prevalence estimates from our own study to estimate PARs: smoking-associated RRs were estimated based on exposure history of the same group of individuals, which should provide better estimates of disease burden due to tobacco smoking in the study population than using data from external sources. Smoking prevalence has declined recently in several high-income Asian countries. However, given the long latency of chronic diseases, typically 15 y and longer, it is reasonable to use smoking prevalence rates assessed in the 1990s to estimate number of deaths due to tobacco smoking in 2004. As most of the cohort studies included in this study were conducted among adults aged ≥45 y, we were unable to estimate the impact of active tobacco smoking in people younger than 45 y old. Again, because of the long latency of chronic diseases, most of the smoking-related diseases tend to occur later in life.

We estimated smoking-associated PARs and numbers of deaths due to tobacco smoking in 2004. As many Asian countries, such as China and India, are still in the early stage of tobacco epidemics, the number of deaths due to tobacco smoking in more recent years in these countries is likely to be larger than that estimated in this study.

Data on secondhand tobacco-smoke exposure was not available in this study. Secondhand smoke has been linked to an elevated risk of multiple chronic diseases [2,28,29]. It has been estimated that approximately 603,000 deaths worldwide may be due to secondhand smoke [29]. We also were unable to evaluate smokeless tobacco, a risk factor for oral cancer and several other chronic diseases [30,31]. Smokeless tobacco use is common in India and Bangladesh, especially among women in these countries. Some individuals who had secondhand tobacco-smoke exposure or used smokeless tobacco may be included in the reference group, which may result in an underestimate of the risk associated with active tobacco smoking. Furthermore, in our study, RRs associated with tobacco smoking were estimated primarily based on the time period from the early 1990s to the mid-2000s. Because smoking-associated risk of death is likely to increase with the maturation of the tobacco epidemic, the total number of deaths due to smoking in 2004 may be underestimated using

Table 8. Population-attributable risk and number of cause-specific deaths due to tobacco smoking in selected Asian populations.

Population	CVD		All Cancers		Lung Cancer		Respiratory Disease	
	PAR (Percent)	Number of Deaths (in Thousands)	PAR (Percent)	Number of Deaths (in Thousands)	PAR (Percent)	Number of Deaths (in Thousands)	PAR (Percent)	Number of Deaths (in Thousands)
Men								
Bangladesh	12.3[a]	16.4 (11.6, 21.3)	31.3[a]	10.8 (8.4, 13.1)	61.1[a]	8.6 (6.6, 10.5)	21.2[a]	6.4 (4.6, 8.3)
India	10.0	130.8 (91.5, 170.0)	26.1	85.6 (65.2, 105.6)	55.0	30.1 (22.1, 38.0)	17.3	69.2 (48.0, 90.0)
Mainland China	10.2	159.4 (101.5, 215.5)	32.0	325.1 (287.6, 361.7)	62.5	154.5 (143.6, 165.7)	19.0	141.0 (78.7, 202.6)
Taiwan	27.9	1.3 (0.8, 1.7)	26.2	7.1 (4.8, 9.4)	58.9	3.4 (3.1, 3.6)	24.9	1.1 (0.3, 1.9)
Singapore	19.8	0.7 (0.5, 0.9)	32.8	0.9 (0.8, 1.1)	59.3	0.5 (0.4, 0.5)	31.2	0.2 (0.1, 0.2)
Republic of Korea	17.3	6.1 (0, 14.3)	34.0	17.0 (10.5, 23.6)	66.5	8.4 (7.8, 8.9)	34.4	3.1 (0, 6.7)
Japan	21.7	31.4 (26.1, 36.9)	38.0	72.0 (66.3, 77.9)	67.0	29.0 (27.2, 30.8)	30.4	9.2 (7.5, 10.9)
East Asians[b]	12.2	212.4 (156.7, 268.2)	32.7	410.6 (369.1, 453.2)	63.2	191.6 (177.6, 205.8)	21.0	164.1 (108.6, 220.4)
South Asians[b]	10.0	144.5 (101.2, 189.3)	26.6	97.1 (74.5, 119.7)	55.5	38.6 (28.5, 48.7)	17.6	75.8 (52.6, 98.7)
All populations[b]	11.4	363.3 (290.0, 439.7)	30.5	494.3 (444.0, 544.5)	60.5	225.5 (203.1, 247.5)	19.8	240.1 (179.5, 300.7)
Women								
Mainland China	3.7	58.5 (42.7, 75.9)	4.3	25.5 (17.2, 34.4)	13.9	15.9 (12.0, 19.7)	1.5	11.7 (0, 32.8)
Japan	4.0	6.2 (5.5, 7.0)	4.3	5.4 (4.3, 6.5)	15.4	2.5 (1.9, 3.1)	3.5	0.7 (0.5, 1.0)
East Asians[b]	3.7	66.3 (43.0, 89.6)	4.6	35.1 (25.2, 44.2)	16.7	23.0 (18.3, 27.5)	1.7	13.8 (0, 32.4)

Estimates are provided for populations age 45 y or older.
[a]PARs were estimated using HRs derived from all South Asian cohorts combined because of unstable HR estimates using Bangladeshi data alone.
[b]PARs were estimated using weighted HRs and smoking prevalence of the study populations.
Thus, the number of deaths attributable to smoking in these populations may not be equal to the sum of the numbers of deaths from countries in the population areas. East Asia: mainland China, Taiwan, Singapore, Republic of Korea, and Japan. South Asia: Bangladesh and India. All populations: all seven countries/regions listed above.
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this set of RRs. Therefore, the true impact of tobacco smoking on mortality in these Asian countries is likely to be even larger than estimated here. Despite some limitations mentioned above, our study provides perhaps the best estimates of tobacco-associated deaths to date in these Asian countries/regions.

Over the past 50 years, the landscape of tobacco smoking has changed dramatically around the world. Smoking prevalence has declined sharply in many high-income countries, resulting in a recent decrease in smoking-related deaths, particularly among men [3,8]. Conversely, prevalence of tobacco use remains high in China, India, and other low- and middle-income countries. As the tobacco epidemic grows in these countries, we anticipate that an increasing number of deaths will be attributable to tobacco smoking in Asia in the coming years. Even in more well-developed Asian countries such as Japan and Republic of Korea, where smoking rates have recently declined, the full impact of tobacco smoking on mortality is unlikely to be seen soon because, as noted above, smokers in recent birth cohorts tend to smoke more and start smoking earlier, elevating their risk of smoking-associated deaths, and because of the long latency of the diseases associated with smoking, these deaths will not accrue immediately. Our study shows that tobacco smoking is a major cause of death in Asia, accounting for ~1.6 million deaths of adults ≥45 y in 2004 in the seven countries/regions in this analysis. If the remaining 29% of the Asian population is experiencing a tobacco epidemic similar to that of these seven countries/regions, we estimate that, in 2004, >2 million deaths in Asia were attributable to tobacco smoking. Thus, of the 5 million deaths currently attributable to active tobacco smoking worldwide [32], nearly 45% occur in Asia. Our study provides sobering evidence that stresses the urgency of implementing comprehensive tobacco control programs in Asia, as recommended by the WHO Framework Convention on Tobacco Control [33]. Tobacco control should be among the top priorities in Asia to reduce the burden of disease.

