Glandular stomach adenocarcinomas induced by NIAN treatment plus *H. pylori* infection were located in the pyloric region, similar to MNNG or MNU treatment plus *H. pylori* infection-induced glandular stomach adenocarcinomas in MGs.[26,27] Meanwhile, no glandular stomach cancers were observed in the groups of *H. pylori*-infected MGs without NIAN treatment, which is consistent with previous studies,[26,27] nor in the group treated with only NIAN. These findings indicated that *H. pylori* is a strong promoter of gastric carcinogenesis. Histological examination revealed that the tumors developed by NIAN + *H. pylori* were of well or moderately differentiated adenocarcinomas. Well or poorly differentiated adenocarcinomas and signet ring cell carcinomas were observed in *H. pylori*-infected MGs treated with MNNG or MNU.[26,27] Further studies are required to clarify the histological variety of stomach adenocarcinomas induced by NIAN, MNNG or MNU, since the type of cancer might depend on the genotoxic action of chemical carcinogens, rather than the effects of *H. pylori* infection.[27] In addition, tumors were observed in skin and kidney, which were suspected to spontaneously develop. The MGs have been reported to develop spontaneous skin tumors such as sebaceous and squamous cell carcinoma.[34]

Epidemiological studies have indicated that nitrate intake increases gastric cancer risk, and major sources are vegetables including Chinese cabbage, spinach and parsley.[14] Indole-3-acetonitrile, a precursor of NIAN, is distributed widely in cruciferous vegetables including Chinese cabbage and sprouts.[35] Furthermore, fava beans (*Vicia faba*), which are commonly consumed in Colombia, give rise to a potent mutagen in the presence of nitrite under acidic conditions.[36] The nitrosatable precursor of the mutagen in fava beans and the major product of nitrosation are reported to be an indole compound, 4-chloro-6-methoxyindole and an *N*-nitroso compound, 4-chloro-2-hydroxy-N^1-nitroso-indolin-3-one oxime, respectively.[37] Other indole compounds are also reported to produce direct-acting mutagens after nitrite treatment under acidic conditions.[38,39] In general, conversion of indole derivatives to nitrosated forms *in vitro* is known to be rapid and efficient at physiologically feasible nitrite concentrations with the low pH of the human stomach.[37] Thus, it is conceivable that nitrosation of indole compounds such as indole-3-acetonitrile probably occurs in human stomach. On the other hand, nitric oxide is suggested to be produced by activated macrophages in inflamed organs with *H. pylori* infection.[18] Therefore, nitrosation of indole compounds could be mediated by both acid catalysis and inflammatory responses in the human stomach.[18,20,37–40] On the basis of the conversion rate of NIAN from indole-3-acetonitrile under physiological conditions, the dose of NIAN used in the present study appears about 500–1000 fold the expected human exposure to NIAN *via* fresh or pickled Chinese cabbage. However, humans continually consume various kinds of foods containing indole compounds and nitrate during ordinary life. Thus, it is probable that the total amount of nitroso-indole compounds would be much closer to the dose of NIAN used in the present study. Moreover, it has been reported that low doses of chemical carcinogens, such as MNNG and MNU, could induce glandular stomach cancers in rodents under inflammation conditions including NaCl treatment and *H. pylori* infection, but hardly induce glandular stomach cancer without NaCl treatment and *H. pylori* infection. Therefore, the continuous intake of indole compounds and nitrate may play an important role for gastric carcinogenesis in East Asian countries still with a high salt consumption and *H. pylori* infection rate.

Gastric cancer is tending to decline in most countries.[41–43] One of the explanations for this tendency is the reduced prevalence of *H. pylori* infection.[42] Changes in dietary habits, mainly being lower salt consumption, could be also related to reduced gastric cancer incidence. However, the gastric cancer prevalence in East Asian countries, such as Japan and Korea, is still high.[2] At present, we have not succeeded in detecting NIAN in human bodies nor the exposure levels of the precursor, indole compounds for humans. Thus, it is necessary to estimate the human exposure levels to nitroso-indole compounds including NIAN, and to study further animal experiments and epidemiological analyses for clarification of contribution of nitroso-indole compounds under *H. pylori* infection in humans gastric carcinogenesis.

In conclusion, the present study demonstrated that NIAN can induce gastric cancer in *H. pylori*-infected MGs. It is noteworthy that nitrosatable precursors widely exist in foods. Thus, it is suggested that *N*-nitroso indole compounds including NIAN might contribute to the frequent development of gastric cancer in East Asian countries such as Japan and Korea in which the prevalence of *H. pylori* infection is relatively high. Further studies of interaction with other dietary elements appear warranted to promote the prevention of human gastric cancer.

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Adult Mortality Attributable to Preventable Risk Factors for Non-Communicable Diseases and Injuries in Japan: A Comparative Risk Assessment

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Abstract

Background: The population of Japan has achieved the longest life expectancy in the world. To further improve population health, consistent and comparative evidence on mortality attributable to preventable risk factors is necessary for setting priorities for health policies and programs. Although several past studies have quantified the impact of individual risk factors in Japan, to our knowledge no study has assessed and compared the effects of multiple modifiable risk factors for non-communicable diseases and injuries using a standard framework. We estimated the effects of 16 risk factors on cause-specific deaths and life expectancy in Japan.

Methods and Findings: We obtained data on risk factor exposures from the National Health and Nutrition Survey and epidemiological studies, data on the number of cause-specific deaths from vital records adjusted for ill-defined codes, and data on relative risks from epidemiological studies and meta-analyses. We applied a comparative risk assessment framework to estimate effects of excess risks on deaths and life expectancy at age 40 y. In 2007, tobacco smoking and high blood pressure accounted for 129,000 deaths (95% CI: 115,000–154,000) and 104,000 deaths (95% CI: 86,000–119,000), respectively, followed by physical inactivity (52,000 deaths, 95% CI: 47,000–58,000), high blood glucose (34,000 deaths, 95% CI: 26,000–43,000), high dietary salt intake (34,000 deaths, 95% CI: 27,000–39,000), and alcohol use (31,000 deaths, 95% CI: 28,000–35,000). In recent decades, cancer mortality attributable to tobacco smoking has increased in the elderly, while stroke mortality attributable to high blood pressure has declined. Life expectancy at age 40 y in 2007 would have been extended by 1.4 y for both sexes (men, 95% CI: 1.3–1.6; women, 95% CI: 1.2–1.7) if exposures to multiple cardiovascular risk factors had been reduced to their optimal levels as determined by a theoretical-minimum-risk exposure distribution.

Conclusions: Tobacco smoking and high blood pressure are the two major risk factors for adult mortality from non-communicable diseases and injuries in Japan. There is a large potential population health gain if multiple risk factors are jointly controlled.

Please see later in the article for the Editors' Summary.

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Abbreviations: CI, confidence interval; HTLV-1, human T-lymphotropic virus type 1; LDL, low density lipoprotein; NHNS, National Health and Nutrition Survey

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Introduction

Controlling risk factors for non-communicable diseases and external causes is essential for the improvement of adult health. Chronic diseases and injuries are the leading causes of global mortality, accounting for 63% and 9%, respectively, of 57 million deaths in 2008 [1]. The five major risk factors for deaths in the world are high blood pressure, tobacco use, high blood glucose, physical inactivity, and overweight and obesity, which contribute to non-communicable diseases and are modifiable with effective interventions [2]. In such an environment, informed decision-making on priority setting for health policies and programs needs consistent and comparative evidence about how many deaths would be averted by changing profiles of preventable risk factors in a population.

The population of Japan has the longest life expectancy at birth in the world. Life expectancy at birth for Japanese women was 54.0 y in 1947 and rapidly increased until 1986, at which point, at 81.0 y, it became the longest in the world for the first time; female life expectancy at birth also reached its highest ever worldwide figure, 86.4 y, in Japan in 2009 [3]. The continuous extension of longevity was largely explained by a decline in the rate of mortality for communicable diseases among children and young adults during the 1950s and the early 1960s and for stroke since the late 1960s [4]. Current leading causes of death are malignant neoplasm, heart disease, and cerebrovascular disease, accounting for more than 50% of total deaths in 2009 [5]. Accidental injuries and suicide have also ranked in the top ten causes of death for the past 50 y [5], and particularly suicide in the working population is a serious social problem reflecting the prolonged economic recession since the 1990s [4]. To further enhance the health status of the Japanese population, it is therefore crucial to prevent deaths from these major causes.

With the aim of increasing the nation's health through the prevention of premature deaths from lifestyle-related diseases, the Japanese government initiated a 10-y national health promotion campaign called Health Japan 21 in 2000 [6]. In this campaign, 59 indicators were established to monitor and improve the management of risk factors and diseases such as diet, smoking, and diabetes. However, the performance of Health Japan 21 was not necessarily satisfactory: there was progress on 60% of the 59 indicators, including decreasing daily salt intake, while deterioration or no improvement was observed for the remaining 40%, for example, the prevalence of overweight and obesity decreased in women aged 40–60 y but increased in men aged 20–60 y [7]. Success of national health promotion campaigns may partly depend on whether the stewardship of central and local governments exists for coordinating diverse activities and investing resources in priority areas with reference to scientific evidence on the disease burden attributable to modifiable risk factors. Although a number of past studies have quantified population-attributable fractions or impacts on life expectancy for individual risk factors in Japan [8–16], no study to our knowledge has used a single comprehensive framework to assess and compare these impacts across multiple risk factors.

