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BRIEF REPORT

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ORIGINAL ARTICLE

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Burden of cancer attributable to tobacco smoke in Japan in 2015

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Abstract: Tobacco is the greatest single cause of many non-communicable diseases, including cancer. We calculated the proportion of cancer incidence and mortality in 2015 attributable to tobacco smoking and exposure to secondhand smoke (SHS). Data on the prevalence of active smoking were derived from the 2005 Japanese National Health and Nutrition Survey by age group and gender. For SHS exposure prevalence, data from a nationwide cross-sectional survey from 2004-2005 were used. Based on standard formulas, population attributable fractions (PAFs) for each cancer causally associated with active smoking, namely the oral cavity and pharynx, esophagus, stomach, colon, rectum, liver, pancreas, nasal, larynx, lung, uterine cervix, kidney, renal pelvis and ureter, bladder, and acute myeloid leukemia, were calculated for each sex and age group and aggregated to obtain the PAF among total cancer incidence and mortality. For SHS exposure, PAFs for lung cancer and total cancer were calculated using the same method. For Japan in 2015, 145,765 new cancer cases and 72,520 cancer deaths, corresponding to a PAF of 15.2% for total cancer incidence and 19.6% for total cancer mortality, were attributable to active tobacco smoking. For SHS exposure, 0.5% of total cancer incidence and 0.7% of total cancer mortality in 2015 were attributable. Tobacco is still one of the major causes of cancer in Japan.

***Keywords*:** cancer, tobacco smoke, secondhand smoke, population attributable fraction, Japan

Introduction

Tobacco smoking is the greatest single preventable cause of cancer (*1*). Globally, there are estimated to be 1,820,000 cancer deaths every year due to active smoking and 125,000 cancer deaths due to secondhand smoke (SHS) exposure (*2*). The incidence of tobacco-caused diseases is particularly high in East Asia. Japan ranks sixth in the world for tobacco consumption (*3*). Smoking prevalence among men aged 30-49 years is 37% (*4*). The latest estimates on the population-attributable fractions (PAFs) of tobacco-related cancers in Japan were released in 2005 (125,898 cases for active smoking and 4,152 cases for SHS exposure) (*5*). With regard to active smoking, other studies have reported similar estimates by including non-cancer diseases attributable to smoking, using data obtained in 2005 (*6*), 2007 (*7*), and 2008 (*8*). These estimates are now somewhat out of date, however, and their selection of smoking-related diseases was based on studies conducted mostly among Westerners.

In 2016, the Committee on Health Effects of Smoking of the Ministry of Health, Labour and Welfare (MHLW) released a comprehensive report on health consequences attributable to smoking (*9*). Following the U.S. Surgeon General's Report (*10*), this report made comprehensive and systematic assessments of the causal relationships between smoking and disease in the Japanese population. This report and studies conducted before and after it included meta-analyses and pooled analyses of large-scale cohort studies performed in Japanese populations, which aimed to explore the association between active smoking and head and neck cancers (*11*), bladder cancer (*12*), hematologic malignancies (*13*), cervical cancer (*14*), and colorectal cancer (*15*), and the association between SHS exposure and lung cancer (*16*). Thanks to these studies, it is now possible to select smoking-related diseases specific to the Japanese population and to calculate their RRs using more representative data. Additionally, the prevalence of smoking in Japanese, particularly among men, has declined over the past 10 years (*4,17*), which is likely a major contributor to changes in the estimates of smoking-attributable cancer incidence and mortality.

Therefore, this study aimed to estimate the proportion of cancer incidence and mortality in 2015 attributable to active tobacco smoking and exposure to SHS.

Materials and Methods

Cancers associated with tobacco smoking

The International Agency for Research on Cancer (IARC) confirmed that tobacco smoking, SHS exposure, and smokeless tobacco were all reaffirmed as carcinogenic to humans (Group 1) (*18*). There are major global and domestic comprehensive assessments: an IARC monograph published in 2012 (*19*), a report of the US Surgeon General in 2014 (*20*), and a domestic assessment by the Research Group for the Development and Evaluation of Cancer Prevention Strategies in Japan (*21*). In Japan, these assessments were further comprehensively evaluated and integrated into the most recent report by the Committee on Health Effects of Smoking in 2016 (*9*). Therefore, we applied the target cancers causally associated with tobacco smoking concluded by this evaluation, namely those that showed sufficient evidence for a positive association with tobacco smoking and for which RR estimates in Japan were available, including cancer of the oral cavity and pharynx, esophagus, stomach, colon, rectum, liver, pancreas, nasal cavity and paranasal sinuses, larynx, lung, cervix uterine, kidney, renal pelvis and ureter, urinary bladder and acute myeloid leukemia. For SHS exposure, the only cancer retained in the analysis was lung cancer among never-smokers.