Supporting Information

Table S1 Association of tobacco smoking status (former or current) with risk of death from all causes in selected study populations in Asia.
(DOC)

Table S2 Population-attributable risk and number of deaths due to smoking in major Asian populations estimated in previous studies.
(DOC)

Text S1 Descriptions of participating cohorts.
(DOC)

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Author Contributions

Conceived and designed the experiments: WZ JDP. Performed the experiments: WZ JDP DFM BAR ZF MT ZF. Analyzed the data: DFM ZF MT ZF WZ. Contributed reagents/materials/analysis tools: WZ JH PCG KR ST FI AT YTG WPK XOS KO YN IT HT CJC JMY YOA KYY HA WHP YLQ DG MSP CS NS TS GY RW YBX WO MK TW IO SLY YS LMB DHK SKP FP SYC JHF CYS EJG JEL RS KM MI DK JDP. Wrote the first draft of the manuscript: WZ. Contributed to the writing of the manuscript: DFM PB YC EJG JEL RS MT ZF JDP. ICMJE criteria for authorship read and met: WZ DFM BAR ZF PB JH PCG KR ST FI AT YTG WPK XOS KO YN IT HT CJC JMY YOA KYY HA WHP YLQ DG MSP CS NS TS GY RW YBX WO MK TW IO SLY YS LMB DHK SKP FP SYC JHF CYS YC EJG JEL RS KM MT MI ZF DK JDP. Agree with manuscript results and conclusions: WZ DFM BAR ZF PB JH PCG KR ST FI AT YTG WPK XOS KO YN IT HT CJC JMY YOA KYY HA WHP YLQ DG MSP CS NS TS GY RW YBX WO MK TW IO SLY YS LMB DHK SKP FP SYC JHF CYS YC EJG JEL RS KM MT MI ZF DK JDP. Enrolled patients:WZ JH PCG KR ST FI AT YTG WPK XOS KO YN IT HT CJC JMY YOA KYY HA WHP YLQ DG MSP CS NS TS GY RW YBX WO MK TW IO SLY YS LMB DHK SKP FP SYC JHF CYS EJG JEL RS KM MI DK JDP.

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Editors' Summary

Background. Every year, more than 5 million smokers die from tobacco-related diseases. Tobacco smoking is a major risk factor for cardiovascular disease (conditions that affect the heart and the circulation), respiratory disease (conditions that affect breathing), lung cancer, and several other types of cancer. All told, tobacco smoking kills up to half its users. The ongoing global "epidemic" of tobacco smoking and tobacco-related diseases initially affected people living in the US and other Western countries, where the prevalence of smoking (the proportion of the population that smokes) in men began to rise in the early 1900s, peaking in the 1960s. A similar epidemic occurred in women about 40 years later. Smoking-related deaths began to increase in the second half of the 20th century, and by the 1990s, tobacco smoking accounted for a third of all deaths and about half of cancer deaths among men in the US and other Western countries. More recently, increased awareness of the risks of smoking and the introduction of various tobacco control measures has led to a steady decline in tobacco use and in smoking-related diseases in many developed countries.

Why Was This Study Done? Unfortunately, less well-developed tobacco control programs, inadequate public awareness of smoking risks, and tobacco company marketing have recently led to sharp increases in the prevalence of smoking in many low- and middle-income countries, particularly in Asia. More than 50% of men in many Asian countries are now smokers, about twice the prevalence in many Western countries, and more women in some Asian countries are smoking than previously. More than half of the world's billion smokers now live in Asia. However, little is known about the burden of tobacco-related mortality (deaths) in this region. In this study, the researchers quantify the risk of total and cause-specific mortality associated with tobacco use among adults aged 45 years or older by undertaking a pooled statistical analysis of data collected from 21 Asian cohorts (groups) about their smoking history and health.

What Did the Researchers Do and Find? For their study, the researchers used data from more than 1 million participants enrolled in studies undertaken in Bangladesh, India, mainland China, Japan, the Republic of Korea, Singapore, and Taiwan (which together account for 71% of Asia's total population). Smoking prevalences among male and female participants were 65.1% and 7.1%, respectively. Compared with never-smokers, ever-smokers had a higher risk of death from any cause in pooled analyses of all the cohorts (adjusted hazard ratios [HRs] of 1.44 and 1.48 for men and women, respectively; an adjusted HR indicates how often an event occurs in one group compared to another group after adjustment for other characteristics that affect an individual's risk of the event). Compared with never smoking, ever smoking was associated with a higher risk of death due to cardiovascular disease, cancer (particularly lung cancer), and respiratory disease among Asian men and among East Asian women. Moreover, the researchers estimate that, in the countries included in this study, tobacco smoking accounted for 15.8% of all deaths among men and 3.3% of deaths among women in 2004—a total of about 1.5 million deaths, which scales up to 2 million deaths for the population of the whole of Asia. Notably, in 2004, tobacco smoking accounted for 60.5% of lung-cancer deaths among Asian men and 16.7% of lung-cancer deaths among East Asian women.

What Do These Findings Mean? These findings provide strong evidence that tobacco smoking is associated with a substantially raised risk of death among adults aged 45 years or older throughout Asia. The association between smoking and mortality risk in Asia reported here is weaker than that previously reported for Western countries, possibly because widespread tobacco smoking started several decades later in most Asian countries than in Europe and North America and the deleterious effects of smoking take some years to become evident. The researchers note that certain limitations of their analysis are likely to affect the accuracy of its findings. For example, because no data were available to estimate the impact of secondhand smoke, the estimate of deaths attributable to smoking is likely to be an underestimate. However, the finding that nearly 45% of the global deaths from active tobacco smoking occur in Asia highlights the urgent need to implement comprehensive tobacco control programs in Asia to reduce the burden of tobacco-related disease.

Additional Information. Please access these websites via the online version of this summary at http://dx.doi.org/10.1371/journal.pmed.1001631.

