Editors' Summary

Background. Worldwide, a small number of modifiable risk factors are responsible for many premature or preventable deaths. For example, having high blood pressure (hypertension) increases a person's risk of developing life-threatening heart problems and stroke (cardiovascular disease). Similarly, having a high blood sugar level increases the risk of developing diabetes, a chronic (long-term) disease that can lead to cardiovascular problems and kidney failure, and half of all long-term tobacco smokers in Western populations will die prematurely from diseases related to smoking, such as lung cancer. Importantly, the five major risk factors for death globally—high blood pressure, tobacco use, high blood sugar, physical inactivity, and overweight and obesity—are all modifiable. That is, lifestyle changes and dietary changes such as exercising more, reducing salt intake, and increasing fruit and vegetable intake can reduce an individual's exposure to these risk factors and one's chances of premature death. Moreover, public health programs designed to reduce a population's exposure to modifiable risk factors should reduce preventable deaths in that population.

Why Was This Study Done? In 2000, the Japanese government initiated Health Japan 21, a ten-year national health promotion campaign designed to prevent premature death from non-communicable (noninfectious) diseases and injuries. This campaign set 59 goals to monitor and improve risk factor management in the Japanese population, which has one of the longest life expectancies at birth in the world (the life expectancy of a person born in Japan in 2009 was 83.1 years). Because the campaign's final evaluation revealed deterioration or no improvement on some of these goals, the Japanese government recently released new guidelines that stress the importance of simultaneously controlling multiple risk factors for chronic diseases. However, although several studies have quantified the impacts on life expectancy and cause-specific death of individual modifiable risk factors in Japan, the effects of multiple risk factors have not been assessed. In this study, the researchers use a "comparative risk assessment" framework to estimate the effects of 16 risk factors on cause-specific deaths and life expectancy in Japan. Comparative risk assessment estimates the number of deaths that would be prevented if current distributions of risk factor exposures were changed to hypothetical optimal distributions.

What Did the Researchers Do and Find? The researchers obtained data on exposure to the selected risk factors from the 2007 Japanese National Health and Nutrition Survey and from epidemiological studies, and information on the number of deaths in 2007 from different diseases from official records. They used published studies to estimate how much each factor increases the risk of death from each disease and then used a mathematical formula to estimate the effects of the risk factors on the number of deaths in Japan and on life expectancy at age 40. In 2007, tobacco smoking and high blood pressure accounted for 129,000 and 104,000 deaths, respectively, in Japan. Physical inactivity accounted for 52,000 deaths, high blood glucose and high dietary salt intake accounted for 34,000 deaths each, and alcohol use for 31,000 deaths. Life expectancy at age 40 in 2007 would have been extended by 1.4 years for both sexes, the researchers estimate, if exposure to multiple cardiovascular risk factors had been reduced to calculated optimal distributions, or by 0.7 years if these risk factors had been reduced to the distributions defined by national guidelines and goals.

What Do These Findings Mean? These findings identify tobacco smoking and high blood pressure as the major risk factors for death from non-communicable diseases among adults in Japan, a result consistent with previous findings from the US. They also indicate that simultaneous control of multiple risk factors has great potential for producing health gains among the Japanese population. Although the researchers focused on estimating the effect of these risk factors on mortality and did not include illness and disability in this study, these findings nevertheless identify two areas of public health policy that need to be strengthened to improve health, reduce death rates, and increase life expectancy among the Japanese population. First, they highlight the need to reduce tobacco smoking, particularly among men. Second and most importantly, these findings emphasize the need to improve ongoing programs designed to help people manage multiple cardiovascular risk factors, including high blood pressure.

Additional Information. Please access these websites via the online version of this summary at http://dx.doi.org/10.1371/journal.pmed.1001160.

- The US Centers for Disease Control and Prevention provides information on all aspects of healthy living
- The *World Health Report 2002—Reducing Risks, Promoting Healthy Life* provides a global analysis of how healthy life expectancy could be increased
- The American Heart Association and the American Cancer Society provide information on many important risk factors for noncommunicable diseases and include some personal stories about keeping healthy
- Details about Health Japan 21 are provided by the Japanese Ministry of Health, Labour and Welfare. Further details about this campaign are available from the World Health Organization
- MedlinePlus provides links to further resources on healthy living and on healthy aging (in English and Spanish)

Annals of Oncology

Annals of Oncology 23: 1362–1369, 2012
doi:10.1093/annonc/mdr437
Published online 2 November 2011

Attributable causes of cancer in Japan in 2005—systematic assessment to estimate current burden of cancer attributable to known preventable risk factors in Japan

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Received 16 May 2011; revised 8 August 2011; accepted 8 August 2011

Background: To contribute to evidence-based policy decision making for national cancer control, we conducted a systematic assessment to estimate the current burden of cancer attributable to known preventable risk factors in Japan in 2005.