Prevalence of tobacco smoking

The data on smoking status were derived from the Japanese National Health and Nutrition Survey (JNHNS) from 2005 (*22*), which presents the proportion of current, former, and never smokers by sex and age group. Smoking prevalence from year 2000 of the JNHNS (*23*) was further used for sensitivity analysis. Sex- and age-group-specific prevalence of tobacco smoking in Japan in 2005 is shown in Table 1. For SHS exposure prevalence, data from a nationwide cross-sectional survey from 2004-2005 funded by Grants-in-aid from Ministry of Health, Labour, and Welfare were used (*24*). This survey collected data on the proportion of non-smoking men and women who were exposed to SHS. The two possible exposure locations considered were home and work. The sex- and age-group-specific prevalence (%) of SHS exposure in Japan in 2005 is shown in Table 2.

Cancer incidence and mortality in Japan in 2015

Cancer incidence data in 2015 were estimated using the annual estimate of cancer incidence in 2013 by the Monitoring of Cancer Incidence in Japan (*25*). This estimate was done using an age and period spline model, a method which is used for short-term projections for cancer incidence in Japan (*26*). The sex- and age-specific incidence data for target cancers were coded by the International Statistical Classification of Diseases and Related Health Problems, 10th edition (ICD-10), using the morphology code of the International Classification of Disease for Oncology, 3rd edition (ICD-O-3).

The data on cancer mortality statistics from 2015 were obtained from the vital statistics of Japan (*27*). We sourced sex- and age-specific mortality data by cause of death from the Health, Labour, and Welfare Statistics Association (*28*). Similar to the cancer incidence data, 4-digit ICD-10 codes were used to classify the cause of death.

Table 1. Sex- and age-group-specific prevalence of tobacco smoking in Japan in 2005

Age at exposure	2005						2000					
	Men			Women			Men			Women		
	Current	Former	Ever	Current	Former	Ever	Current	Former	Ever	Current	Former	Ever
0 - 4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
5 - 9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
10 - 14	1.0	0.0	1.0	0.5	0.0	0.5	2.5	0.0	2.5	0.9	0.0	0.9
15 - 19	7.0	0.0	7.0	2.5	0.0	2.5	18.8	0.0	18.8	5.5	0.0	5.5
20 - 24	44.4	3.2	47.7	15.4	3.5	19.0	52.3	3.9	56.2	17.6	2.9	20.5
25 - 29	52.3	8.4	60.6	20.7	7.3	28.0	63.9	5.5	69.4	17.5	6.1	23.6
30 - 34	54.7	10.0	64.7	19.6	9.8	29.4	56.0	9.6	65.6	16.3	5.1	21.4
35 - 39	55.3	13.8	69.1	16.0	8.0	24.0	59.1	11.5	70.6	16.8	4.5	21.3
40 - 44	49.7	20.2	69.9	14.5	7.0	21.6	58.0	16.6	74.6	14.5	4.3	18.8
45 - 49	44.9	24.7	69.6	13.9	5.2	19.1	56.2	19.8	76.0	12.0	2.4	14.4
50 - 54	48.1	24.7	72.8	13.6	4.7	18.3	55.5	21.3	76.8	11.0	2.1	13.2
55 - 59	43.4	27.6	71.1	10.2	2.9	13.1	49.0	24.2	73.2	7.9	2.8	10.6
60 - 64	37.7	29.5	67.2	8.7	3.8	12.5	42.2	30.1	72.3	7.2	1.9	9.1
65 - 69	30.1	30.5	60.6	5.5	2.9	8.3	34.7	38.2	73.0	6.8	1.9	8.7
70 - 74	24.2	35.1	59.3	4.5	2.7	7.1	34.2	42.6	76.8	4.2	3.2	7.4
≥ 75	18.8	35.3	54.1	2.5	3.1	5.7	26.9	48.1	75.0	3.2	2.5	5.7
Total	40.8	23.5	64.4	11.1	4.9	15.9	47.6	25.0	72.6	10.6	3.2	13.7

Data source: The National Health and Nutrition Survey, Japan, 2005.