- The World Health Organization provides information about the dangers of tobacco (in several languages) and about the WHO Framework Convention on Tobacco Control, an international instrument for tobacco control that came into force in February 2005 and requires parties to implement a set of core tobacco control provisions including legislation to ban tobacco advertising and to increase tobacco taxes; its 2013 report on the global tobacco epidemic is available
- The US Centers for Disease Control and Prevention provides detailed information about all aspects of smoking and tobacco use
- The UK National Health Services Choices website provides information about the health risks associated with smoking
- MedlinePlus has links to further information about the dangers of smoking (in English and Spanish)
- SmokeFree, a website provided by the UK National Health Service, offers advice on quitting smoking and includes personal stories from people who have stopped smoking
- Smokefree.gov, from the US National Cancer Institute, offers online tools and resources to help people quit smoking

RESEARCH ARTICLE

What is the Most Effective Strategy for Improving the Cancer Screening Rate in Japan?

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Abstract

Background: Cancer screening rates in Japan are much lower than those in Western countries. This study evaluated the relationship between cancer screening rates and strategies used to improve screening rates, and determined which strategy is the most effective. Materials and Methods: All municipalities are responsible for conducting gastric, lung, colorectal, cervical, and breast cancer screenings in Japan. Of the 1,746 municipalities in total, 92-99% were included in the analyses for each cancer screening. Using national data in 2009, the correlations between cancer screening rates and strategies for improving screening rates of all municipalities, both large (populations of over 30,000) and small (populations of under 30,000), were determined. The strategies used were as follows: sending personal invitation letters, personal visits by community health workers, use of a clinical setting for screening, and free screening. Results: Of all four strategies used to improve cancer screening rates, sending personal invitation letters had the highest correlations with all screening rates, with the exception of breast cancer screening. The partial correlation coefficients linking this strategy with the screening rates in all municipalities were 0.28, 0.32, 0.30, and 0.26 for gastric, lung, colorectal, and cervical cancer screening, respectively. In large municipalities, the correlations between the number of examinees in a clinical setting and the screening rates were also relatively high, particularly for cervical cancer screening (r=0.41). Conclusions: Sending personal invitation letters appears to be particularly effective in improving cancer screening rates in all municipalities. All municipalities should implement a system that sends personal invitation letters for cancer screening. In large municipalities, increasing the availability of screening in a clinical setting is also effective in improving cancer screening rates.

Keywords: Cancer screening - screening rate - strategy to increase participation- correlation - Japan

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Introduction

Since population-based screening for cancer was introduced under the Health and Medical Service Act for the elderly in 1983, municipalities have been responsible for conducting cancer screenings in Japan. Screening programs for five kinds of cancers (gastric, lung, colorectal, cervical, and breast cancers) have become continuously conducted by all municipalities. However, cancer screening rates in Japan are much lower than those in Western countries and Korea, including examinations other than population-based screening that are conducted as part of a public policy to reduce mortality rates. While the screening rates for breast and cervical cancer in 2010 were 80.4% and 85.0%, respectively, in the United States, 70.9% and 67.9% in Korea, and 73.4% and 78.5%, in the United Kingdom, both screening rates were 24.3% in Japan (OECD, 2011; Suh et al., 2013).

To improve cancer screening rates, effective strategies that motivate people to be screened need to be successfully implemented. The U.S. Center for Disease Control and Prevention (CDC) conducted systematic reviews on the effectiveness of various interventions in increasing the screening rates for breast, cervical, and colorectal cancers, and published guidelines based on their findings, which recommend certain interventions for improving the screening rates for these cancers (Baron et al., 2008a; Sabatino et al., 2012; Community Preventive Services Task Force (CPSTF), 2013). The guidelines also aid decision makers in choosing an appropriate intervention (Townsend et al., 2009; Blumenthal et al., 2010; Lobb et al., 2011; Hannon et al., 2012).

In Japan, there are no guidelines on the types of strategies that improve cancer screening rates. Some studies have previously evaluated the effectiveness of various strategies (Hisamichi et al., 1991; Watanabe, 2003; Shimada et al., 2010a; Shimada et al., 2010b; Matsuda et al., 2011; Takaku, 2011; Kuroki, 2012; Yoshida et al., 2012), but it was difficult to compare the effectiveness of these strategies, as each study focused on

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the effectiveness of an individual strategy using different subjects and methodologies. As the most effective strategy in improving cancer screening rates differs depending on the country and region (McAvoy and Raza, 1991; King et al., 1994; Saywell et al., 1999; Champion et al., 2003; Saywell et al., 2003; Saywell et al., 2004; Blumenthal at al., 2010; Lee et al., 2012; Frie et al., 2013), it remains unclear which strategy would be the most effective in Japan. Therefore, a study comparing the effectiveness of different strategies used to improve cancer screening rates in Japan is warranted and poised to be very useful for decision makers.

The aim of the present study was to quantitatively evaluate the relationships between cancer screening rates and strategies used to improve screening rates, as well as to determine which strategy is the most effective in Japan.

Materials and Methods

Subjects

The subjects were selected from a total of 1,746 municipalities that conducted gastric, lung, colorectal, cervical, and breast cancer screening in Japan. Cancer screening rates of municipalities were determined from data in the Report on Regional Public Health Services and Health Promotion Services between April 2009 and March 2010, which was prepared by the Ministry of Health, Labour, and Welfare (MHLW, 2010). In this report, the number of participants and persons eligible for the cancer screenings was tallied by sex and age in 1,746 municipalities. Persons eligible for the cancer screenings conducted by municipalities included women aged ≥20 years for cervical cancer screening, women aged ≥40 years for breast cancer screening, and both men and women aged ≥40 years for other cancer screenings. Using this report, the following characteristics of municipalities were determined: the number of eligible persons, the ratio of males to females, and percentage of those aged ≥65 years.

Data on strategies implemented by each municipality for cancer screening were obtained from a survey on the implementation of cancer screening among the different municipalities, which was conducted by the MHLW in January 2010. In this survey, the MHLW collected data on the content of examinations, strategies, and out-of-pocket costs for cancer screening among the different municipalities. 1,740 of all municipalities (99.7%) had responded to this survey. The CDC recommends interventions that use client reminders and small media, and interventions that include one-on-one education by telephone or via face-to-face encounters for colorectal, cervical, and breast cancer screening (Sabatino et al., 2012). It also recommends interventions that make screening accessible and easier for colorectal and breast cancer, and reduce out-of-pocket costs for breast cancer screening (Baron et al., 2008a; Sabatino et al., 2012; CPSTF, 2013). Based on these recommendations, similar strategies were assessed, in particular: sending personal invitation letters, personal visitations by community health workers, number of individuals screened in a clinical setting, and free screening. The use of newsletters in place of small media was not evaluated because about 90% of municipalities already implemented this strategy.