In the present study, we therefore aimed to provide the most comprehensive and comparative assessment of preventable risk factors for mortality from non-communicable diseases and injuries in the Japanese adult population. We employed a comparative risk assessment strategy to quantify contributions of health risks to disease outcomes [17,18]. This standard systematic approach has already been applied to examine the burden of disease and injury across major risk factors in a few other countries [19–22]. Using national data sources on risk exposures and cause-specific mortality, as well as epidemiologic evidence on their causal association from large-scale prospective studies and meta-analyses in Japan, this analysis identifies the most important risk factors for deaths and life expectancy at the population level; the results could inform policymakers of which risk factors need to be prioritized in formulating and revising health policies and programs.

Methods

We estimated the number of deaths that would have been saved in 2007 if multiple risk factors had been controlled at their optimal levels as determined by a theoretical-minimum-risk exposure distribution. To quantify and compare the mortality attributable to excess health risks, we used comparative risk assessment methods that have been described in detail elsewhere [18,20]. To summarize, we first calculated the population-attributable fraction of cause-specific mortality for each risk factor, which measures a proportional reduction in mortality that would be achieved if risk factor exposures of a population shifted to an alternative counterfactual distribution that is more favorable. We used the following formula to calculate population-attributable fractions for continuous exposure variables:

$$\text{Population} - \text{attributable fraction} = \frac{\int_x RR(x)P(x)dx - \int_x RR(x)P'(x)dx}{\int_x RR(x)P(x)dx}, \quad (1)$$

where $P(x)$ and $P'(x)$ are actual and counterfactual distributions of exposure in the population, respectively, and $RR(x)$ is the relative risk of mortality at exposure level x. The first and second terms in the numerator of this equation represent the total risk of mortality weighted by exposures in the population under current and counterfactual distributions, respectively. This approach allowed us to compute effects of all nonoptimal exposures of individuals for all risk factors in a consistent and comparable way [21]. For risks measured in multiple categories, we used the following generalized formula to calculate population-attributable fractions:

$$\text{Population} - \text{attributable fraction} = \frac{\sum_{i=1}^{n} P_i(RR_i - 1)}{\sum_{i=1}^{n} P_i(RR_i - 1) + 1}, \quad (2)$$

where i signifies the level of individual categories ($i = 1,\ldots, n$).

We then multiplied the number of cause-specific deaths by population-attributable fractions to estimate mortality from diseases (causes of death) associated with each risk factor. The number of deaths attributable to a single risk factor was summed across different causes to obtain the total number of deaths attributable to that risk factor. The number of deaths from a single cause, however, could not be added across risk factors, because they may be causally related and we did not account for such relationships in the estimation of population-attributable fractions of individual risk factors.

We conducted all analyses separately by sex, using Stata version 11 (StataCorp). We restricted analyses to individuals aged 30 y and over, because the number of deaths from non-communicable diseases is small for younger ages. However, we included those aged 20 to 29 y when estimating deaths from external causes attributable to alcohol use, because the burden was assumed to be substantial in this age group.

Mortality Data

We obtained data on the number of cause-specific deaths in 2007 from vital records [23]. We applied algorithms developed for the Global Burden of Disease 2010 Study to redistribute ill-defined codes (e.g., cardiac arrest, heart failure, and senility) on death certificates that were not supposed to be underlying causes of death [24,25]. This method enabled us to obtain valid, reliable, and comparable data on cause-specific mortality by ensuring consistency and resolving changes across revisions of the *International Statistical Classification of Diseases and Related Health Problems*.

Selection of Risk Factors and Diseases

We included 16 risk factors in this analysis (Table 1). In the selection of risk factors paired with their relevant diseases or injuries, we employed the criteria of a previous study: (i) an availability of evidence on causality or association from high-quality epidemiological studies, (ii) an existence of interventions to modify exposures, and (iii) an availability of data on risk exposures from nationally representative surveys or large population studies [20]. We also included infection by several agents—hepatitis B virus, hepatitis C virus, the bacterium *Helicobacter pylori*, human papillomavirus, and human T-lymphotropic virus type 1 (HTLV-1)—because they are important risk factors for cancer deaths in Japan [26,27].

Measures and Data Sources of Risk Factor Exposures

Table 2 lists measurements and data sources for the risk factor exposures used in this analysis, and Table 3 shows their basic statistics by sex and age group in 2007. With the exception of tobacco smoking, infections, and alcohol use related to deaths from traffic road accidents, we used individual records from the National Health and Nutrition Survey (NHNS) in 2007. NHNS was a survey based on a nationally representative probabilistic sample to provide data on the health and nutritional status of the Japanese population. This survey included an in-person interview on medication use and lifestyle-related risk factors, a physical examination by health care professionals, and self-administered questionnaires on diet and lifestyle [28].

We used self-reports to quantify exposures to physical inactivity and alcohol use, while we used measured data for other risk factors. In the physical examination for the 2007 NHNS, a blood test was intended to be conducted more than 4 h after a meal, although a number of blood samples were actually drawn less than 4 h after a meal. Because fasting plasma glucose was the unit for relative risk for high blood glucose adopted in the present study, we applied the following conversion equation proposed by the Committee of the Japan Diabetes Society [29,30] to predict equivalents of fasting plasma glucose from measurements of hemoglobin A1c:

Table 1. Risk factors and disease outcomes included in the study.

Risk Factor	Disease Outcomes
High blood glucose	IHD, stroke, diabetes mellitus
High LDL cholesterol	IHD, ischemic stroke
High blood pressure	IHD, stroke, hypertensive diseases, other cardiovascular diseases[a]
Overweight/obesity	IHD; ischemic stroke; hypertensive disease; postmenopausal breast, colon, corpus uteri, kidney, and pancreatic cancers; diabetes mellitus
Alcohol use	IHD; ischemic stroke; hemorrhagic stroke; hypertensive diseases; cardiac arrhythmias; cancers of breast, colorectal, esophagus, mouth, liver, larynx, pharynx, and selected other sites[b]; diabetes mellitus; liver cirrhosis; acute and chronic pancreatitis; road traffic injuries; falls; homicide and suicide; other injuries
Tobacco smoking	IHD; stroke; aortic aneurysms and dissection; diabetes mellitus; lung, esophagus, mouth, pharynx, stomach, liver, pancreas, cervix, bladder, kidney, and other urinary cancers; leukemia; chronic obstructive pulmonary disease; lower respiratory tract infections; asthma; tuberculosis
Physical inactivity	IHD, ischemic stroke, breast and colon cancers, diabetes mellitus
High dietary trans fatty acids	IHD
Low dietary polyunsaturated fatty acids	IHD
High dietary salt	IHD, stroke, hypertensive disease, other cardiovascular diseases[a], stomach cancer
Low intake of fruit and vegetables	IHD; ischemic stroke; colorectal, esophagus, lung, mouth, pharynx, and stomach cancers
Hepatitis B virus	Liver cancer
Hepatitis C virus	Liver cancer
H. pylori	Stomach cancer
Human papillomavirus	Cervix uteri cancer
HTLV-1	Adult T-cell lymphoma/leukemia

[a]This category includes rheumatic heart disease, endocarditis, cardiomyopathy, aortic aneurysms, peripheral vascular disorders, and other ill-defined cardiovascular diseases.
[b]This category includes *International Statistical Classification of Diseases and Related Health Problems, 10th edition* (ICD-10) codes D00–D24 (except D09.9), D26–D37 (except D37.9), and D38–D48 (except D38.6, D39.9, D40.9, D41.9, and D48.9).
IHD, ischemic heart disease.
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Table 2. Measurements, data sources, and alternative distributions of risk exposures.

Risk Factor, Exposure Metric, Data Source[a]	Optimal	Guidelines/National Goals
High blood glucose		
Fasting plasma glucose (mmol/l)	4.9 (0.3)	5.6 (0.3) [66]
High LDL cholesterol		
LDL cholesterol (mmol/l)	2.0 (0.4)	3.1 (0.7) [54]
High blood pressure		
Systolic blood pressure (mm Hg)	115 (6)	130 (7) [53]
Overweight/obesity		
Body mass index (kg/m^2)	21 (1)	22 (1) [67]
Alcohol use		
Current alcohol consumption volumes and patterns	No alcohol use[b]	
Alcohol-related road traffic accidents, national road accident data, 2004 [40]	No alcohol use	
Tobacco smoking		
Smoking impact ratio, vital statistics 2007 data [23–25], pooled cohort studies [15,35,36]	No smoking	
Physical inactivity		
Intensity of physical activity	Highly active	
High dietary trans fatty acids		
Percent of total calories from dietary trans fatty acids	0.5 (0.05)	
Low dietary polyunsaturated fatty acids		
Percent of total calories from dietary polyunsaturated fatty acids	10 (1)	
High dietary salt		
Dietary sodium adjusted for total calories (g/d)	0.5 (0.05)	10 (1) [7]
Low intake of fruit and vegetables		
Dietary fruit and vegetable intake adjusted for total calories (g/d)	600 (50)	350 (29) [7]
Hepatitis B virus		
Seropositivity for hepatitis B surface antigen, blood donors' cohort, 1991–1993 [37]	No infection	
Hepatitis C virus		
Seropositivity for antibody to hepatitis C, blood donors' cohort, 1991–1993 [37]	No infection	
H. pylori		
Seropositivity for anti-*H. pylori* immunoglobulin G, multi-center study, late 1990s [38]	No infection	

Values are means, with standard deviations in parentheses.
[a]We obtained exposure data from the 2007 National Health and Nutrition Survey [28] unless stated otherwise.
[b]The optimal category for liver cancer and suicide was "occasional drinkers" because previous studies used it as the reference category for estimation of relative risks.
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$$\text{Fasting plasma glucose (mg/dl)} = -9.2 + 21.9 \times \text{hemoglobin A1c}_{\text{JDS}}\ (\%) \quad (3)$$

where hemoglobin $A1c_{JDS}$ is a value standardized by calibrators provided by the Japan Diabetes Society and lower than an internationally used value by around 0.4% [29]. As a minor adjustment, we further deducted from this equation a difference in means between predicted fasting plasma glucose and measured casual plasma glucose among 165 participants in the 2007 NHNS who had fasted for more than 8 h (6.4 mg/dl).