Table 2. Sex- and age-group-specific prevalence (%) of secondhand smoking in Japan in 2005

Age at exposure	Men		Women	
	At home	At work	At home	At work
0 - 4	6.2	0.0	31.1	0.0
5 - 9	6.2	0.0	31.1	0.0
10 - 14	6.2	0.0	31.1	0.0
15 - 19	6.2	0.0	31.1	0.0
20 - 24	6.2	29.4	31.1	18.2
25 - 29	6.2	29.4	31.1	18.2
30 - 34	6.2	29.4	31.1	18.2
35 - 39	6.2	29.4	31.1	18.2
40 - 44	6.2	29.4	31.1	18.2
45 - 49	6.2	29.4	31.1	18.2
50 - 54	6.2	29.4	31.1	18.2
55 - 59	6.2	29.4	31.1	18.2
60 - 64	6.2	29.4	31.1	18.2
65 - 69	6.2	29.4	31.1	18.2
70 - 74	6.2	29.4	31.1	18.2
≥ 75	6.2	29.4	31.1	18.2

Data source: Report of the nationwide survey on adolescent smoking behavior in Japan, Grants-in-aid for the Comprehensive Health Sciences from the Ministry of Health, Labour, and Welfare, Japan. 2016 (*24*).

Estimation of relative risks

The sources for the site-specific RR of cancer with relation to active smoking and SHS exposure are shown in Table 3. As a general rule, we prioritized meta-analyses or pooled analyses published for Japanese populations, followed by Asian populations, then studies from other nations. Studies that differentiated between current and past smokers were prioritized over studies that differentiated between ever- and non-smokers. RRs presented by sex were used. If the studies only presented RR for ever- or current smokers, these were used by considering the RR of former smokers to be 1.

For SHS exposure at home, the summary RR was derived from a meta-analysis of Japanese studies; for SHS exposure at work, summary RR was derived from an international meta-analysis since a sufficient number of studies was not available for Japan.

Estimation of population attributable fractions (PAFs)

For active smoking, PAFs were calculated using the method of Levin's formula for multiple categories (*29*), proposed by Hanley (*30*). This method distinguishes between current and former smokers. PAF for active smoking was calculated for each sex and age group according to the formula:

$$\mathrm{PAF} = \frac{P_c(RR_c - 1) + P_f(RR_f - 1)}{1 + P_c(RR_c - 1) + P_f(RR_f - 1)}$$

Where P_c is the proportion of the population currently smoking, RR_c is the RR for current smokers compared to never smokers, P_f is the proportion of the population of former smokers, and RR_f is the RR of former smokers compared to never smokers.

For SHS, PAF was calculated using the method described by Gan *et al.* (*31*). First, the PAF of non-smokers exposure to SHS (PAF_{shns}) was calculated using the following formula:

$$PAF_{shns} = \frac{P(RR - 1)}{1 + P(RR - 1)}$$

Where P and RR refer to the proportion of SHS exposure and RR for non-smokers, respectively, compared to non-smokers who were not exposed to SHS. We then calculated the PAF for SHS (PAF_{shs}) for the entire population by:

$$PAF_{shs} = PAF_{shns} \times (1 - PAF_c) \times (1 - P_c)$$

Where PAF_c refers to PAF of current smokers and P_c refers to the proportion of current smokers in the population. PAF for SHS was only separated by gender; age groups were pooled due to the limited sample size and prevalence.

Results

Table 4 summarized the estimated PAF of cancer incidence and mortality in 2015 attributed to tobacco smoke in Japan.

Active smoking was estimated to have caused 23.6% of total cancer incidence among men and 4.0% among women. For major cancers, smoking caused 61.7% (men) and 20.9% (women) of lung cancer cases, and 57.5% (men) and 20.4% (women) of esophageal cancer cases. Similarly, the estimated number and PAF of cancer mortality in 2015 attributed to active smoking were 29.8% for men and 4.7% for women. For lung cancer deaths, 60.9% (men) and 18.3% (women) of cases may be attributable to smoking. For men and women combined, 15.2% of cancer incidence and 19.6% of cancer mortality in 2015 could be attributable to active tobacco smoking. Based on these results, 145,765 cases of cancer incidence (129,502 in men and 16,263 in women) (Table S1, online data, *https://www.ghmopen.com/site/supplementaldata.html?ID=32*) and 72,520 cancer deaths (65,416 in men and 7,105 in women) (Table S2, online data, *https://www.ghmopen.com/site/supplementaldata.html?ID=32*) were estimated to be attributable to active smoking.