Methods: We first estimated the population attributable fractions (PAFs) of each cancer attributable to known risk factors from relative risks derived primarily from Japanese pooled analyses and large-scale cohort studies and the prevalence of exposure in the period around 1990. Using nationwide vital statistics records and incidence estimates, we then estimated the attributable cancer incidence and mortality in 2005.

Results: In 2005, ~55% of cancer among men was attributable to preventable risk factors in Japan. The corresponding figure was lower among women, but preventable risk factors still accounted for nearly 30% of cancer. In men, tobacco smoking had the highest PAF (30% for incidence and 35% for mortality, respectively) followed by infectious agents (23% and 23%). In women, in contrast, infectious agents had the highest PAF (18% and 19% for incidence and mortality, respectively) followed by tobacco smoking (6% and 8%).

Conclusions: In Japan, tobacco smoking and infections are major causes of cancer. Further control of these factors will contribute to substantial reductions in cancer incidence and mortality in Japan.

Key words: cancer, Japan, population attributable fraction, risk factor

introduction

Japan has experienced a drastic change in disease structure and pattern over the past five decades [1, 2], due to economic, demographic, and lifestyle changes experienced after World War II. Together with rapid aging, the transition in patterns of disease from communicable diseases such as tuberculosis and pneumonia to noncommunicable diseases, including cancer [1, 2], poses challenges to health systems and to public health in Japan. Cancer has been the leading cause of death in Japan since 1981, accounting for ~30% of all deaths in recent years. Cancer registry data in 2005 suggest that 54% of Japanese men and 41% of Japanese women will be diagnosed with cancer during their lifetime [3].

It is well known that cancers are largely caused as a result of lifestyle and environmental factors that are potentially preventable. On the other hand, substantial differences in the pattern of cancer by geographical region and socioeconomic level may be identified [4]. Cancer control policies in any country must therefore be tailored to reflect the local burden of cancer and characteristics of the health system.

The first national systematic quantitative assessment of multiple cancers was reported in the United States in 1981 [5] and was followed by updated estimates for the United States [6, 7], estimates for European countries including the Nordic countries [8, 9], and France [10, 11] and global estimates [12]. Although the cancer burden attributable to sectioned individual risk factors has been reported for East Asian countries [13–16], no single study has provided a reliable estimation of attributable fraction for known risk factors on multiple cancer risks in Japan.

In the present study, we conducted a systematic assessment to estimate the current burden of cancer attributable to known preventable risk factors in Japan in 2005.

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methods

We estimated the population attributable fraction (PAF) of site-specific cancers occurring in Japan in 2005. PAF in the present study is the fraction of total cancer incidences or mortality that is attributable to a particular exposure and that could be avoided if that exposure were eliminated or reduced to an alternative scenario that would result in the lowest risk, or in other words, the theoretical minimum risk exposure distribution [17].

data sources

Estimation of PAF of known causes of cancer in Japanese requires the availability of cancer incidence and mortality data in Japan, data on the prevalence of exposure to each risk factor and relative risk (RR) for each causally related cancer.

selection of risk factors for cancer in Japan. Risk factors included in this study were those for which there is evidence for a causal association with cancer (Table 1). These factors were selected based on the agents classified by the International Agency for Research on Cancer (IARC) [18] as Group 1 carcinogens in humans; risk and protective factors that were judged as 'convincing', with the exception of 'convincing' or 'probable' for vegetable, fruit, and salt intake by the second 'Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective' report, produced by the World Cancer Research Fund and American Institute for Cancer Research in 2007 [19]; and the conditions evaluated by the IARC Cancer Prevention Handbook Series [20] as causally associated with a reduced risk. Some established carcinogens, such as infection with *Schistosoma haematobium* (blood fluke), *Opisthorchis viverrini* (liver fluke), human immunodeficiency virus, and intake of aflatoxin, were not included in this study due to their very rare or very low prevalence in Japan. Further, due to the lack of reliable prevalence data in Japan, we did not include risk factors such as occupational exposure, air pollution, and ultraviolet and radiation exposure.

cancer incidence and mortality in Japan in 2005. Cancer incidence data in 2005 were obtained from the annual estimate by the Japan Cancer Surveillance Research Group as part of the Monitoring of Cancer Incidence in Japan project [3] on the basis of data collected from population-based cancer registries in Japan. We obtained sex- and age-specific incidence data for target cancers using code of the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10), with morphology code of the International Classification of Disease for Oncology, 3rd Edition (ICD-O-3).