Table 1. Characteristics of Cancer Screening in Japan between April 2009 and March 2010

Variable	Gastric	Lung	Colorectal	Cervical	Breast
			All municipalities		
Number of municipalities	1,718	1,610	1,726	1,717	1,693
Screening rate(%); mean (S.D.)	15.8 (12.0)	27.4 (18.9)	21.4 (13.6)	16.9 (10.4)	13.2 (10.8)
Strategies					
Sending personal invitation letters; n (%)	946 (55.1)	889 (55.2)	947 (54.9)	966 (56.3)	933 (55.1)
Personal visitations by community health workers; n (%)	105 (6.1)	99 (6.2)	107 (6.2)	104 (6.1)	102 (6.0)
Number of individuals screened in clinical settings; mean (S.D.)	613 (2,891)	1,369 (6,582)	1,947 (6,967)	1,691 (5,091)	759 (2,706)
Free screening; n (%)	143 (8.3)	362 (22.5)	167 (9.7)	161 (9.4)	119 (7.0)
Characteristics of eligible persons					
Number of eligible persons; mean (S.D.)	22,315 (47,190)	22,821 (43,855)	22,946 (49,320)	18,701 (41,438)	13,747 (29,503)
Ratio of males to females; mean (S.D.)	0.73 (0.16)	0.72 (0.17)	0.73 (0.17)	-	-
Percentage of those aged ≥65 years; mean (S.D.)	52.9 (12.1)	53.4 (12.3)	53.0 (12.1)	42.6 (13.0)	53.2 (11.9)
		Large municipalities (population ≥30,000)			
Number of municipalities	809	767	812	808	800
Screening rate(%); mean (S.D.)	12.3 (9.0)	22.1 (15.7)	18.3 (10.9)	15.2 (8.1)	12.2 (8.6)
Strategies					
Sending personal invitation letters; n (%)	407 (50.3)	396 (51.6)	416 (51.2)	422 (52.2)	406 (50.8)
Personal visitations by community health workers; n (%)	24 (3.0)	21 (2.7)	24 (3.0)	22 (2.7)	22 (2.8)
Number of individuals screened in clinical settings; mean (S.D.)	1,255 (4,116)	2,806 (9,326)	4,052 (9,736)	3,455 (7,011)	1,538 (3,786)
Free screening; n (%)	70 (8.7)	162 (21.1)	79 (9.7)	75 (9.3)	45 (5.6)
Characteristics of eligible persons					
Number of eligible persons; mean (S.D.)	42,401 (62,911)	43,018 (57,003)	43,709 (65,937)	36,094 (55,436)	26,134 (39,346)
Ratio of males to females; mean (S.D.)	0.69 (0.17)	0.68 (0.17)	0.69 (0.17)	-	-
Percentage of those aged ≥65 years; mean (S.D.)	52.0 (12.4)	52.3 (12.5)	52.0 (12.4)	39.8 (12.2)	51.5 (11.4)
		Small municipalities (population <30,000)			
Number of municipalities	909	843	914	909	893
Screening rate(%); mean (S.D.)	18.9 (13.4)	32.2 (20.2)	24.1 (15.0)	18.4 (11.9)	14.2 (12.4)
Strategies					
Sending personal invitation letters; n (%)	539 (59.3)	493 (58.5)	531 (58.1)	544 (59.9)	527 (59.0)
Personal visitations by community health workers; n (%)	81 (8.9)	78 (9.3)	83 (9.1)	82 (9.0)	80 (9.0)
Number of individuals screened in clinical settings; mean (S.D.)	41 (175)	62 (263)	78 (285)	122 (228)	62 (127)
Free screening; n (%)	73 (8.0)	200 (23.7)	88 (9.6)	86 (9.5)	74 (8.3)
Characteristics of eligible persons					
Number of eligible persons; mean (S.D.)	4,439 (3,126)	4,445 (3,084)	4,500 (3,124)	3,241 (2,321)	2,650 (1,864)
Ratio of males to females; mean (S.D.)	0.77 (0.15)	0.76 (0.16)	0.77 (0.16)	-	-
Percentage of those aged ≥65 years; mean (S.D.)	53.8 (11.8)	54.5 (12.1)	53.9 (11.8)	45.0 (13.1)	54.8 (12.1)

Municipalities were excluded from the study if there were missing values in these variables or <10 eligible persons. Furthermore, municipalities were also excluded if they did not perform the following examinations: gastric X-ray for gastric cancer, chest X-ray for lung cancer, fecal occult blood tests for colorectal cancer, Pap smear for cervical cancer, and mammography for breast cancer. These examinations are recommended for population-based screening as there is sufficient evidence to suggest that these tests reduce the cancer mortality rate in Japan (Hamashima et al., 2008; Hamashima et al., 2010; National cancer center, 2013). Of all municipalities, 1,718 (98.4%), 1,610 (92.2%), 1,726 (98.9%), 1,717 (98.3%), and 1,693 (97.0%) municipalities were included in the analyses for gastric, lung, colorectal, cervical, and breast cancer screening, respectively.

Statistical analysis

Partial correlation coefficients were calculated to quantitatively evaluate the relationships between cancer screening rates and the strategies used to improve screening rates in various municipalities. The coefficients indicate how closely each strategy is related to the cancer screening rate after excluding the effects of confounding factors, including the other three strategies, the number of eligible persons, the ratio of males to females, and the percentage of elderly.

The relationships between cancer screening rates and the strategies may vary with the population size of the municipalities. Therefore, partial correlation coefficients were also separately calculated for large municipalities (with populations of over 30,000) and small municipalities (with populations of under 30,000). In 2009, a municipality was seen as a city if the population was over 30,000, but seen as a town or village if not. All analyses were performed using STATA version 12 (StataCorp, College Station, TX, USA).