In the NHNS, health care professionals measured the blood pressure of seated persons in their right upper arm after 5 min of rest, using a Riva-Rocci mercury manometer. For a trend analysis of cardiovascular mortality attributable to high blood pressure, which is described below, we used the National Nutrition Surveys for 1980–2002 and the NHNS for 2003–2007. These surveys took only one blood pressure measurement per individual until starting to collect two measurements per individual in the 2000 survey. We therefore used a single measurement for the surveys in 1980–1999 and the second measurement for the 2000–2007 surveys. We excluded pregnant or breastfeeding women from the analysis of blood pressure.

For dietary risk exposure variables, dieticians visited households to distribute questionnaires and explain the survey method for diet and lifestyle. Household representatives weighed and recorded the quantity of each food item consumed for one day (excluding holidays). Dieticians visited households again during the survey period to check and correct completed questionnaires. We estimated intakes of dietary trans fatty acids using conversion factors of food items provided by the Cabinet of Japan Food Safety Committee [31]. Considering that nutrition intakes are correlated with energy intake determined by body size, physical activity, and metabolic efficiency, we adjusted intakes of fruit, vegetables, and dietary sodium for total energy intake with a simple linear regression equation having nutrient intake as a dependent variable and total caloric intake as an independent variable [32]. Calorie-adjusted nutrient intakes were computed as the sum of residuals from the regression model and the expected nutrient intake for a person with mean caloric intake.

Table 3. Exposure to risk factors by sex and age group in 2007.

Sex, Risk Factor	Age														
	30–44 y			45–59 y			60–69 y			70–79 y			≥80 y		
	n[a]	Mean	SE	*n*[a]	Mean	SE	*n*[a]	Mean	SE	*n*[a]	Mean	SE	*n*[a]	Mean	SE
Men															
Fasting plasma glucose (mmol/l)	300	5.4	0.1	374	5.7	0.0	411	6.0	0.1	339	5.9	0.0	107	5.9	0.1
LDL cholesterol (mmol/l)	300	3.3	0.0	375	3.4	0.0	413	3.1	0.0	340	3.0	0.0	108	2.9	0.1
Systolic blood pressure (mm Hg)	312	124.2	0.8	394	133.9	0.9	427	140.9	0.9	359	142.2	1.0	116	144.1	1.8
Body mass index (kg/m^2)	673	23.9	0.1	777	23.8	0.1	620	23.8	0.1	470	23.6	0.2	155	22.6	0.3
Dietary TFA (% of total calories)	806	0.3	0.0	858	0.3	0.0	664	0.2	0.0	517	0.2	0.0	179	0.3	0.0
Dietary PUFA (% of total calories)	806	5.7	0.1	858	5.6	0.1	664	5.3	0.1	517	5.1	0.1	179	5.0	0.1
Dietary SFA (% of total calories)	806	6.8	0.1	858	6.2	0.1	664	5.7	0.1	517	5.6	0.1	179	5.9	0.2
Dietary salt intake (g/d)	806	11.4	0.2	858	12.3	0.2	664	12.6	0.2	517	12.2	0.2	179	10.9	0.3
Fruit and vegetable intake (g/d)	804	288.6	6.0	856	342.5	6.6	663	432.3	8.8	515	446.8	9.6	178	463.5	15.9
Never or former drinkers (%)[b]	850	26.6	1.5	950	25.9	1.4	699	28.9	1.7	525	40.8	2.1	184	55.4	3.7
Alcohol-related accidents/four-wheel vehicle road traffic accidents, 2004 (%) [40][c]		1.7			1.7			1.7			1.7			1.7	
Have intense physical activity (%)	808	34.8	1.7	869	34.5	1.6	667	28.8	1.8	518	42.1	2.2	179	21.8	3.1
Never or former smokers (%)	850	45.2	1.7	946	53.6	1.6	698	65.9	1.8	524	78.6	1.8	184	82.1	2.8
Smoking impact ratio		0.0			0.6			0.5			0.5			0.7	
Hepatitis B virus (%) [37]		0.9			0.9			0.9			0.6			0.6	
Hepatitis C virus (%) [37]		0.6			1.6			2.6			7.9			7.9	
H. pylori (%) [38]		23.6			47.4			66.1			73.4			72.6	
Women															
Fasting plasma glucose (mmol/l)	563	5.3	0.0	620	5.7	0.0	523	5.9	0.0	408	5.9	0.0	154	5.9	0.1
LDL cholesterol (mmol/l)	565	2.9	0.0	622	3.4	0.0	523	3.5	0.0	410	3.3	0.0	154	3.2	0.1
Systolic blood pressure (mm Hg)	527	112.4	0.6	652	128.1	0.8	560	135.8	0.8	433	138.9	0.8	170	143.2	1.4
Body mass index (kg/m^2)	874	21.4	0.1	905	22.7	0.1	723	23.3	0.1	534	23.1	0.2	248	22.4	0.3
Dietary TFA (% of total calories)	955	0.4	0.0	957	0.3	0.0	762	0.3	0.0	561	0.3	0.0	285	0.2	0.0
Dietary PUFA (% of total calories)	955	5.9	0.1	957	6.0	0.1	762	5.6	0.1	561	5.3	0.1	285	5.3	0.1
Dietary SFA (% of total calories)	955	7.8	0.1	957	7.0	0.1	762	6.2	0.1	561	5.9	0.1	285	5.7	0.2
Dietary salt intake (g/d)	955	9.6	0.1	957	10.7	0.1	762	10.9	0.2	561	10.6	0.2	285	10.0	0.2
Fruit and vegetable intake (g/d)	951	346.0	6.1	957	460.2	7.6	761	541.3	9.0	561	522.8	9.7	284	490.3	13.2
Never or former drinkers (%)[b]	1,014	54.9	1.6	1,047	61.1	1.5	795	75.5	1.5	579	83.4	1.5	310	88.7	1.8
Alcohol-related accidents/four-wheel vehicle road traffic accidents, 2004 (%) [40][c]		1.7			1.7			1.7			1.7			1.7	
Have intense physical activity (%)	958	36.3	1.6	959	40.9	1.6	765	39.0	1.8	562	45.4	2.1	286	21.3	2.4
Never or former smokers (%)	1,014	81.8	1.2	1,047	87.1	1.0	794	92.1	1.0	579	96.5	0.8	310	95.5	1.2
Smoking impact ratio		0.0			0.1			0.2			0.2			0.2	
Hepatitis B virus (%) [37]		0.5			0.5			0.5			0.6			0.6	
Hepatitis C virus (%) [37]		0.4			1.6			3.5			7.0			7.0	
H. pylori (%) [38]		23.6			47.4			66.1			73.4			72.6	

[a]Sample size in the National Health and Nutrition Survey in 2007.
[b]For those aged 20–29 y, the mean (standard error) was 40.4 (2.7) in men ($n = 324$) and 53.9 (2.5) in women ($n = 395$).
[c]Reported for the total age group of both sexes combined.
PUFA, polyunsaturated fatty acids; SE, standard error; SFA, saturated fatty acids; TFA, trans fatty acids.
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We used a smoking impact ratio as a more reliable indicator of accumulated exposure to tobacco smoking than the prevalence of current smokers. The smoking impact ratio was defined as total lung cancer mortality in excess of never-smokers in a study

population relative to the excess lung cancer mortality among current smokers in a reference population [33,34]. We used the following formula to calculate smoking impact ratios by age group and sex:

$$\text{Smoking impact ratio} = \frac{C_{LC} - N_{LC}}{S^*_{LC} - N^*_{LC}} \times \frac{N^*_{LC}}{N_{LC}}, \quad (4)$$

where C_{LC} and N_{LC} denote lung cancer mortality of the total population and never-smokers, respectively, in a study population (i.e., the Japanese population), and S^*_{LC} and N^*_{LC} signify lung cancer mortality among current smokers and never-smokers, respectively, in a reference population. We obtained total lung cancer mortality from the redistributed data of vital records described above. Our reference population was residents included in a pooled study of three large-scale cohorts in Japan [15,35,36]. Because we also adopted never-smokers' lung cancer mortality in the Japanese population from this pooled study, N_{LC} and N^*_{LC} were equivalent to each other in our analysis.

We obtained data on the prevalence of infections with hepatitis B and C viruses and the bacterium *H. pylori* from epidemiological studies undertaken in Japan in the 1990s [37,38]. Assuming that infection rates do not vary within birth cohorts over time, we applied infection rates by age group in the 1990s to those of corresponding age in 2007. For example, the infection rate for hepatitis B virus in men aged 60–69 y in 2007 was that of men aged 45–54 y in 1991–1993. We considered that all deaths from cervix uteri cancer and adult T-cell lymphoma/leukemia were caused by infections with human papillomavirus and HTLV-1, respectively [26,39].