Data on cancer mortality statistics in 2005 were obtained from the vital statistics of Japan. We extracted sex-, age-, and cause-specific mortality from an electronic database obtained from the Japanese Ministry of Health, Labour and Welfare, with permission. Cause of death was classified using the ICD-10.

Table 2 summarizes cancer incidence and mortality in Japan in 2005.

prevalence of exposures to each risk factor. The current burden of cancer reflects the cumulative effect of past exposures. For most cancers and risk factors, average latency between first exposure and diagnosis is ~15 years [11]. We therefore assumed a latency time of ~15 years and considered exposures around 1990. We collected prevalence data of exposures to each risk factor from different sources, giving priority to representative Japanese surveys. No latency time was considered and current prevalence was applied for exogenous hormone use (hormone replacement therapy and oral contraceptive use) in women given the assumption that cancer risk decreases rapidly after the cessation of use of exogenous hormones [21]. Occupational exposures such as asbestos, etc. were not included in this analysis due to a lack of reliable prevalence data in Japan.

selection of RR for each causally related cancer. Data on RR included in this study were obtained from epidemiologic studies identified from different sources, including PubMed, *Ichushi*, and websites, in either English or Japanese. We employed priority ranking for the inclusion and selection of RRs as follows: for selection, a study should include RR and corresponding 95% confidence intervals (CIs). Among these studies, highest priority was given to meta-analyses that included pooled analyses of Japanese populations. When meta-analyses were not available, we selected the most

Table 1. Risk factors and cancers included in the present analysis

Risk factor	Definition of theoretical minimum risk exposure distribution	Target cancers associated with risk factor
Tobacco smoking (active)	Never smoking	Oral and pharynx, esophagus, stomach, colorectum, liver, pancreas, larynx, lung, cervix uteri, ovary, bladder, kidney, myeloid leukemia
Passive smoking	No exposure	Lung (nonsmokers)
Alcohol drinking	No alcohol intake	Oral and pharynx, esophagus, colorectum, liver, female breast
Overweight and obesity	Body mass index <25	Colon, pancreas, postmenopausal breast, endometrial, kidney
Physical inactivity	Average daily total physical activity level + three METs/day	Colon, breast, endometrial
Vegetable intake	Higher than the lowest intake group	Esophagus, stomach
Fruit intake	Higher than the lowest intake group	Esophagus, stomach, lung
Salt intake	Intake of ≤6 g/day	Stomach
Infection	No infection	
Helicobacter pylori		Noncardia stomach, gastric MALT lymphoma
Hepatitis C virus		Liver
Hepatitis B virus		Liver
Human papillomavirus		Oral cavity, oropharynx, anus, penis, vulva, vagina, cervix uteri
Human T-cell leukemia type I		Adult T-cell lymphoma/leukemia
Epstein–Barr virus		Nasopharynx, Burkitt lymphoma, Hodgkin lymphoma
Exogenous hormone use	No use	Female breast
Hormone replacement therapy		
Oral contraceptives		

MALT, mucosa-associated lymphoid tissue; MET, metabolic equivalents.

Table 2. Incidence[a] and mortality[b] of cancer in Japan in 2005

Site	ICD-10	Men		Women		Both sexes	
		Incidence	Mortality	Incidence	Mortality	Incidence	Mortality
Oral and pharynx	C00–C14	7417	4151	3498	1528	10 915	5679
Esophagus	C15	14 818	9465	2678	1717	17 496	11 182
Stomach	C16	80 102	32 643	37 035	17 668	117 137	50 311
Colon	C18	37 126	13 436	31 069	13 685	68 195	27 121
Rectum	C19–C20	22 344	8710	13 517	4999	35 861	13 709
Anus	C21	430	137	248	130	678	267
Liver	C22	28 729	23 203	13 465	11 065	42 194	34 268
Gall-bladder, etc.	C23–C24	9237	7845	9399	8741	18 636	16 586
Pancreas	C25	13 108	12 284	11 691	10 643	24 799	22 927
Sinonasal	C30–C31	826	261	673	174	1499	435
Larynx	C32	3903	1006	214	84	4117	1090
Lung	C33–C34	58 264	45 189	25 617	16 874	83 881	62 063
Skin	C44	4405	347	3702	321	8107	668
Breast	C50	312	87	47 582	10 721	47 894	10 808
Vulva	C51			704	226	704	226
Vagina	C52			221	102	221	102
Cervix uteri	C53			8474	2465	8474	2465
Corpus uteri	C54			8189	1459	8189	1459
Ovary	C56			8304	4467	8304	4467
Penis	C60	308	128			308	128
Prostate	C61	42 997	9265			42 997	9265
Kidney	C64	6871	2600	3153	1233	10 024	3833
Renal pelvis	C65–C66, C68	2887	1419	1731	880	4618	2299
Bladder	C67	12 619	4141	3858	1888	16 477	6029
Thyroid	C73	2126	446	7093	1024	9219	1470
Hodgkin disease	C81	422	89	501	43	923	132
Non-Hodgkin lymphoma	C82–C85, C96	8571	4772	7386	3676	15 957	8448
Multiple myeloma	C88–C90	2242	1972	2171	1917	4413	3889
Leukemia	C91–C95	5200	4311	3832	2972	9032	7283
All sites	C00–C97	379 436	196 603	267 366	129 338	646 802	325 941