Results

The characteristics of cancer screening in Japan are presented in Table 1. The average screening rates for gastric, lung, colorectal, cervical, and breast cancer were 15.8%, 27.4%, 21.4%, 16.9%, and 13.2%, respectively. The strategy of sending invitation letters was implemented at about 55% of the municipalities, whereas personal visitations by community health workers were implemented at only 6% of all municipalities. Free screening was implemented at 23% of all municipalities for lung cancer screening and at 7-10% of all municipalities

Table 2. Partial Correlations between Cancer Screening Rates and Strategies Used to Improve Screening Rates in Japan

Variable	Gastric	Lung	Colorectal	Cervical	Breast
			All municipalities		
Number of municipalities	1,718	1,610	1,726	1,717	1,693
Strategies					
Sending personal invitation letters d	0.28^a	0.32^a	0.30^a	0.26^a	0.13^a
Personal visitations by community health workers d	0.23^a	0.15^a	0.22^a	0.18^a	0.12^a
Number of individuals screened in clinical settings	0.17^a	0.19^a	0.21^a	0.25^a	0.18^a
Free screening d	0.03	0.13^a	0.06^b	0.08^a	0.01
Characteristics of eligible persons					
Number of eligible persons	-0.24^a	-0.26^a	-0.23^a	-0.28^a	-0.21^a
Ratio of males to females	0.07^a	0.09^a	0.03	-	-
Percentage of those aged ≥65 years	0.07^a	0.20^a	0.12^a	-0.01	-0.13^a
			Large municipalities (population ≥30,000)		
Number of municipalities	809	767	812	808	800
Strategies					
Sending personal invitation letters d	0.39^a	0.39^a	0.36^a	0.30^a	0.17^a
Personal visitations by community health workers d	0.15^a	0.11^a	0.15^a	0.06^c	0.07^b
Number of individuals screened in clinical settings	0.28^a	0.31^a	0.35^a	0.41^a	0.28^a
Free screening d	0.05	0.14^a	0.08^b	0.04	0.03
Characteristics of eligible persons					
Number of eligible persons	-0.32^a	-0.32^a	-0.33^a	-0.43^a	-0.31^a
Ratio of males to females	-0.02	0.02	-0.07^b	-	-
Percentage of those aged ≥65 years	0.05	0.17^a	0.03	0.01	-0.06^c
			Small municipalities (population <30,000)		
Number of municipalities	909	843	914	909	893
Strategies					
Sending personal invitation letters d	0.25^a	0.30^a	0.29^a	0.24^a	0.11^a
Personal visitations by community health workers d	0.22^a	0.13^a	0.22^a	0.20^a	0.12^a
Number of individuals screened in clinical settings	0.15^a	0.09^a	0.11^a	0.20^a	0.19^a
Free screening d	0.02	0.13^a	0.02	0.09^a	0.00
Characteristics of eligible persons					
Number of eligible persons	-0.36^a	-0.29^a	-0.34^a	-0.36^a	-0.28^a
Ratio of males to females	-0.01	0.02	-0.02	-	-
Percentage of those aged ≥65 years	0.01	0.16^a	0.10^a	-0.05	-0.15^a

* ^{a}p values ≤0.01; ^{b}p values ≤0.05; ^{c}p values ≤0.1; ^{d}Dummy variables

for other types of cancer screening. The average number of individuals that had been screened in the clinical setting was the largest for colorectal cancer screening, and the smallest for gastric cancer screening.

The average cancer screening rates were higher in small municipalities than large municipalities for all cancer screening. Personal visitations by health workers were implemented in about 9% of all small municipalities, which was about 6% higher than that of large municipalities for all screenings. The average number of individuals screened in the clinical setting of large municipalities was more than 20-fold greater than that of small municipalities for all cancer screening. This may be because many small municipalities did not implement cancer screening in the clinical setting (i.e., about 80% for gastric, lung, and colorectal cancers, 27% for cervical cancers, and 43% for breast cancers).

The partial correlation coefficients for the relationships between cancer screening rates and the strategies used in Japan are presented in Table 2. In all municipalities, there were positive correlations between the screening rates for all cancers and the strategies used, with the exception of free screening ($p<0.01$). Of the four strategies, sending personal invitation letters had the highest correlation coefficients with cancer screening rates. They were as follows: 0.28 for gastric cancer screening, 0.32 for lung cancer screening, 0.30 for colorectal cancer screening, and 0.26 for cervical cancer screening. For cervical cancer screening, the correlation between the number of individuals screened in the clinical setting and the screening rates was similar to that of sending invitation letters. For breast cancer screening, all strategies had a low or no correlation with the screening rates in all municipalities.

In large municipalities, the correlation coefficients between sending invitation letters and the screening rates were relatively high. Specifically, they were as follows: 0.39 for gastric cancer screening, 0.39 for lung cancer screening, 0.36 for colorectal cancer screening, and 0.30 for cervical cancer screening. In large municipalities, the correlation coefficients between the number of individuals screened in the clinical setting and the screening rates were also relatively high, particularly for cervical cancer screening ($r=0.41$). For breast cancer screening, the correlation coefficient rose to 0.28 in large municipalities. In small municipalities, the correlation coefficients between cancer screening rates and the strategies used were similar to those of all municipalities, with the exception of the number of individuals screened in the clinical setting.

Discussion

In Japan, the National Cancer Control Plan was published in 2007 with the aim of increasing cancer screening rates above 50% within 5 years (MHLW, 2012a). To achieve this goal, municipalities had to implement effective strategies that would increase screening for various types of cancer. Previous studies have shown that sending personal invitation letters (Watanabe, 2003; Shimada et al., 2010a; Shimada et al., 2010b; Matsuda et al., 2011), distributing leaflets and pamphlets (Hisamichi et al., 1991; Yoshida et al., 2012), and increasing the availability of cancer screening in clinical settings (Takaku, 2011) were effective in improving cancer screening rates in Japan. However, it was unclear which strategy was the most effective. In the present study, after excluding the effects of confounding factors, correlations between four different strategies and cancer screening rates were evaluated.

Of all strategies, sending personal invitation letters had the highest positive correlations with screening rates for gastric, lung, colorectal, and cervical cancers. This strategy appears to be particularly effective in improving cancer screening rates in large municipalities. In most Western countries, the importance of a national call-recall system, which gives call and recall notifications by mail or telephone, is well recognized by the government for the purposes of increasing cancer screening (Quinn et al., 1998; Baron et al., 2008b). In Japan, municipalities are responsible for implementing strategies to improve cancer screening rates. However, nearly half of the municipalities did not implement this strategy. To improve cancer screening rates, all municipalities need to prioritize establishing a system that sends personal invitation letters for cancer screening.

The number of individuals that had been screened in the clinical setting also demonstrated positive correlations with all cancer screening in large municipalities. The correlation was particularly high for cervical cancer screening. Previous studies reported on the effectiveness of making access to screening easier by reducing the time or distance between the service delivery settings and the examinees in increasing colorectal and breast cancer screening in Western countries (Dolan et al., 1999; Baron et al., 2008c). Thus, increasing the availability of screening in the clinical setting should be effective in improving the screening rates for not only colorectal and breast cancer, but also for cervical cancer, in Japan. However, the quality assurance of cancer screening in the clinical settings was insufficient compared to that of mass screening in Japan (Arisue et al., 2007; Osaka City, 2010). Additionally, many small municipalities did not implement cancer screening in the clinical setting (i.e., about 80% for gastric, lung, and colorectal cancers, 27% for cervical cancers, and 43% for breast cancers). This may be due to several reasons. For example, small municipalities have been under more severe fiscal constraints than large municipalities (Ministry of Internal Affairs and Communications, 2011), and consequently are more likely not to have any incentives for increasing cancer screening in the clinical settings (Takaku, 2011). Thus, to increase cancer screening in the clinical setting, particularly in small municipalities, these problems need to be resolved.