Likewise, SHS was estimated to have caused 0.2% of total cancer incidence among men and 0.9% among women. Lung cancer incidence in 2015 attributable to SHS exposure at home and work in total was 1.3% (men) and 8.7% (women). The PAFs for mortality were

Table 3. Relative risk of cancer associated with passive and secondhand smoking compared with never smoking in Japan

Cancer site (ICD-10 code)	Exposure category	RR (95% CI)		Sources
		Men	Women	
Active smoking				
Oral cavity and pharynx (C00-C14)	Current	2.68 (2.08 - 3.44)	2.68 (2.08 - 3.44)	Koyanagi *et al.* (Japanese meta-analysis) (*11*)
	Former	1.49 (1.05 - 2.11)	1.49 (1.05 - 2.11)	
Esophagus (C15)	Current	3.73 (2.16 - 6.43)	3.73 (2.16 - 6.43)	Oze *et al.* (Japanese meta-analysis) (*43*)
	Former	2.21 (1.60 - 3.06)	2.21 (1.60 - 3.06)	
Stomach (C16)	Current	1.79 (1.51 - 2.12)	1.22 (1.07 - 1.38)	Nishino *et al.* (Japanese meta-analysis) (*44*)
	Former	-	-	
Colon (C18)	Current	1.18 (1.06 - 1.31)	1.12 (0.96 - 1.31)	Akter *et al.* (Japanese pooled analysis) (*15*)
	Former	1.20 (1.09 - 1.32)	0.98 (0.73 - 1.30)	
Rectum (C19-C20)	Current	1.27 (1.12 - 1.44)	1.05 (0.83 - 1.34)	Akter *et al.* (Japanese pooled analysis) (*15*)
	Former	1.10 (0.95 - 1.26)	1.42 (0.99 - 2.04)	
Liver (C22)	Current	1.81 (1.49 - 2.20)	1.73 (1.21 - 2.48)	Katanoda *et al.* (Japanese pooled analysis) (*6*)
	Former	1.63 (1.32 - 2.01)	1.23 (0.63 - 2.39)	
Pancreas (C25)	Ever	1.57 (1.30 - 1.89)	1.83 (1.35 - 2.48)	Matsuo *et al.* (Japanese meta-analysis) (*45*)
Nasal cavity (C30)	Ever	2.49 (1.86 - 3.34)	3.12 (1.62 - 5.99)	Koyanagi *et al.* (Japanese meta-analysis) (*11*)
Larynx (C32)	Current	5.47 (1.29 - 23.11)	1.00	Katanoda *et al.* (Japanese pooled analysis) (*6*)
	Former	3.03 (0.65 - 14.01)	1.00	
Lung (C33-C34)	Current	4.65 (3.70 - 5.85)	3.75 (2.89 - 4.86)	Meta-analysis of Japanese studies (*32*)
	Former	2.38 (1.86 - 3.05)	2.96 (1.92 - 4.56)	
Cervix uteri (C53)	Ever		2.03 (1.49 - 2.57)	Sugawara *et al.* (Japanese meta-analysis) (*14*)
Kidney (C64)	Current	1.57 (0.81 - 3.06)	0.60 (0.08 - 4.47)	Katanoda *et al.* (Japanese pooled analysis) (*6*)
	Former	1.46 (0.71 - 3.00)	1.55 (0.21 - 11.52)	
Renal pelvis and ureter (C65-C66)	Current	5.35 (2.47 - 11.57)		Katanoda *et al.* (Japanese pooled analysis) (*6*)
	Former	2.76 (1.21 - 6.31)		
	Ever		1.30 (0.59 - 2.88)	
Bladder (C67)	Ever	2.14 (1.87 - 2.44)	2.14 (1.87 - 2.44)	Masaoka *et al.* (Japanese meta-analysis) (*12*)
Acute myeloid leukemia (C92.0, C92.4, C92.5)	Current	1.44 (0.97 - 2.14)	1.44 (0.97 - 2.14)	Ugai *et al.* (Japanese pooled analysis) (*46*)
	Former	1.42 (0.91 - 2.22)	1.42 (0.91 - 2.22)	
Secondhand smoking				
Lung (C33-C34)	Home	1.28 (1.10 - 1.48)	1.28 (1.10 - 1.48)	Hori *et al.* (Japanese meta-analysis) (*16*)
	Workplace	1.12 (0.86 - 1.50)	1.22 (1.10 - 1.35)	Surgeon General Report meta-analysis (*39*)