[a]Japan Cancer Surveillance Research Group as part of the Monitoring of Cancer Incidence in Japan project [3].
[b]Vital statistics of Japan [1].
ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th Revision.

comprehensive studies of Japanese available. Results from cohort studies had priority over case–control studies. When RRs for Japanese populations were not available, we then substituted the data with those for other Asian populations and finally with non-Asian values from the literature.

analysis

PAF was calculated based on the RR of cancer associated with exposure to the risk factor and the prevalence of exposure to the risk factor in the total population (P) [22] using the following formula:

$$\text{PAF} = \frac{P\times(\text{RR}-1)}{P\times(\text{RR}-1)+1}.$$

When RR or exposure data were reported in multiple exposure categories, they were combined in a dichotomous variable [10, 23].

Different methods were used for estimations related to infection. To estimate major infectious causes of cancer in Japanese such as *Helicobacter pylori*, hepatitis B virus and hepatitis C virus (HCV), we used an alternative formula [23, 24] based on the distribution of exposure in cases (Pc) since the prevalence of each infection among cases was more stable than that among control or reported populations in the literature:

$$\text{PAF} = Pc\times\frac{\text{RR}-1}{\text{RR}}.$$

For other infectious agents, we applied the PAF values from a previous estimation [25] due to a lack of prevalence or RR data for Japanese.

For physical inactivity and salt intake, we derived the risk of cancer per unit increase in exposure and average RR for the whole population based on the average level of exposure, assuming a log-linear relationship between exposure and risk, by means of the following formula [10]:

$$\text{Risk} = [\ln(\text{risk per unit})\times\text{average exposure level}];$$

$$\text{PAF} = \frac{\text{Risk}-1}{\text{Risk}}.$$

To account for interactions among multiple risk factors, such as tobacco smoking and alcohol drinking, we used the following formula under the assumption of independent exposures and effect [26]:

$$PAF = 1 - \prod_{i=1}^{n} (1 - PAF_i),$$

where i refers to ith risk factor.

To account for uncertainty in the estimation of PAFs arising from RRs and the exposure prevalence of risk factors, the 95% CI of PAF was calculated using the variance of PAF based on a delta method, where P was the prevalence of exposure and β was defined as ln (RR):

$$\mathrm{Var}(PAF) = \frac{[Exp(\beta)-1]^2 \cdot Var(P) + [P.Exp(\beta)]^2 \cdot Var(\beta)}{\{P[Exp(\beta)-1]+1\}^4}$$

The variance of prevalence was considered null when the prevalence data were based on the whole population. When PAF was derived directly from the literature, as with some infectious agents, estimation of 95% CI was carried out under the assumption of no variability for the PAF.

results

Overall, ~55% of cancer (53% for incidence and 57% for mortality, respectively) among men was attributable to preventable risk factors in Japan. The corresponding figure was lower among women, but preventable factors still accounted for nearly 30% of cancer (28% and 30%; Table 3; detailed results of cancer burden by risk factor are shown in supplemental Appendix Tables A1–A8, available at *Annals of Oncology* online).

The estimated PAFs for each risk factor are summarized in Table 3. Tobacco smoking and infectious agents are the major risk factors for cancer in Japan, followed by alcohol drinking. Other risk factors such as salt intake, excess body mass index (BMI), vegetable intake and fruit intake, physical inactivity, and female exogenous hormone use accounted for a small share (<2%) of both cancer incidence and mortality. A substantial difference is seen in the pattern of cancer attributable to preventable risk factors by sex, primarily due to differences in the past cumulative exposure to tobacco smoking. In men, tobacco smoking, including both active and passive smoking, had the highest PAF (30% and 35% for incidence and mortality, respectively), followed by infectious agents (23% and 23%). Among women, in contrast, infectious agents had the highest PAF (18% and 19% for incidence and mortality, respectively), followed by tobacco smoking, including active and passive (6% and 8%).