In order to measure exposure levels of alcohol use related to deaths from road traffic injuries, we employed a proportion of alcohol-impaired driving, which was defined as driving with breath alcohol concentrations above 0 mg/l, to the total number of cases of road traffic accidents involving four-wheeled vehicles and motorcycles in 2004 (1.7%). We obtained this figure from a past study on alcohol concentrations in the breath of drivers, which used a national dataset prepared by the Japan Institute for Traffic Accident Research and Data Analysis [40].

Selection of Relative Risks

Tables S1, S2, S3, S4, S5, S6, S7 provide details of relative risks used in this analysis. We conducted a literature review of prospective studies evaluating effects of risk factors on cause-specific deaths in Japan. Strategies for the database search involved contacting authors of key reports and leading experts in the field, and we critically appraised the identified literature. Our motive for undertaking the literature search was to identify evidence from past studies in the Japanese population to be backed up with pooled evidence establishing causalities or associations from the Global Burden of Disease Study [20]. Criteria for the selection of evidence for the Japanese population were: (i) pooled or individual estimates from large-scale prospective observational studies and (ii) confirming causalities or associations that had been already established in past studies. When there was no study for the Japanese population satisfying these conditions, we sought evidence from the Asia-Pacific Cohort Studies Collaboration. If we could not find evidence from this source, then we adopted relative risks identified in the Global Burden of Disease Study. We considered relative risks to be null if they were statistically insignificant. In addition, we had to restrict the source of evidence on relative risks for tobacco smoking to the pooled analysis of large-scale cohorts in Japan, because we used their estimates of current smokers' and never-smokers' lung cancer mortality of a reference population to calculate smoking impact ratios. We excluded mortality from tuberculosis and diabetes mellitus associated with tobacco smoking, because the studies did not examine these causes.

Counterfactual Distributions of Risk Exposures

As an alternative distribution of risk exposures, we used an optimal distribution in which harmful effects of each risk factor on morbidity and mortality would be minimized in a population (i.e., a theoretical-minimum-risk exposure distribution). With the exception of infections, we obtained information on theoretical-minimum-risk exposure distributions from a previous study in the United States (Table 2) [20].

In the analysis of gains in life expectancy and probabilities of death, we also investigated alternative counterfactual distributions of risk exposures that followed recommendations of clinical guidelines and goals of Health Japan 21. This analysis enabled quantification of potential health gains that would be more realistic than theoretical minimums. We included risk factors in this part of our analysis only if specific control targets were available from these sources and units of measurement corresponded to those of relative risks (Table 2). In order to obtain counterfactual distributions for numerical risks, we used their control threshold as the mean and applied the coefficient of variation to estimate the standard deviation.

The relationship between dietary salt intake and cardiovascular mortality was based on a convincing effect of high dietary salt on systolic blood pressure that was estimated from a meta-analysis of dietary trials (Table S6) [20]. In order to obtain hazards of excess dietary salt intake on cardiovascular death, we first estimated the decrease in systolic blood pressure associated with a reduction in dietary salt intake to individual optimal levels and then applied relative risks of high systolic blood pressure for relevant cardiovascular diseases (Table S1).

Effects on Life Expectancy and Probabilities of Death

We translated mortality changes into gains in life expectancy at 40 y of age to understand the potential impact of the management of risk factors on longevity. We constructed life tables using observed age-specific mortality rates and mortality that would be expected if risk factor exposures were controlled at alternative levels. We took the differences between these values as showing life expectancy gains that would occur when shifting from an actual risk factor exposure to a counterfactual. We also calculated effects on probabilities of dying between the ages of 15 and 60 y ($_{45}q_{15}$) and between 60 and 75 y ($_{15}q_{60}$).

Joint Effects of Multiple Risk Factors for Cardiovascular Mortality

We estimated joint effects of multiple risk factors on excess mortality from cardiovascular diseases and the additional life expectancy at age 40 y that would be achieved under counterfactual distributions. Risk factors included in this part of the analysis were high body mass index, high blood pressure, and high concentrations of blood glucose and low density lipoprotein (LDL) cholesterol. We took account of high dietary sodium intake to compensate for its indirect effect through elevated blood pressure, using the steps described above. We also adopted a 50% reduction of the excess risk of high body mass index on cardiovascular deaths to incorporate a mediation of its associations through other risk factors [21]. We used an additive excess risk scale to correct for correlations of these risk factors and calculate joint relative risks at the individual level. This approach has been described in detail elsewhere [21]. We summed the combined relative risks for individual records to compute population-attributable fractions for the joint effects of these cardiovascular risks.

Long-Term Trends in Attributable Deaths

To examine contributions of the management of modifiable risk factors to the improvement of life expectancy over time, we estimated the number of deaths from cancers attributable to tobacco smoking and deaths from stroke associated with high blood pressure from 1980 to 2007. We employed the algorithm described above to obtain consistent mortality data throughout this period, from which we used total lung cancer mortality in each year to calculate smoking impact ratios over time. For the analysis of high blood pressure and stroke, we excluded people over 80 y of age because the sample size was insufficient. We also incorporated the above-mentioned mediated effects of dietary sodium intake through raised blood pressure at the individual level.

Uncertainty Analyses

We conducted statistical simulation to deal with the uncertainty that was introduced by using sample estimates for risk exposures and relative risks [41]. To account for sampling variability, we randomly drew 1,000 sets of values of all components based on samples. In each sequential step of the simulation, we drew for each age–sex group: (i) a random sample of participants in the 2007 NHNS with replacement to obtain the original sample size of those who had no missing value for each risk factor, (ii) a relative risk for each risk–disease pair from a log-normal distribution with means and standard deviations reported in epidemiological studies, (iii) coefficients of the regression of hemoglobin A1c on fasting plasma glucose from a normal distribution with standard deviations that we calculated from information given in a past study (1.0 for the constant term and 0.2 for the coefficient of hemoglobin A1c) [30], (iv) the difference in means between predicted fasting plasma glucose and measured casual plasma glucose in the 2007 NHNS from a normal distribution with mean of 6.4 mg/dl and standard deviation of 1.1 mg/dl that we estimated from the survey data, (v) the proportion of the excess risk of body mass index mediated through systolic blood pressure and fasting plasma glucose from a normal distribution with mean of 0.5 and standard deviation of 0.1 [21], and (vi) lung cancer mortality of current smokers and never-smokers from a normal distribution with means and standard deviations estimated from the pooled analysis of Japanese cohorts [15,35]. We used each sampled set of risk exposures and relative risks to compute population-attributable fractions, mortality attributable to each risk factor or a combination of risk factors, and changes in life expectancy under counterfactual distributions. We defined a 95% confidence interval (CI) by a span across the estimates of each outcome at the 2.5th and 97.5th percentiles of the 1,000 simulations.

Results

Contributions of Health Risks to Cause-Specific Mortality in 2007

Tables S8 and S9 provide population-attributable fractions of the 16 modifiable risk factors and a combination of physiological risk factors for mortality from non-communicable diseases and injuries by age group and sex in 2007. These fractions cannot to be summed across risk factors for a single cause of death, because causal relationships between risk factors are not considered in the analysis of individual risk factors.

Under the theoretically minimum counterfactuals listed in Table 2, tobacco smoking and high blood pressure were the two major single contributors to the number of deaths from non-communicable diseases and injuries (Table 4). Among the total of 960,000 deaths from causes included in this study, tobacco smoking was associated with 129,000 deaths (95% CI: 115,000–154,000). Approximately three-quarters of these deaths occurred in men (95,000 deaths, 95% CI: 88,000–103,000), although the attributable mortality was still substantial for women (34,000 deaths, 95% CI: 23,000–57,000). In men, 70% of deaths attributable to this risk factor were caused by cancers and took place among those aged 45–79 y. In women, cardiovascular diseases and cancers accounted for 42% and 36%, respectively, of the mortality attributable to tobacco smoking. By disease subtypes for sexes combined, lung cancer was the leading cause (42,000 deaths, 95% CI: 39,000–45,000), followed by ischemic heart disease (27,000 deaths, 95% CI: 19,000–42,000) and chronic obstructive pulmonary disease (13,000 deaths, 95% CI: 9,000–16,000).

High blood pressure was associated with 104,000 cardiovascular deaths (95% CI: 86,000–119,000) in 2007. This was the greatest risk factor for cardiovascular mortality of all risk factors included in this analysis, and the mortality burden was shared evenly between the sexes. A majority of deaths attributable to high blood pressure occurred among people aged 70 y and over (85,000 deaths) and were caused by stroke (47,000 deaths, 95% CI: 38,000–56,000) or ischemic heart disease (28,000 deaths, 95% CI: 15,000–39,000).

Although the numbers of attributable deaths for other physiological, lifestyle, dietary, and infectious factors were small when compared to those for tobacco smoking and high blood pressure, most of these other factors were associated with tens of thousands of deaths from non-communicable diseases and external causes. Physical inactivity was associated with 52,000 deaths (95% CI: 47,000–58,000), and 75% of them occurred among people aged 70 y and older. Ischemic heart disease was the major cause of mortality attributable to this risk factor (31,000 deaths, 95% CI: 28,000–35,000). High blood glucose was associated with 34,000 deaths (95% CI: 26,000–43,000), of which 75% occurred among people aged 70 y and over and 68% were caused by ischemic heart disease. High dietary salt intake was associated with 19,000 cardiovascular deaths (95% CI: 16,000–22,000), which were included in cardiovascular mortality attributable to high blood pressure, and there were 15,000 deaths from stomach cancer (95% CI: 9,000–20,000). Seventy-six percent of deaths attributable to this risk factor occurred among people aged 70 y and over.