Personal visitations by community health workers had low, but positive, correlations with cancer screening rates compared to sending invitation letters and the number of individuals that were screened in the clinical setting. However, these correlations were higher in small municipalities versus large municipalities. This may be because this strategy was implemented better in small municipalities than large municipalities. This strategy is unlikely to be implemented in large municipalities because it is difficult to employ many community health workers for the number of eligible persons. It was previously reported that the cost effectiveness of one-on-one education per additional mammogram increased substantially if the cost of labor increased (Stockdale et al., 2000). Thus, each municipality needs to pay sufficient attention to fiscal constraints and decide whether to implement this strategy.

Free screening had a weak correlation with cancer screening rates. To improve screening rates, the MHLW had initiated a strategy that distributed free coupons to some individuals for breast and cervical cancer screening beginning in 2009 and for colorectal cancer screening beginning in 2011. The distribution of free coupons improved the screening rates for women who had not been screened for cervical cancer in Fukuoka Prefecture (Kuroki, 2012). However, changes in price for cancer screenings had little influence on demand for screenings in Hokkaido Prefecture (Takemura et al., 2001). The CDC recommends interventions that reduce out-of-pocket costs for breast cancer screening, but does not recommend such interventions for cervical and colorectal cancer screening due to insufficient evidence (Baron et al., 2008a; Sabatino et al., 2012; CPSTF, 2013). Therefore, reducing the out-of-pocket costs alone appears to be insufficient for improving the cancer screening rates.

However, it should be mentioned that none of the strategies had strong (or very high) correlations with cancer screening rates. For breast cancer screening, even sending personal invitations had a very low correlation with the screening rates. Therefore, just sending personal invitation letters and increasing the availability of screening in the clinical settings does not appear to greatly improve the cancer screening rates. The CDC recommends provider-oriented interventions, which evaluate the providers' performance and present the providers with the results, to increase cancer screening (Sabatino et al, 2008). The MHLW reported that implementing cancer screening and specific health checkups simultaneously improved cancer screening rates in some municipalities (MHLW, 2012b). In addition to these strategies, future studies that determine other effective strategies for improving cancer screening rates are warranted, including where screening occurs and the medical personnel involved (Tsunematsu et al., 2013).

This study has several limitations that need to be discussed. First, while using partial correlation analysis to determine the relationships between cancer screening rates and the strategies has provided some foundational knowledge on the topic, the causality of these relationships is still unclear. It is also necessary to consider that these findings may be a result of reverse causality, meaning that the implementation of strategies is influenced by cancer screening rates. Second, data on costs of the strategies implemented by each municipality could not be used in the analyses (Saywell et al., 1999; Stockdale et al., 2000; Saywell et al., 2003; Saywell et al., 2004). The cost-effectiveness of these strategies should be evaluated. Third, some municipalities might have conducted cancer screening not for all eligible persons but for very limited persons, such as those who sought to receive screening or had received a year before. Such municipalities should be excluded in the analyses. Fourth, it is necessary to further evaluate which strategies are more effective than those studied herein.

In conclusion, of the strategies used to improve cancer screening rates, sending personal invitation letters had the greatest positive correlations with screening rates for gastric, lung, colorectal, and cervical cancers. This strategy appears to be particularly effective in improving cancer screening rates in large municipalities. All municipalities should predominantly focus on establishing a system that sends personal invitation letters for cancer screening. In large municipalities, increasing the availability of screening in the clinical setting may also be effective in improving cancer screening rates.

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TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (8): Gastric cancer

Current issues and future perspectives of gastric cancer screening

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Abstract

Gastric cancer remains the second leading cause of cancer death worldwide. About half of the incidence of gastric cancer is observed in East Asian countries, which show a higher mortality than other countries. The effectiveness of 3 new gastric cancer screening techniques, namely, upper gastrointestinal endoscopy, serological testing, and "screen and treat" method were extensively reviewed. Moreover, the phases of development for cancer screening were analyzed on the basis of the biomarker development road map. Several observational studies have reported the effectiveness of endoscopic screening in reducing mortality from gastric cancer. On the other hand, serologic testing has mainly been used for targeting the high-risk group for gastric cancer. To date, the effectiveness of new techniques for gastric cancer screening has remained limited. However, endoscopic screening is presently in the last trial phase of development before their introduction to population-based screening. To effectively introduce new techniques for gastric cancer screening in a community, incidence and mortality reduction from gastric cancer must be initially and thoroughly evaluated by conducting reliable studies. In addition to effectiveness evaluation, the balance of benefits and harms must be carefully assessed before introducing these new techniques for population-based screening.

Key words: Gastric cancer screening; Mortality; Upper gastrointestinal endoscopy; Upper gastrointestinal X-ray; Serum pepsinogen test; *Helicobacter pylori* antibody

Core tip: The effectiveness of new gastric cancer screening technique has remained limited to date. The present review of 3 new gastric cancer screening techniques, namely, upper gastrointestinal endoscopy, serological testing, and "screen and treat" method provides invaluable insights on how screening tests should be instituted. To effectively introduce new techniques for gastric cancer screening in a community, incidence and mortality reduction from gastric cancer must be initially and thoroughly evaluated by conducting reliable studies. In addition to effectiveness evaluation, the balance of benefits and harms must be assessed before introducing these new techniques for population-based screening.

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INTRODUCTION

Gastric cancer remains the second leading cause of cancer death worldwide. Over the last 3 decades, the incidence of gastric cancer has decreased around the world, and a similar trend can be observed in Asian countries. However, although mortality from gastric cancer has markedly improved, its burden remains substantial.

In 2012, an estimated 1 million new cases of gastric cancer have occurred, with half of the world total occurring in Eastern Asia[1]. The age-standardized incidence rates are about three times as high in men as in women; 35.4 for 100000 men and 13.8 for 100000 women in the world. The highest mortality rates are observed in Eastern Asia, occurring at 24.0 per 100000 men and 9.8 per 100000 women.