Summary results for individual cancers are shown in Table 4. In both sexes, infections and tobacco smoking remained the major causes of site-specific cancer, i.e. oral cavity and pharynx, stomach, and liver in men and nasopharynx, liver, and cervix uteri in women due to both tobacco smoking and infection; esophagus, larynx, and urinary tract in men due to tobacco smoking; and anus in men and women due to infection. For other cancers, on the other hand, such as pancreas and leukemia; male prostate; and female colorectum, breast, corpus uteri, ovary, and urinary tract, no strong associations with the currently known preventable risk factors were seen.

discussion

This is the first study in Japan to systematically analyze the current burden of cancer attributable to multiple known preventable risk factors. Our study suggests that ~45% of cancer incidence and mortality in Japan in 2005 was potentially preventable.

The major advantage of the present study was the use of best available evidence from the Japanese population, particularly given that exposure–disease relationships can vary substantially between populations even after adjustment for potential confounders. A well-known example of this is the difference in tobacco smoking and BMI between Western and Asian populations [27, 28]. RRs of cancer incidence and mortality used in the present study were derived primarily from pooled analyses or large-scale cohort studies of Japanese, which enabled a more appropriate and realistic estimation than studies that extrapolate RRs from other populations.

Our results confirmed that tobacco smoking and infectious agents are currently the major causes of cancer in Japan.

The prevalence of current smokers among Japanese men has constantly decreased, from 53% in 1990 to 39% in 2005. The higher prevalence of ever smokers in 1990 (73%) than recently led to the large attribution of tobacco smoking in Japanese men. In women, in contrast, the prevalence of current smoking has been stable since 1990 (10%–11%) despite an increasing trend in younger age groups (aged 20–40 years: 11% in 1990 and 18% in 2005) [2]. We anticipate that the burden of cancer attributable to tobacco smoking will decrease in men but not in women in the next few decades due to the 20- to 30-year time lag between tobacco exposure and diagnosis.

Previous studies have consistently shown that the RR of tobacco smoking on cancer is lower in the Japanese as well as other East Asian populations than in Western populations [29]. There are several potential reasons for this. First, the uptake of smoking began later in the Japanese than in Western populations and the shortage of cigarettes during and shortly after World War II meant that consumption in this period at least was lower [27]. Secondly, Japanese nonsmokers have a higher incidence of cancers due to environmental tobacco smoke [30] and other indoor air pollutants [31]. Thirdly, susceptibility to tobacco smoke appears to have a genetic component; and finally, other lifestyle or environmental factors commonly found in the Japanese population appear to have a protective effect [27].

Another important finding from our study is its confirmation of the notion that infectious agents are a major cause of cancer in the East Asian region [16]. Its advanced socioeconomic status and high degree of hygiene and sanitation notwithstanding, Japan is not an exception: *H. pylori* and HCV are major infectious causes that account for a relatively large share of preventable cancers. In contrast, the contribution of infectious agents has recently been reported as <5% in Western populations [6, 9, 10]. The prevalence of these infectious agents shows a strong cohort effect, namely a huge variation by birth cohort, and has been declining rapidly among younger birth cohorts.

The majority of gastric cancer in Japan is derived from the noncardia stomach (91% in men and 94% in women in 2000) [32], and the prevalence of *H. pylori* is >80% in the birth cohort born before 1950 and 40%–50% in those born after 1950 [33, 34]. Because of this cohort effect, gastric cancer is expected to decline rapidly in a next few decades after the reduction of *H. pylori* infection in Japan. Hepatocellular carcinoma, which accounts for 90% of all liver cancer cases, is primarily caused by

Table 3. Number and PAF (%) of cancer incidence and mortality attributable to selected risk factors in Japan in 2005