Alcohol use was associated with 31,000 deaths (95% CI: 27,000–35,000) from non-communicable diseases and injuries, 84% of which occurred among men. A major cause of death attributable to this risk factor was liver cirrhosis (11,000 deaths, 95% CI: 10,000–12,000), followed by liver cancer (6,000 deaths, 95% CI: 4,000–8,000), esophagus cancer (5,000 deaths, 95% CI: 4,000–5,000), and colon cancer (4,000 deaths, 95% CI: 4,000–5,000). Alcohol use was associated with 3,000 (95% CI: 2,000–5,000) out of 83,000 deaths of people aged 20 y and over from external causes included in this study. Two thousand deaths were from suicide (95% CI: 1,000–4,000), and there were fewer than 1,000 deaths each attributable to falls, road traffic accidents, homicide, and other injuries. Most of the suicide deaths attributable to alcohol use occurred among men, particularly those aged 30 to 59 y (71%).

Infection with *H. pylori* was associated with 31,000 deaths from gastric cancer in 2007 (95% CI: 27,000–34,000). Seventy-two

Table 4. The number of deaths attributable to risk factors in Japan, 2007 (in thousands).

Sex, Risk Factor	Total		Cardiovascular		Cancer		Diabetes Mellitus		Respiratory		Other NCD		Injuries	
Sexes combined														
High blood glucose	34.1	(26.4, 43.1)	27.2	(19.5, 36.2)			6.9							
High LDL cholesterol	23.9	(16.7, 31.2)	23.9	(16.7, 31.2)										
High blood pressure	103.9	(86.0, 119.1)	103.9	(86.0, 119.1)										
High body mass index	19.0	(16.1, 21.9)	13.8	(11.1, 16.4)	4.1	(3.4, 4.9)	1.1	(0.8, 1.3)						
Alcohol use	30.6	(27.5, 34.7)	−2.0	(−4.0, 0.0)	18.2	(16.2, 20.8)	−0.1	(−0.1, −0.1)			11.6	(10.6, 12.7)	2.9	(1.9, 4.6)
Tobacco smoking	128.9	(115.5, 153.6)	33.4	(25.4, 48.8)	77.4	(72.3, 83.9)			18.1	(12.6, 26.4)				
Physical inactivity	52.2	(46.7, 57.7)	42.2	(36.6, 47.6)	9.3	(8.5, 10.0)	0.7	(0.6, 0.9)						
High TFA intake	0.0	(0.0, 0.0)	0.0	(0.0, 0.0)										
Low PUFA intake	21.2	(8.1, 38.7)	21.2	(8.1, 38.7)										
High dietary sodium intake	34.0	(27.3, 39.4)	19.0	(16.1, 22.3)	14.9	(8.8, 19.6)								
Low fruit and vegetable intake	8.9	(6.7, 10.8)	5.1	(3.3, 6.7)	3.8	(2.5, 4.9)								
Hepatitis B virus	11.6	(9.8, 13.5)			11.6	(9.8, 13.5)								
Hepatitis C virus	23.0	(21.3, 24.5)			23.0	(21.3, 24.5)								
H. pylori	30.6	(27.2, 33.5)			30.6	(27.2, 33.5)								
Human papillomavirus	2.6				2.6									
HTLV-1	1.1				1.1									
Joint risk[a]	157.0	(144.0, 173.4)	157.0	(144.0, 173.4)										
Men														
High blood glucose	17.2	(12.7, 22.2)	14.3	(9.8, 19.3)			2.9							
High LDL cholesterol	12.2	(8.1, 15.9)	12.2	(8.1, 15.9)										
High blood pressure	50.1	(39.9, 58.5)	50.1	(39.9, 58.5)										
High body mass index	12.1	(10.0, 14.3)	9.6	(7.6, 11.6)	2.0	(1.6, 2.6)	0.5	(0.4, 0.7)						
Alcohol use	25.8	(22.6, 29.5)	−1.7	(−3.7, 0.2)	15.9	(13.7, 18.2)	−0.1	(−0.1, −0.1)			9.0	(8.2, 9.7)	2.8	(1.7, 4.4)
Tobacco smoking	94.9	(87.7, 103.4)	19.3	(15.4, 24.5)	66.5	(61.8, 71.2)			9.1	(6.8, 10.9)				
Physical inactivity	25.9	(22.8, 29.4)	21.0	(18.1, 24.4)	4.6	(4.0, 5.1)	0.3	(0.3, 0.4)						
High TFA intake	0.0	(0.0, 0.0)	0.0	(0.0, 0.0)										
Low PUFA intake	12.0	(5.3, 29.3)	12.0	(5.3, 29.3)										
High dietary sodium intake	18.4	(13.0, 22.7)	8.8	(7.3, 10.2)	9.7	(4.4, 13.7)								
Low fruit and vegetable intake	7.6	(5.5, 9.5)	4.3	(2.5, 5.9)	3.3	(2.1, 4.4)								
Hepatitis B virus	8.0	(6.6, 9.6)			8.0	(6.6, 9.6)								
Hepatitis C virus	14.8	(13.4, 16.1)			14.8	(13.4, 16.1)								
H. pylori	20.0	(17.0, 22.4)			20.0	(17.0, 22.4)								
HTLV-1	0.6				0.6									
Joint risk[a]	78.5	(70.8, 87.8)	78.5	(70.8, 87.8)										
Women														
High blood glucose	16.9	(11.6, 23.3)	12.9	(7.6, 19.3)			4.0							
High LDL cholesterol	11.7	(6.5, 18.0)	11.7	(6.5, 18.0)										
High blood pressure	53.9	(40.0, 66.9)	53.9	(40.0, 66.9)										
High body mass index	6.8	(5.0, 8.9)	4.2	(2.5, 5.9)	2.1	(1.6, 2.6)	0.5	(0.3, 0.8)						
Alcohol use	4.8	(3.8, 6.3)	−0.3	(−0.5, −0.1)	2.3	(1.7, 3.3)	−0.0	(−0.1, −0.0)			2.6	(2.1, 3.4)	0.2	(0.1, 0.3)
Tobacco smoking	34.0	(22.9, 56.5)	14.1	(7.3, 28.2)	10.9	(8.3, 15.7)			9.0	(4.0, 17.4)				
Physical inactivity	26.3	(21.6, 30.9)	21.2	(16.5, 25.9)	4.7	(4.2, 5.2)	0.4	(0.3, 0.5)						
High TFA intake	0.0	(0.0, 0.0)	0.0	(0.0, 0.0)										
Low PUFA intake	9.3	(4.0, 16.1)	9.3	(4.0, 16.1)										
High dietary sodium intake	15.6	(11.3, 19.2)	10.3	(7.7, 13.1)	5.3	(1.9, 7.5)								

Table 4. Cont.

Sex, Risk Factor	Total		Cardiovascular		Cancer		Diabetes Mellitus	Respiratory	Other NCD	Injuries
Low fruit and vegetable intake	1.3	(0.9, 1.7)	0.8	(0.4, 1.2)	0.5	(0.3, 0.6)				
Hepatitis B virus	3.6	(2.8, 4.5)			3.6	(2.8, 4.5)				
Hepatitis C virus	8.2	(7.3, 9.0)			8.2	(7.3, 9.0)				
H. pylori	10.6	(8.9, 12.0)			10.6	(8.9, 12.0)				
Human papillomavirus	2.6				2.6					
HTLV-1	0.5				0.5					
Joint risk[a]	78.5	(66.9, 91.1)	78.5	(66.9, 91.1)						

Values in parentheses indicate lower and upper bounds of 95% CI.

[a]A combination of high blood glucose, high LDL cholesterol, high blood pressure (directly, and indirectly through high dietary salt intake), and high body mass index.

NCD, non-communicable disease; PUFA, polyunsaturated fatty acids, TFA, trans fatty acids.

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percent of these deaths occurred among people aged 70 y and older. Infection with hepatitis C virus was associated with 23,000 deaths from liver cancer (95% CI: 21,000–24,000). Forty-five percent of these deaths were in people aged 70–79 y, including those born in the early 1930s. For both *H. pylori* and hepatitis C virus infections, around 65% of the attributable mortality took place in men.

High LDL cholesterol was associated with 24,000 cardiovascular deaths (95% CI: 17,000–31,000), largely from ischemic heart disease (23,000 deaths, 95% CI: 16,000–30,000). Low dietary intake of polyunsaturated fatty acids was associated with 21,000 deaths from ischemic heart disease (95% CI: 8,000–39,000), and 47% of these deaths occurred among people aged 80 y and over. High body mass index was associated with 19,000 deaths (95% CI: 16,000–22,000): 64% of these deaths occurred in men, and ischemic heart disease was the major cause (11,000 deaths, 95% CI: 8,000–13,000).

If systolic blood pressure (directly, and indirectly through dietary salt intake), blood glucose, LDL cholesterol, and body mass index were controlled jointly to their optimal distributions, i.e., theoretical-minimum-risk exposure distributions, 157,000 cardiovascular deaths would have been prevented in 2007 (95% CI: 144,000–173,000). The mortality burden attributable to the combination of these risks was shared equally between the sexes, and a majority of the burden occurred among people aged 70 y and older.