In Japan, there are more than 360000 cancer deaths, with gastric cancer accounting for 13.6% of the total number of cancer deaths[2]. In 2012, the reported age-standardized mortality rate of gastric cancer was 17.6 per 100000 men and 6.7 per 100000 women. Over the last 2 decades, the cancers causing mortality have changed. Particularly, mortality from gastric cancer in men has decreased. In 2005, the gastric cancer mortality rate was half that in 1975.

HISTORY OF GASTRIC CANCER SCREENING

Gastric cancer screening using upper gastrointestinal series (radiographic screening), which was developed in Japan, has been conducted since the 1960s[3]. In 1983, nationwide cancer screening programs were started under the Health Service Law for the Aged. These programs have been conducted as a public policy for the last 3 decades. In 2000, Hisamichi[4] assessed the effectiveness of radiographic screening based on a literature review, and they recommended this screening technique in their report. In 2005, the Japanese guidelines for gastric cancer screening also recommended radiographic screening based on a systematic review[5]. In the guidelines, upper gastrointestinal endoscopy and serological testing [*i.e.*, *Helicobacter pylori* (*H. pylori*) antibody and serum pepsinogen screening] were also evaluated. These were not, however, recommended because of insufficient evidence.

Since the introduction of population-based screening, radiographic equipment has been improved and radiation exposure has gradually decreased. In the last decade, filming has efficiently progressed to digital imaging. High-density barium has been used for radiographic screening in the 2000s. Compared with previous techniques, the sensitivities of new screening techniques remain equal, but their specificities have seen a considerable improvement[6]. Although radiographic screening has been conducted in most municipalities in Japan, the screening rate has gradually decreased nationwide over the last decade[7]. On the other hand, endoscopic screening has been performed in clinical settings as opportunistic screening[8-10]. The serum pepsinogen method has been used mainly in clinical settings with multiphasic health check-ups[11-13], but the use of this method has been limited to communities[14,15].

In other Asian countries, gastric cancer screening using both methods has been performed as opportunistic screening[16]. Both radiographic screening and radiographic screening and endoscopic screening has been introduced as national programs since 2000 in South Korea[17]. Although the target age group is the same as in Japan, the screening interval is every 2 years in South Korea. People can choose the screening method at their own preference, and a high selection preference for endoscopic screening has been observed.

CURRENT STATUS OF GASTRIC CANCER SCREENING IN JAPAN

Five cancers, namely, stomach, colon and rectum, lung, breast and cervical cancer have been screened by nationwide screening programs in Japan. The results of population-based screening are shown in Table 1[7]. Interestingly, the rate of gastric cancer screening has been shown to be lower than that of other organs, although the rates of all cancer screening programs are below 25%. Since the introduction of gastric cancer screening in 1983, the screening rate has gradually decreased and remained at about 10%. Except for cervical cancer, the target groups in these screening programs are individuals 40 years and over. There is no upper age limit in these programs and individuals over 70 years have constituted about 35% of the participants in gastric cancer screening. The screening interval for gastric, colorectal, and lung cancer is every year. For gastric cancer screening, about 4 million people participate each year. The positive rate is about 10% and further examination is needed for definitive diagnosis. The participant rate of diagnostic examinations is approximately 80% and is higher than that for colorectal cancer screening. There were 6769 newly detected gastric cancers in 2011. However, the detection rate in gastric cancer screening has remained at 0.1% to 0.2%.

There are several problems with the continued use of nationwide radiographic screening in Japan. The upper gastrointestinal series (UGI) with double-contrast study was originally adopted for radiographic screening. Special training is needed for the interpretation of UGI radiographs in gastric cancer screening. The use of UGI has now seen a rapid decrease in the clinical setting and is presently replaced by upper gastrointestinal endoscopy, which becomes a requisite technique for general physicians, particularly for the young generation. Inadequate manpower for radiographic screening will become evident in the future because of the advanced age of experts who can interpret UGI radiographs. Since the burden of gastric cancer still remains substantial, new techniques, including endoscopy, serological tests for *H. pylori* antibody and serum pepsinogen, a maker of atrophy have

Table 1 Results of population-based screening in Japan

	Stomach	Colon and rectum	Lung	Breast	Cervix
Total participants	3874128	6975281	7059318	2541993	4666826
Screening rate	9.6%	16.8%	17.2%	18.8%	23.7%
Positive rate	9.4%	7.3%	2.8%	8.6%	1.6%
Participant rate of diagnostic examination	81.1%	63.6%	77.7%	83.5%	66.2%
Cancer detection rate	0.17%	0.23%	0.06%	0.32%	0.08%
Positive predictive value	1.9	3.2	2.2	3.7	4.9

Adapted from reference [7].

Table 2 Sensitivity of endoscopy and radiography for gastric cancer screening

Screening round	Method	Sensitivity By the detection method	Specificity By the detection method	Sensitivity By the incidence method
Prevalence screening	Endoscopic screening	0.955 (0.875-0.991)	0.851 (0.843-0.859)	0.886 (0.698-0.976)
	Radiographic screening	0.893 (0.718-0.977)	0.856 (0.846-0.865)	0.831 (0.586-0.964)
Incidence screening	Endoscopic screening	0.977 (0.919-0.997)	0.888 (0.883-0.892)	0.954 (0.842-0.994)
	Radiographic screening	0.885 (0.664-0.972)	0.891 (0.885-0.896)	0.855 (0.637-0.970)

Adapted from reference [22].

been anticipated for gastric cancer screening. A "screen and treat" strategy is also anticipated for *H. pylori* eradication and surveillance for the high-risk group.

NEW CANCER SCREENING METHODS

Endoscopic screening

Endoscopic screening for gastric cancer was not recommended in the 2005 version of the Japanese guidelines[5]. Although new studies have been reported since the publication of the Japanese guidelines, these studies were insufficient to validate the effectiveness of endoscopic screening[8-9,18-20]. Endoscopic screening has been performed in 18.3% of municipalities as population-based screening in Japan[21]. Several studies have reported that endoscopic screening has a higher detection rate than radiographic screening[8-10]. Endoscopic screening can detect cancer earlier which can be adopted for endoscopic submucosal resection.