Risk factor	Definition of exposure category	Incidence		Mortality	
		PAF (%) (95% CI)	Number	PAF (%) (95% CI)	Number
Men					
Total number			379 436		196 603
Tobacco smoking	Ever smoking	29.7 (29.6–29.8)	112 622	34.4 (34.3–34.5)	67 697
Passive smoking	Passive smoking	0.2 (0.2–0.2)	913	0.4 (0.4–0.4)	708
Infection	Positive (*Helicobacter pylori*, HCV, HBV, HPV, EBV, HTLV-I)	22.8 (22.8–22.8)	86 529	23.2 (23.2–23.2)	45 619
Alcohol drinking	Alcohol intake	9.0 (9.0–9.0)	34 151	8.6 (8.6–8.6)	16 905
Salt intake	>6 g/day	1.9 (1.8–1.9)	7137	1.5 (1.4–1.5)	2908
Body mass index	≥25 (overweight and obesity)	0.8 (0.7–0.8)	2848	0.5 (0.5–0.5)	1046
Fruit intake	Lowest intake group	0.7 (0.7–0.7)	2621	0.7 (0.7–0.8)	1441
Vegetable intake	Lowest intake group	0.7 (0.7–0.7)	2549	0.7 (0.7–0.7)	1395
Physical inactivity	Without three METs/day exercise	0.3 (0.3–0.3)	1169	0.2 (0.2–0.2)	423
All above risk factors (adjusted for overlaps)		53.3 (53.2–53.4)	202 257	56.9 (56.8–57.0)	111 901
Women					
Total number			267 366		129 338
Tobacco smoking	Ever smoking	5.0 (4.9–5.0)	13 276	6.2 (6.1–6.2)	8002
Passive smoking	Passive smoking	1.2 (1.2–1.2)	3238	1.6 (1.6–1.7)	2133
Infection	Positive (*H. pylori*, HCV, HBV, HPV, EBV, HTLV-I)	17.5 (17.5–17.6)	46 869	19.4 (19.3–19.4)	25 040
Alcohol drinking	Alcohol intake	2.5 (2.5–2.6)	6769	2.5 (2.4–2.5)	3176
Salt intake	>6 g/day	1.2 (1.2–1.3)	3300	1.2 (1.2–1.2)	1574
Body mass index	≥25 (overweight and obesity)	1.6 (1.5–1.6)	4167	1.1 (1.1–1.1)	1431
Fruit intake	Lowest intake group	0.8 (0.8–0.8)	2162	0.8 (0.8–0.9)	1079
Vegetable intake	Lowest intake group	0.4 (0.4–0.4)	1082	0.4 (0.4–0.5)	562
Physical inactivity	Without three METs/day exercise	0.6 (0.5–0.6)	1462	0.4 (0.4–0.4)	521
Exogenous hormone use	Current use	0.4 (0.4–0.4)	999	0.2 (0.2–0.2)	241
All above risk factors (adjusted for overlaps)		27.8 (27.6–27.9)	74 234	29.9 (29.8–30.1)	38 736
Both sexes					
Total number			646 802		325 941
Tobacco smoking	Ever smoking	19.5 (19.4–19.5)	125 898	23.2 (23.2–23.3)	75 699
Passive smoking	Passive smoking	0.6 (0.6–0.7)	4152	0.9 (0.9–0.9)	2842
Infection	Positive (*H. pylori*, HCV, HBV, HPV, EBV, HTLV-I)	20.6 (19.7–21.5)	133 398	21.7 (20.4–22.9)	70 660
Alcohol drinking	Alcohol intake	6.3 (6.3–6.4)	40 920	6.2 (6.1–6.2)	20 081
Salt intake	>6 g/day	1.6 (1.6–1.6)	10 437	1.4 (1.3–1.4)	4483
Body mass index	≥25 (overweight and obesity)	1.1 (1.1–1.1)	7014	0.8 (0.7–0.8)	2476
Fruit intake	Lowest intake group	0.7 (0.7–0.8)	4783	0.8 (0.8–0.8)	2520
Vegetable intake	Lowest intake group	0.6 (0.5–0.6)	3631	0.6 (0.6–0.6)	1957
Physical inactivity	Without three METs/day exercise	0.4 (0.4–0.4)	2631	0.3 (0.3–0.3)	945
Exogenous hormone use	Current use	0.2 (0.2–0.2)	999	0.1 (0.1–0.1)	241
All above risk factors (adjusted for overlaps)		42.7 (42.6–42.9)	276 491	46.2 (46.1–46.3)	150 637

PAF, population attributable fraction; CI, confidence interval; HCV, hepatitis C virus; HBV, hepatitis B virus; EBV, Epstein–Barr virus; HPV, human papillomavirus; HTLV-I, human T-cell leukemia type I; MET, metabolic equivalents.

chronic HCV infection in Japan. The peak incidence between the 1970s and the 1990s in Japanese men was affected by the birth cohort effect among those born during 1931–1935, which was attributed to HCV outbreaks in Japan [35]. This spread was ended by the early 1990s by the control of parenteral HCV transmission and interferon therapy for patients with chronic HCV infection, followed by a community-based anti-HCV screening system started in 2002. Japanese liver cancer incidence is therefore likely to decline further in the next decade [35].

Other important infections in Japan include human T-cell leukemia type I (HTLV-I), which is the main cause of adult T-cell leukemia (ATL). However, the attribution of this agent to total cancer burden is small due to the low prevalence of HTLV-I and small proportion of carriers (6% and 2% among men and women, respectively) who develop ATL [36].