Effects of Risk Factors on Life Expectancy and Probabilities of Death

Japanese life expectancy at age 40 y was 40.4 y for men and 46.8 y for women in 2007 [3]. Figure 1 illustrates gains in life expectancy at age 40 y and percentage changes in probabilities of death that would have been expected in 2007 if risk factors had been controlled to their theoretically minimum distributions individually or jointly with others. For men, tobacco smoking was associated with the largest potential increase in life expectancy at age 40 y (1.8 y, 95% CI: 1.6–1.9), followed by a joint effect of multiple physiological factors (1.4 y, 95% CI: 1.3–1.6) and single effects of high systolic blood pressure (0.9 y, 95% CI: 0.7–1.0) and alcohol use (0.5 y, 95% CI: 0.5–0.6). A considerable part of the smoking effect (1.2 y, 95% CI: 1.1–1.3) was accounted for by an expected associated fall in cancer mortality through a decrease in probabilities of dying between the ages of 15 and 60 (45q15) by 8% (95% CI: 7–10) and between the ages of 60 and 75 (15q60) by 13% (95% CI: 12–14). A drop in cardiovascular mortality through the joint control of multiple risks was associated with an expected percentage decrease of 13% (95% CI: 12–15) in 45q15 and 11% (95% CI: 10–13) in 15q60, while controlling high blood pressure was associated with an expected fall of 7% both in 45q15 (95% CI: 6–8) and 15q60 (95% CI: 5–8). Decreasing alcohol use was associated with an expected percentage decrease of 9% (95% CI: 7–11) in 45q15 and 5% (95% CI: 5–6) in 15q60 for men. A substantial part of the potential change in the probability of death among young and middle-aged men through moderate drinking was explained by a fall in mortality from other non-communicable diseases including liver cirrhosis and liver cancer (4%, 95% CI: 4–4) and injuries (2%, 95% CI: 1–4).

For women, controlling systolic blood pressure and tobacco smoking to optimal counterfactuals would have extended life expectancy at age 40 y by 0.9 y (95% CI: 0.7–1.1) and 0.6 y (95% CI: 0.4–1.0), respectively. The impact of tobacco smoking on a probability of death in older women was estimated to be 8% (95% CI: 5–13), which was comparable to that of high blood pressure (7%, 95% CI: 6–8). A joint effect of cardiovascular risk factors on female life expectancy at age 40 y was estimated to be 1.4 y (95% CI: 1.2–1.7), with a decrease in probability of death of 8% (95% CI: 7–10) for younger adults and 11% (95% CI: 10–12) for older ages.

Table 5 shows changes in life expectancy at age 40 y and probabilities of death under the more practical counterfactuals defined by clinical guideline recommendations and national goals. Overall, the gains were less than half of those under theoretically minimum distributions. In both sexes, life expectancy at age 40 y would have increased by 0.7 y (95% CI: 0.6–0.9) through the joint control of cardiovascular risks and by 0.4 y (95% CI: 0.3–0.5) through reducing systolic blood pressure to the distribution recommended by clinical guidelines.

Trends in Mortality Attributable to Tobacco Smoking and High Blood Pressure in 1980–2007

Figure 2 illustrates trends in the number of deaths from cancers that were attributable to tobacco smoking from 1980 to 2007. A continuous increase has been observed in men over 70 y old and women over 80 y old. A fall after a peak around 1995 among men aged 60–69 y reflected the fact that the lifetime smoking prevalence reached a peak in the birth cohort of the late 1920s and decreased in the cohort of the late 1930s [42]. This effect manifested again as a peak in attributable cancer mortality around 2005, when the birth cohort of the late 1920s was 70–79 y old. A temporary halt in the increase of cancer deaths attributable to

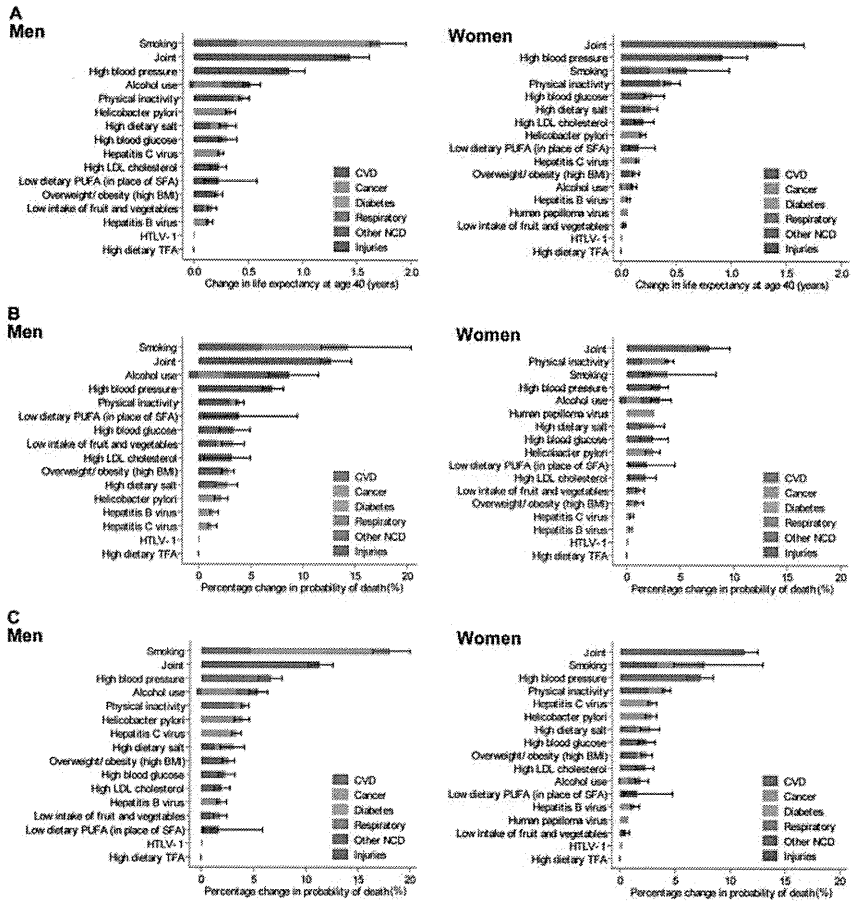

Figure 1. Changes in life expectancy at age 40 y and the probability of death under optimal distributions of risk factors in Japan, 2007. (A) Life expectancy at age 40. (B) Probability of death between 15 and 60 y of age. (C) Probability of death between 60 and 75 y of age. Joint risk is a combination of high blood pressure (directly, or indirectly through high dietary salt intake), high blood glucose, high LDL cholesterol, and high body mass index. BMI, body mass index; CVD, cardiovascular disease; NCD, non-communicable diseases; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids; TFA, trans fatty acids.
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tobacco smoking for men over 80 y old in the early 2000s reflected a reduction in this population group as a result of the 1918 influenza pandemic.

Figure 3 demonstrates trends in the number of deaths from stroke that were attributable to high blood pressure. Stroke deaths associated with this risk factor, either directly or indirectly through high dietary sodium intake, consistently declined for both sexes under 80 y of age. This favorable trend continued in the 2000s for women and for men under the age of 60 y, but it ceased for elderly men by the mid-1990s.

Table 5. Changes in life expectancy at age 40 y (e40) and percentage changes in the probability of death between 15 and 60 y of age (45q15) and between 60 and 75 y of age (15q60) under counterfactual distributions of risk factors defined by clinical guidelines and national goals.

Risk Factor	e40 (Years)		45q15 (Percent)		15q60 (Percent)	
Men						
High blood glucose	0.1	(0.0, 0.2)	−0.1	(−1.0, −0.1)	−0.7	(−1.2, −0.2)
High LDL cholesterol	0.0	(0.0, 0.0)	−0.6	(−1.3, −0.1)	0.0	(−0.1, 0.0)
High blood pressure	0.4	(0.3, 0.5)	−1.2	(−2.1, −0.3)	−3.0	(−3.7, −2.3)
High body mass index	0.1	(0.1, 0.2)	−1.8	(−2.2, −1.4)	−1.6	(−2.0, −1.2)
High dietary salt intake	0.0	(0.0, 0.0)	−3.4	(−0.2, 0.0)	−2.4	(−0.5, −0.1)
Low fruit and vegetable intake	0.0	(0.0, 0.0)	−0.5	(−0.9, −0.3)	0.0	(0.0, 0.0)
Joint risk[a]	0.7	(0.6, 0.9)	−5.8	(−8.4, −5.1)	−6.0	(−7.4, −5.2)
Women						
High blood glucose	0.1	(0.1, 0.2)	−0.2	(−0.9, 0.0)	−0.7	(−1.2, −0.2)
High LDL cholesterol	0.0	(0.0, 0.0)	−0.4	(−0.8, 0.0)	−0.4	(−0.7, −0.3)
High blood pressure	0.4	(0.3, 0.5)	0.0	(0.0, 0.0)	−2.8	(−3.5, −2.1)
High body mass index	0.0	(0.0, 0.1)	−0.1	(−0.4, 0.0)	−1.1	(−1.5, −0.8)
High dietary salt intake	0.0	(0.0, 0.0)	−0.2	(−0.3, −0.1)	−0.4	(−0.5, −0.2)
Low fruit and vegetable intake	0.0	(0.0, 0.0)	0.0	(−0.1, 0.0)	0.0	(0.0, 0.0)
Joint risk[a]	0.7	(0.6, 0.9)	−3.1	(−2.6, −1.0)	−5.6	(−6.6, −4.9)

Values in parentheses indicate lower and upper bounds of 95% CI.
[a]A combination of high blood glucose, high LDL cholesterol, high blood pressure (directly, and indirectly through high dietary salt intake), and high body mass index.
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Discussion

To our knowledge, this is the first study in Japan to assess and compare effects of a comprehensive list of modifiable risk factors on life expectancy and death from non-communicable diseases and injuries under the framework of comparative risk assessment. Our study indicates that major risks for adult mortality from these causes are tobacco smoking and high blood pressure, as well as a combination of multiple cardiovascular risks. We also demonstrate that, over the past 27 y, cancer mortality attributable to tobacco smoking has increased, especially in the older population, while stroke death associated with high blood pressure has decreased.