A comparison of the sensitivity of endoscopic and radiographic screenings has been reported[22,23]. In a Korean study, the sensitivity of endoscopic screening was reported as 69.4% (95%CI: 66.4-72.4) for the first round and 66.9% (95%CI: 59.8-74.0) for the subsequent round[23]. On the other hand, the sensitivity of radiographic screening was reported as 38.2% (95%CI: 35.9-40.5) for the first round and 27.3% (95%CI: 22.6-32.0) for the subsequent round[23]. Although the definition of interval cancer was different between South Korea and Japan, the sensitivity of endoscopic screening was always higher than that of radiographic screening. However, there are possibilities of an increase in the frequency of overdiaganosis by endoscopic screening because it can detect cancer earlier than radiographic screening. Although the detection method is commonly used to measure the sensitivity of the screening method, it cannot exclude cases of overdiagnosis. The incidence method was developed to calculate sensitivity, avoiding cases of overdiaganosis[24]. Screening for breast, lung, and colorectal cancers has been evaluated using the incidence method[25-27]. In a Japanese study, the sensitivities of endoscopic and radiographic screening were calculated by both methods[22] (Table 2). By the detection method, it was found that the sensitivity of endoscopic screening was higher than that of radiographic screening in both rounds (prevalence screening: $P = 0.255$, incidence screening: $P = 0.043$). By the incidence method, the sensitivity of endoscopic screening for prevalence and incidence screenings was also higher than that of radiographic screening (prevalence screening: $P = 0.626$, incidence screening: $P = 0.117$). Even if the incidence method is used, the sensitivity of endoscopic screening was always higher than that of radiographic screening in both rounds.

Recently, the results of a community-based case-control study of endoscopic screening have been reported[28,29]. Based on the results of a larger case-control study, the findings suggest a 30% reduction in gastric cancer mortality by endoscopic screening compared with no screening within 36 mo before the date of diagnosis of gastric cancer[28]. Although the sample size is small in the Nagasaki study, a higher mortality reduction from gastric cancer by 80% was reported[29]. Although these results suggest that gastric cancer mortality could be reduced by endoscopic screening, prudence must be ob-

Table 3 Results of prediction based on a combination of *Helicobacter pylori* antibody and serum pepsinogen screening

	Ohata *et al*[38]	Watabe *et al*[40]	Mizuno *et al*[39]
Basic characteristics			
Year published	2004	2005	2009
Location	Wakayama	Chiba	Kyoto
Total number	4655	6983	2859
Men/Women	4655/0	3320/2260	1011/1848
Age	48.3 (average)	48.9 (average)	≥ 35
Follow-up (yr)	7.7 (average)	4.7 (average)	10 (maximum)
HP positive rate (%)	78.6	46.1	75
PG positive rate (%)	28.9	21.8	39.2
Number of detected cancer	45	43	61
Incidence of gastric cancer (/1000)	9.67	6.16	21.3
HP-/PG-			
Total number	967	3324	647
Number of detected cancer	0	7	2
Incidence of gastric cancer (/1000)	-	2.11	3.09
HP+/PG-			
Total number	2341	2134	1094
Number of detected cancer	19	6	15
Incidence of gastric cancer (/1000)	8.12	2.81	13.71
HP+/PG+			
Total number	1316	1082	1054
Number of detected cancer	24	18	41
Incidence of gastric cancer (/1000)	18.24	16.64	38.9
HP-/PG+			
Total number	31	443	69
Number of detected cancer	2	12	3
Incidence of gastric cancer (/1000)	64.52	27.09	43.48

HP: *Helicobacter pylori* antibody; PG: Serum pepsinogen.

served in interpreting positive results because these case-control studies may have included self-selection bias.

TARGETING THE HIGH-RISK GROUP

Although serologic testing has been used for targeting the high-risk group for gastric cancer, the effectiveness of these screenings has not been fully clarified. A small case-control study reported mortality reduction from gastric cancer using serum pepsinogen screening[30]; however, this screening is insufficient to confirm the effectiveness of serological testing. In a meta-analysis by Dinis-Ribeiro *et al*[31], they found that the sensitivity of serum pepsinogen screening for gastric cancer was 77% and that the specificity was 73% using pepsinogen I ≤ 70 and pepsinogen I / II ratio ≤ 3 as cut-off values for atrophy. Since high specificity is a major requirement for cancer screening[32], tests with lower specificity such as serum pepsinogen testing are not suitable for primal screening.

The 3 current serological screening methods commonly used to identify the high-risk group are as follows: (1) serum pepsinogen screening; (2) *H. pylori* antibody screening; and (3) a combination of the serum pepsinogen and *H. pylori* antibody screening. Although cytotoxin associated gene A (cagA) has also been anticipated as a new biomarker for gastric cancer, its use has been limited to research-based screening[33]. Most of the reported studies are cross-sectional studies in which the serologic test was performed simultaneously with upper endoscopic screening. Although several studies have been reported from European countries, their outcomes were mainly for chronic atrophic gastritis which is a surrogate end-point even if it can be a precursor of gastric cancer[33-35]. Lomba-Viana *et al*[36] previously reported the results of a 5-year follow-up study of the serum pepsinogen test for the early detection of gastric cancer in Portugal. The constraint of their study was that the subjects were limited only to 4% of the primary subjects who were screened by the serum pepsinogen tests. For the successful introduction of a screening procedure for population-based screening, a direct evaluation of the reduction in gastric cancer incidence is required. Therefore, a long-term follow-up for the whole target population is needed to evaluate the possibility of predicting the incidence of gastric cancer.

At present, the most commonly used strategy for serologic testing is a combination of serum pepsinogen and *H. pylori* antibody screening, or the so-called "ABC method"[37]. This combination method has been most anticipated since it can theatrically stratify the risk of gastric cancer. However, the effects of long-term follow-up have not yet been clarified. Thus far, there are 3 studies on predicting the incidence of gastric cancer based on long-term follow-up[38-40]. In all of these studies, the follow-up periods were less than 10 years. Moreover, the incidence rates of gastric cancer were different among these studies (Table 3). The 4 groups identified on the basis of serum pepsinogen and *H. pylori* infections were as follows: Group A = negative *H. pylori* infection and negative atrophy; Group B = positive *H. pylori* infection and negative atrophy; Group C = positive *H. pylori* infection and positive atrophy; Group D = negative *H. pylori* infection and positive atrophy. As shown in Figure 1, a meta-analysis was conducted on the base of the results of these studies using a random effect model by Stats Direct3 (Stats Direct Ltd. Cheshire United Kingdom). Although there was no cancer in group A in Wakayama study by Ohata *et al*[38], it assumed that there was 1 cancer in group A in this study for meta-analysis. Because of the small number of group D, groups C and D were combined. Although the risk of gastric cancer of group C + D was higher than that of group A [relative risk (RR) = 10.81, 95%CI: 5.54-21.09], the difference in gastric cancer risk between group A and group B cannot be identified (RR = 2.93, 95%CI: 0.97-8.80). Group C + D was clearly divided by group B (RR = 3.34, 95%CI: 1.91-5.84). Although serologic testing could be used to detect the high-risk group for gastric cancer, the exclusion of the low-risk group