Table 4. PAF (%) of incidence and mortality attributable to known risk factors by site of cancer in Japan in 2005

Site	ICD-10	Men	Women	Both sexes	
		Incidence/mortality, PAF (%) (95% CI)	Incidence/mortality, PAF (%) (95% CI)	Incidence, PAF (%) (95% CI)	Mortality, PAF (%) (95% CI)
Oral cavity	C00–C09	72.8 (72.5–73.1)	30.3 (30.0–30.7)	54.9 (54.6–55.3)	56.1 (55.8–56.4)
Oropharynx	C10	75.3 (75.0–75.6)	36.8 (36.5–37.1)	71.2 (70.9–71.5)	70.5 (70.2–70.9)
Nasopharynx	C11	97.2 (97.2–97.2)	92.8 (92.8–92.9)	95.9 (95.7–95.9)	96.3 (96.3–96.3)
Hypopharynx, etc.	C12–C14	71.9 (71.6–72.3)	28.2 (27.8–28.5)	64.9 (64.5–65.2)	66.9 (66.5–67.2)
Esophagus	C15	84.8 (84.7–85.0)	51.6 (51.2–52.0)	79.7 (79.5–80.0)	79.7 (79.5–79.9)
Stomach	C16	82.5 (82.3–82.6)	72.0 (71.7–72.2)	79.1 (79.0–79.3)	78.8 (78.6–79.0)
Colon	C18	51.0 (50.8–51.1)	12.8 (12.6–13.0)	33.6 (33.4–33.8)	31.7 (31.5–31.9)
Rectum	C19–C20	46.6 (46.5–46.7)	6.5 (6.4–6.6)	31.5 (31.3–31.6)	31.9 (31.8–32.1)
Anus	C21	90.0 (90.0–90.0)	90.0 (90.0–90.0)	90.0 (90.0–90.0)	89.9 (89.9–89.9)
Liver	C22	92.2 (92.1–92.3)	91.8 (91.6–92.0)	92.1 (91.9–92.2)	92.1 (91.9–92.2)
Pancreas	C25	23.9 (23.7–24.1)	11.6 (11.5–11.8)	18.1 (18.0–18.3)	18.2 (18.0–18.4)
Larynx	C32	71.9 (71.5–72.2)	30.1 (29.7–30.5)	69.7 (69.3–70.1)	68.6 (68.3–69.1)
Lung	C33–C34	69.1 (69.0–69.2)	36.5 (36.3–36.8)	59.2 (59.0–59.3)	60.2 (60.1–60.4)
Breast	C50		10.5 (10.4–10.7)/11.0 (10.8–11.1)	10.5 (10.4–10.7)	11.0 (10.8–11.1)
Vulva	C51		40.0 (40.0–40.0)	40.1 (40.1–40.1)	39.8 (39.8–39.8)
Vagina	C52		40.0 (40.0–40.0)	39.8 (39.8–39.8)	40.2 (40.2–40.2)
Cervix uteri	C53		100 (100.0–100.0)	100 (100.0–100.0)	100 (100.0–100.0)
Corpus uteri	C54		15.5 (15.2–15.8)	15.5 (15.2–15.8)	15.5 (15.2–15.8)
Ovary	C56		0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)
Penis	C60	40.0 (40.0–40.0)		39.9 (39.9–39.9)	39.8 (39.8–39.8)
Prostate	C61	0.0 (0.0–0.0)		0.0 (0.0–0.0)	0.0 (0.0–0.0)
Kidney	C64	37.4 (37.0–37.8)	12.0 (11.7–12.2)	29.4 (29.0–29.7)	29.2 (28.9–29.6)
Renal pelvis	C65–C66, C68	70.7 (70.5–70.9)	3.6 (3.4–3.7)	45.5 (45.3–45.7)	45.0 (44.8–45.2)
Bladder	C67	70.7 (70.5–70.9)	3.6 (3.4–3.7)	54.9 (54.8–55.1)	49.6 (49.5–49.8)
Hodgkin disease	C81	48.0 (48.0–48.0)	48.0 (48.0–48.0)	48.0 (48.0–48.0)	48.5 (48.5–48.5)
NHL	C82–C85, C96	4.0 (4.0–4.0)	3.8 (3.9–3.9)	3.9 (3.9–4.0)	3.8 (3.8–3.8)
Leukemia	C91–C95	29.2 (29.0–29.4)/32.0 (31.8–32.2)	14.7 (14.7–14.7)	23.0 (22.9–23.1)	25.0 (20.8–25.1)

PAF, population attributable fraction; CI, confidence interval; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th Revision; NHL, non-Hodgkin lymphoma.

Alcohol consumption in Japan and the proportion of heavy drinkers increased for decades until 1990 and have now peaked [2]. Our estimates of the PAF of alcohol drinking should be interpreted with caution because Japanese have a high prevalence of an aldehyde dehydrogenase 2-deficient phenotype, a deficiency that results in greater exposure to acetaldehyde, which is a known carcinogen in alcohol. This genetic difference may be one reason for the stronger RR in Japanese than Western populations [37]. In addition, the nonexposure referent group in many Japanese studies includes lifetime abstainers who are genetically unable to metabolize acetaldehyde, as well as past drinkers who quit drinking due to symptoms caused by alcohol drinking, which may have resulted in the underestimation of RR.