The leading single risk factors for adult mortality from non-communicable diseases and injuries in Japan, i.e., tobacco smoking, high blood pressure, physical inactivity, and high blood glucose concentrations, agree with those in the world and the US [2,20]. The number of deaths attributable to tobacco smoking for Japanese men is large relative to the number attributable to high blood pressure, even compared with the proportion among American men. This result may be related to a substantially higher prevalence of male smokers in Japan than in the US for the past 25 y [43]. Moreover, high body mass index ranks only tenth for both sexes in Japan, while it is one of the top five contributors to mortality in other high- and middle-income countries [2]. This finding reflects the fact that mean body mass index in Japan is low for the income level of the country [44].

Our estimate of the impact of tobacco smoking on male life expectancy at age 40 y (1.8 y) was smaller than those of past cohort studies in Japan. Previous studies showed that, according to smoking status at the time of the baseline survey, life expectancy for men aged 40 y in the total population was shorter than that of never-smokers by around 2.5 y [14,16]. Use of different exposure measurements may explain part of the difference in estimated impacts of tobacco smoking between the present and past studies. We believe that the smoking impact ratio used in our study is useful for quantifying accumulated smoking risk over a lifetime.

Our results suggest that the threat of tobacco smoking for mortality is enormous in men and has been increasing over time through the accumulation of exposure to this risk in the older population. A previous study showed that lifetime smoking prevalence was low for the generation born in the late 1930s who experienced the deprivation in the early postwar years, but rose thereafter until it peaked for the birth cohort of the 1950s [42]. These findings imply that, without effective policy interventions, the increasing trend in tobacco-associated mortality may continue until at least the late 2030s, when the birth cohort of the late 1950s reaches the age of 80 y. Aiming to decrease the disease burden related to tobacco smoking in the population, the Japanese government enacted the Health Promotion Act in 2002 to support prevention of passive smoking in public places. Based on this legislation, Health Japan 21 specified four targets for tobacco smoking: (i) increasing knowledge of the adverse health effects of smoking, (ii) prohibiting minors from smoking, (iii) strengthening separation of smoking areas in public spaces and the workplace, and (iv) dissemination of smoking cessation programs in all municipalities. A final appraisal of Health Japan 21 concluded that there was improvement for all of these targets [7]. However, the prevalence of smoking in the male working population is still high at around 50%, although it has been gradually declining after the implementation of a series of antismoking policies. Moreover, although Japan ratified the World Health Organization Framework Convention on Tobacco Control in 2004, compliance is lagging behind international standards for smoke-free policies, bans on advertising, health warnings on cigarette packages, and antitobacco mass media campaigns [45]. The retail price of the most popular brand of cigarettes is lower than the average among high-income countries [45]. The recent tobacco tax increase in October 2010 was insufficient to induce smokers to give up

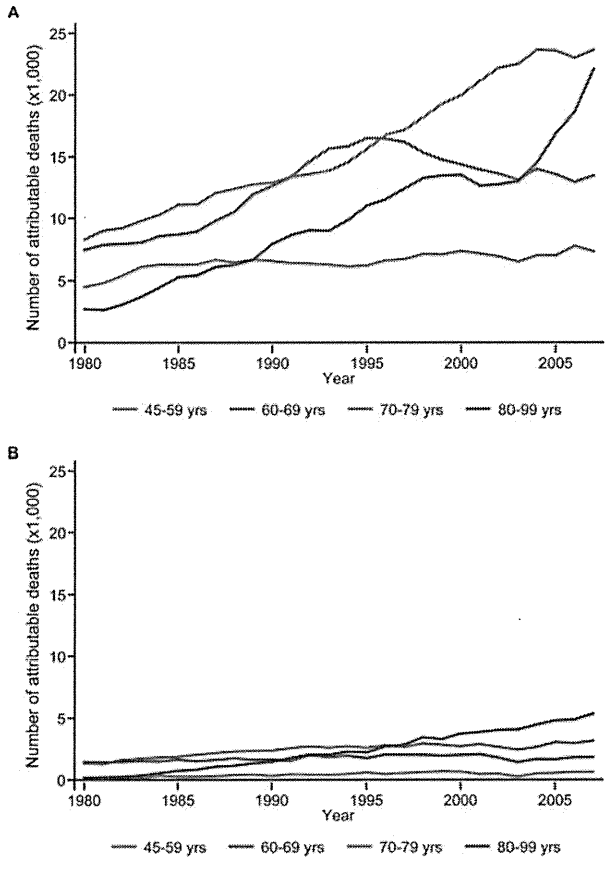

Figure 2. Cancer deaths attributable to tobacco smoking, by age group, 1980–2007. Data for (A) men and (B) women.
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purchasing tobacco products. Thus, the progress in tobacco control policies is slow, largely because Japanese society is relatively tolerant of this unhealthy behavior. In order to improve the health of the population, policymakers need to implement further stringent antismoking measures that appropriately assess the health impacts of smoking on non-smokers as well as on the smokers themselves.

Our study suggests that a decrease in population blood pressure partly accounts for a reduced mortality from stroke at least since 1980, although the downward trend leveled off for elderly men in the early 1990s. Stroke mortality started decreasing in the late 1960s and has been the major contributor to the increase of life expectancy in Japan [4]; our finding backs up the idea that a reduction in population blood pressure has contributed to improved longevity. Potential key factors for the decline of blood pressure in the Japanese population may include increased use of blood-pressure-lowering drugs among patients with hypertension, and a reduction in dietary salt intake [46]. These successes may be attributed to the support of the national government for community-based programs for hypertension control that were proven to be effective in pilot studies conducted in the 1960s and 1970s [47]. In 1982, a national act on health and medical care was enacted that required all municipalities to provide residents aged 40 y and over with health screening and

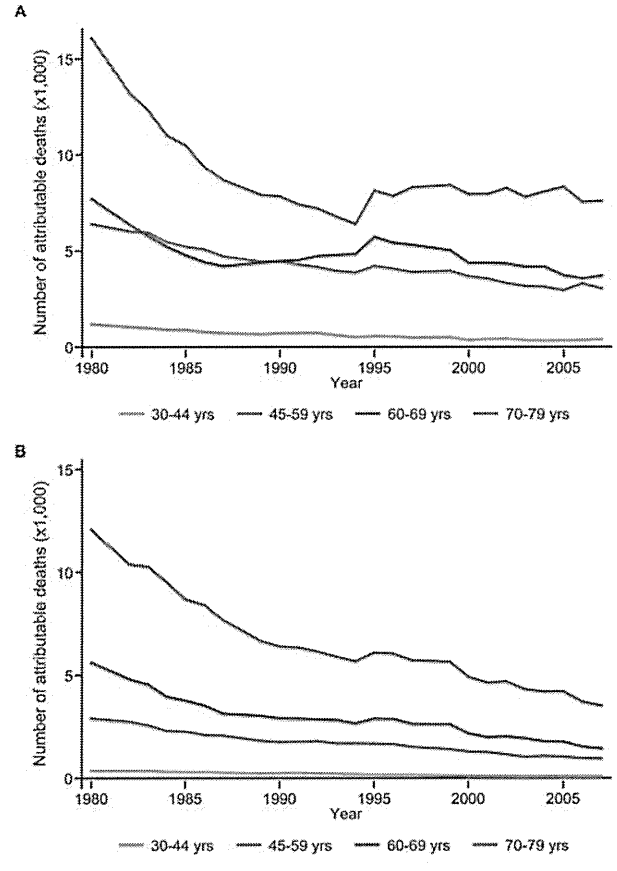

Figure 3. Stroke deaths attributable to high blood pressure, by age group, 1980–2007. Data for (A) men and (B) women.
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educational services for prevention of cardiovascular diseases [47].

Despite the decrease in stroke mortality attributable to high blood pressure, this is still the major risk factor for cardiovascular mortality in Japan. The management of high blood pressure is not adequate even under the practical standards of domestic clinical guidelines. In 2007, less than 60% of hypertensive patients took antihypertensive medication daily, and only 20% had their blood pressure controlled [48]. These treatment coverage and control rates are substantially lower than those in the US [48]. Previous studies pointed out that an acceptance of higher control thresholds of blood pressure among physicians [49] and insufficient treatment regimens [50] might partly explain the poor control of blood pressure with antihypertensive drugs in Japanese clinical practice. A thorough investigation is necessary to understand what makes the quality of care for hypertension so low at the population level, including investigating adherence of patients to prescriptions. Furthermore, lowering dietary sodium intake is crucial for decreasing blood pressure as well as mortality from stomach cancer in Japan. The Japanese diet is traditionally high in salt, which mainly comes from soy sauce, miso soup, and salted vegetables and fish [51]. Although Health Japan 21 was successful in decreasing average daily salt intake from 13.5 g in the baseline year to 10.7 g in 2009 [7], it is well above the global target of 5 g/

d set by the World Health Organization [52]. Extra efforts by the industrial sector on ingredient labeling for consumers and reducing sodium content in commercially processed products are essential.