Other risk factors tended to contribute only a relatively small portion of the overall burden. For example, the prevalence of overweight and obesity (BMI ≥25) in Japan has gradually increased in men (22% in 1990 and 29% in 2005) but has been stable in women at ~21%–22% for decades according to the National Nutrition Survey [38]. In addition, the prevalence of obesity (BMI ≥30) has been ~3% in both sexes. As long as the Japanese maintain current BMI levels, the overall cancer burden derived from excess BMI may be small. Rather, the prevalence of underweight (BMI <18.5) in Japan has been greater (5% in men and 10% in women) than that of obesity. Given that many previous studies in Japanese and Asian populations have associated low BMI with an increased risk of cancer [28, 39], PAF for low BMI may warrant further investigation.

Physical inactivity, high salt intake, low vegetable and fruit intake, and female exogenous hormone use are associated with an increased risk of some cancers, but the contribution from these exposures based on our definition of exposed category was modest, due to the low prevalence of exposed category and/or an insufficient or inadequate definition of exposure level. It is notable that the intake of highly salt-concentrated preserved foods rather than salt intake as a whole salt equivalent is suggested to increase the risk of cancer [40], and estimation by the latter instead of the former may underestimate the real PAF. In addition, the prevalence of exogenous hormone use in Japan was and remains significantly low compared with Western populations, which may have led to its small contribution. More accurate estimates of the impact of these factors in Japanese will require a better scientific understanding of the association and more reliable data for Japanese.

Several limitations of these estimates warrant mention. Due to a lack of reliable prevalence data in Japan, we did not include

risk factors such as occupational, air pollution, or ultraviolet or radiation exposures. From previous estimates from Western populations [41], the PAF of occupational exposure may be expected to be ~5% in men, which is not negligible, while the PAF of other factors may not be substantial. Regarding infectious agents, we substituted our estimates with the PAF obtained in a previous estimate [25] due to a lack of prevalence and RR data in Japan, such as for human papillomavirus and Epstein–Barr virus, or excluded them from the present estimate due to the very small number of cases in this population. In addition, the RR estimates and prevalence data were extracted independently. Combining biases by using data from multiple sources would increase the bias of PAF estimation. More generally, most cancers have a multifactorial etiology, and a logically multivariate approach is more realistic. Due to an absence of information on most interactions and the joint prevalence of multiple exposures, we took account of the overlap of risk factors. Nevertheless, the results should be interpreted with caution due to uncertainties over the interactions among risk factors of cancer [8, 11, 42]. Since we used the best estimate of RR and prevalence currently available for Japanese, measured with the most suitable methodology, we believe that our estimates of PAFs are the best that can be currently calculated for Japanese. Nevertheless, many PAFs in the present analysis were based on RRs derived from a single study, not from pooled or meta-analyses, and estimates based on them will require updating when more appropriate evidence become available. At the same time, the cause of more than half of Japanese cancers remains unexplained. Solving this issue will require more research targeted at cancer etiology.

Allowing for these methodological issues, this first comprehensive assessment of cancer burden attributable to multiple risk factors in Japan showed that ~55% of cancer in men, 30% of cancer in women, and 45% of cancer in both sexes was attributable to known risk factors. Our estimate also confirmed that tobacco smoking and infectious agents are currently the main causes of cancer in Japan. These estimates have major implications for national health policy for cancer prevention and control strategies in Japan, namely that public health targeting aimed at substantial reductions in current Japanese cancer incidence and mortality should more strongly focus on the control of tobacco smoking and reduction of chronic infections such as *H. pylori* and HCV.

acknowledgements

Contributors—MIn and ST developed the study concept. MIn, NS, MIw, SS, and TS undertook reviews of published studies. TM and KS prepared statistical data for analysis. MIn and NS analyzed the data and prepared the results. MIn wrote the draft of the report. NS, TM, MIw, SS, TS, KS, and ST critically revised the manuscript. All authors have seen and approved the final version.

funding

Health and Labour Sciences Research Grants for the Third Term Comprehensive Control Research for Cancer (H22-3jigan-ippan-014, H21-3jigan-ippan-013, H22-3jigan-ippan-003); Research on Policy Planning and Evaluation from the Ministry of Health, Labour and Welfare (H22-seisaku-shitei-033); a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture of Japan [Scientific Research (B) No. 22390130].

disclosure

The authors declare no conflicts of interest.

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