Another key finding of our study is that a considerable number of deaths from cardiovascular diseases would be prevented through joint control of multiple risk factors in Japan. In addition to the traditional approach of focusing on single risk factors, health education and effective treatment based on absolute risk have great potential for improving primary and secondary prevention of cardiovascular mortality. Our results support current domestic efforts to target high-risk populations, such as cardiovascular risk stratification according to categories of multiple risks [53,54] and the development of risk assessment charts for Japanese people [55].

Our study suggests that physical inactivity contributes to a substantial mortality from non-communicable diseases in Japan. Lack of exercise is common: in 2008, two-thirds of the Japanese adult population engaged in less than 30 min of moderate activity per week or less than 20 min of vigorous activity three times per week [56]. Considering global efforts to promote physical activity for the prevention of non-communicable diseases [57], it is important to strengthen policies for improving public understanding of the role of physical training in disease prevention, and provide support for individual's efforts to start having regular exercise.

Our results suggest that mortality from external causes, such as suicide and traffic accidents, associated with alcohol use is fairly small in Japan. For suicide, relative risks of alcohol use were insignificant, except for heavy drinking, in a large Japanese cohort study [58]. Major reasons for suicide in the male working population are psychiatric disorders and economic reasons such as business failure, unemployment, and debts [59], which suggest that direct risk factors for deaths from suicide are psychosocial, and alcohol use itself may have only an indirect effect. Regarding road traffic accidents, it remains to be seen in future research how robust our result is, because our information on road traffic accidents was limited to published crude estimates on risk exposures and relative risks. We also applied relative risks of suicide to falls, homicide, and other injuries because of the lack of evidence. In order to make a convincing argument on mortality from alcohol-related injuries in Japan, we need to wait for more detailed data and evidence to be accumulated and be made accessible.

One of distinctive characteristics of adult mortality in Japan is a large number of cancer deaths attributable to infectious agents, which is possibly common in East-Asian countries [26,60]. Mortality from stomach cancer related to *H. pylori* is substantial in Japan, because of the relatively high prevalence of this infection [26]. However, a decline in the prevalence of *H. pylori* infection was observed among people born after 1955 [38], who experienced improved hygienic conditions under rapid economic growth in early childhood. This favorable trend predicts a future reduction in the burden of gastric cancer attributable to *H. pylori* in Japan. Moreover, chronic infection from hepatitis C virus is responsible for the majority of cases of hepatocellular carcinoma in Japan, while hepatitis B virus plays the major role in most Asian countries [61]. A considerable part of mortality attributable to hepatitis C virus infection occurred among people born in the early 1930s. The risk of becoming infected with hepatitis viruses was high in this birth cohort, because intravenous use of methamphetamines was endemic in Japan in their young adulthood [27,62]. The spread of hepatitis viruses from drug abusers to the general population in the 1950s and 1960s was most likely mediated by transfusion of unscreened or commercial blood and blood products and by medical practices such as needle sharing for immunizations [62]. The decreasing prevalence of infections with hepatitis C virus after the birth cohort of around 1935 indicates that the mortality burden of this infectious agent will diminish in the foreseeable future.

Will the estimated improvements in population health outcomes be worth all the efforts required of the government, citizens, and health care workers involved in the modification of risk factors? The overall increases in life expectancy associated with improved risk factor exposures may appear small in comparison with observed improvements in Japanese longevity over previous decades. This is, however, consistent with a past study's finding showing that even complete elimination of deaths from major causes would not affect life expectancy as much as anticipated in the US, and an additional drop in mortality would have only a marginal effect in countries where the rapid increases of life expectancy have already ended [63]. A study in Sweden also suggested that the main improvements in increasing a life span come from changes in death rates among the oldest groups [64]. In order for the aging population to continue the constant progress in longevity, it is essential to decrease mortality in older ages through the control of risk factors for non-communicable diseases and injuries. Working on risk factors in younger generations is especially important from this standpoint to ensure further improvement in Japanese life expectancy in the long run.

Our study was based on global efforts of various agencies to pool evidence on causality and consistency of relative risks. We also used Japanese population evidence from large-scale cohort studies if they confirmed established causality, although effects of excess risks should not vary across populations [20]. We believe, however, that our effort was justified because the pooled estimates of these large-scale studies reflected the magnitude of the proportional effects of risk factors in the specific context of the Japanese population.

Our analysis had several limitations that should be noted. First, we focused on impacts of risk factors on mortality relative to changes in life expectancy and did not account for morbidity and disability. It is important in future studies to integrate these nonfatal health outcomes and examine disability-adjusted life years under the framework of comparative risk assessment in Japan. This is particularly true because the prognosis of non-communicable diseases has been improving with enhanced access to care, advances in medical technologies, and the standardization of treatment. Second, we could not incorporate standard metabolic equivalents in the categorization of exposures to physical inactivity because of the lack of detailed data from the 2007 survey, but instead we adopted a broader classification based on only the intensity and duration of physical activity that was used in the Global Burden of Disease Study in 2000. Third, data on dietary sodium intake until 1995 were recorded at the household level, which might increase uncertainty concerning the estimated stroke mortality attributable to high blood pressure in the early years. Fourth, we employed LDL cholesterol as an exposure metric for high concentrations of serum cholesterol, because it is the major atherogenic lipoprotein and a primary target for prevention of coronary heart disease [65]. It is, however, also a possibility for future studies to examine effects of low concentrations of high density lipoproteins, because growing evidence indicates that it plays an important role in atherogenesis [65]. Last, some of the Japanese population studies included in this analysis did not exclude disease end points occurring within a certain period after baseline in estimating relative risks. A few studies, however, conducted additional analyses and proved that changes in their results were minor.

To sustain the trend of longevity in Japan for the 21st century, additional efforts in a variety of fields are required for decreasing adult mortality from chronic diseases and injuries. A first step will be to powerfully promote effective programs for smoking cessation. Indeed, tobacco smoking is deeply rooted in Japanese society, and coordinating among interests of ministries and industries is hard. Health care professionals, including physicians, who are highly conscious of the harms of tobacco will play the primary role in treatment of smoking and creating an environment for implementation of stringent tobacco control policies. Moreover, it is urgent to establish a monitoring system for management of high blood pressure at the national level. Further investigation through national health surveys will help understand factors that contribute to the inadequate control of blood pressure in the Japanese population. Measuring the quality of the care that is actually delivered by interventions will be of paramount importance in the assessment of current policies and programs for the treatment of multiple cardiovascular risks including hypertension. These concerted actions in research, public health, clinical practice, and policymaking will be the key for maintaining good population health in the aging society.

Supporting Information

Alternative Language Article S1 Translation of the article into Japanese by the authors.
(DOCX)

Table S1 Relative risks for the effects of physiological risk factors on non-communicable diseases.
(DOCX)

Table S2 Relative risks for the effects of alcohol use on disease outcomes from meta-analyses.
(DOCX)

Table S3 Relative risks for the effects of alcohol use on disease outcomes from Japanese studies.
(DOCX)

Table S4 Relative risks for the effects of tobacco smoking on disease outcomes.
(DOCX)

Table S5 Relative risks for the effects of physical inactivity on disease outcomes.
(DOCX)

Table S6 Relative risks for the effects of dietary risk factors on disease outcomes.
(DOCX)

Table S7 Relative risks for the effects of infections on disease outcomes.
(DOCX)

Table S8 Population-attributable fractions of cause-specific mortality attributable to individual risk factors in men in 2007.
(DOCX)

Table S9 Population-attributable fractions of cause-specific mortality attributable to individual risk factors in women in 2007.
(DOCX)

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Author Contributions

Conceived and designed the experiments: NI ME KS. Performed the experiments: NI KS. Analyzed the data: NI. Contributed reagents/materials/analysis tools: MN ME. Wrote the first draft of the manuscript: NI. Contributed to the writing of the manuscript: MI HIso SI TSatoh MN TM HImano ES KK TSobue ST MN ME KS. ICMJE criteria for authorship read and met: NI MI HIso SI TSatoh MN TM HImano ES KK TSobue ST MN ME KS. Agree with manuscript results and conclusions: NI MI HIso SI TSatoh MN TM HImano ES KK TSobue ST MN ME KS. Supervised the research: KS. Literature search and data collection of exposures, relative risks and mortality: NI MI HIso MN TM HImano ES KK TSobue ST MN ME KS.

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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)

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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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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:

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

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:

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

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]:

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

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

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]:

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

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):

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

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

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 PAF (%) (95% CI)	Incidence Number	Mortality PAF (%) (95% CI)	Mortality 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.

H. pylori infection in Japan. Hepatocellular carcinoma, which accounts for 90% of all liver cancer cases, is primarily caused by 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].

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

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

Site	ICD-10	Men Incidence/mortality, PAF (%) (95% CI)	Women Incidence/mortality, PAF (%) (95% CI)	Both sexes Incidence, PAF (%) (95% CI)	Both sexes 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.

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.

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disclosure

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