0.3% for men and 1.3% for women for total cancers, and 1.4% and 9.1% for lung cancer, respectively. For men and women combined, 0.5% of total cancer incidence (3.7% of lung cancer) and 0.7% of total cancer mortality (3.6% of lung cancer) in 2015 were attributed to SHS. Based on these results, 4,579 cancer cases (1,095 in men and 3,483 in women; total number is not equal to the sum of men and women due to rounding) (Table S3, online data, *https://www.ghmopen.com/site/supplementaldata.html?ID=32*) and 2,667 cancer deaths (735 in men and 1,932 in women) (Table S4, online data, *https://www.ghmopen.com/site/supplementaldata.html?ID=32*) were estimated to be attributable to SHS exposure.

Discussion

In this study, we estimated that in Japan, 145,765 (15.2%) newly diagnosed cancer cases and 72,520 (19.6%) cancer deaths in 2015 were attributable to active smoking. The PAFs were nearly 50% or even larger for lung, larynx, and esophagus for both cancer incidence and mortality. Men exhibited a much larger PAF of active smoking than women (23.6% *vs.* 4.0% for incidence and 29.8% *vs.* 4.7% for mortality of total cancers). For SHS exposure, we estimated that 4,579 (3.7%) cases of lung cancer incidence and 2,667 (3.6%) lung cancer deaths were attributable in Japan annually. In contrast to active smoking, the PAF of SHS exposure was larger in women

Table 4. Proportion (%) of cancer in 2015 attributable to tobacco smoke in Japan

Cancer Site (ICD-10)	Incidence			Mortality		
	Men	Women	Both sexes	Men	Women	Both sexes
Active tobacco smoking						
Oral cavity and pharynx (C00-C14)	43.4	13.3	34.1	41.8	10.0	32.6
Esophagus (C15)	57.5	20.4	51.7	56.5	18.3	50.1
Stomach (C16)	21.5	1.6	15.3	19.9	1.3	13.6
Colon (C18)	10.8	0.9	6.2	10.6	0.7	5.6
Rectum (C19-C20)	11.5	2.0	8.2	11.0	1.8	7.7
Liver (C22)	31.9	5.2	22.6	31.3	3.4	21.8
Pancreas (C25)	26.8	7.7	17.5	26.7	7.2	17.1
Nasal (C30-C31)	48.9	19.7	38.8	48.4	17.1	36.4
Larynx (C32)	68.5	0.0	63.6	66.7	0.0	61.7
Lung (C33-C34)	61.7	20.9	48.5	60.9	18.3	48.8
Uterine cervix (C53)		15.6	15.6		13.1	13.1
Kidney (C64)	25.8	2.2	18.5	24.6	1.8	17.0
Renal pelvis and ureter (C65-C66)	66.1	2.8	43.9	64.7	2.4	39.9
Bladder (C67)	41.6	9.5	33.5	40.7	8.0	30.5
Acute myeloid leukemia (C92.0, C92.4, C92.5)	20.6	5.3	14.5	21.2	4.4	14.8
Total	23.6	4.0	15.2	29.8	4.7	19.6
Secondhand smoking						
Lung (C33-C34)	1.3	8.7	3.7	1.4	9.1	3.6
Total	0.2	0.9	0.5	0.3	1.3	0.7

than in men (8.7% *vs.* 1.3% for incidence and 9.1% *vs.* 1.4% for mortality of lung cancer). We reconfirmed that tobacco is still one of the major causes of cancer in Japan.

The PAFs estimated in the present study were slightly smaller than those reported in previously. In men, the PAF of cancer incidence attributable to active smoking was 29.7% in 2005 (*5*), which decreased to 23.6% in the present study (in 2015). A major reason for this is the decrease in smoking prevalence in Japan. Male ever smoking prevalence reduced from 72.9% (in 1990) (*5*) to 64.4% (in 2005) in the present study. Our additional analysis showed that the PAF estimates were closely similar when we applied the same value for ever smoking prevalence (data not shown). Another factor is a change in methodology. First, we assumed a 10-year latency period from exposure to outcome versus a 15-year period in our previous study. In a sensitivity analysis we used a 15-year latency period instead (*i.e.* smoking prevalence in 2000), and found that the PAFs for all cancers combined were slightly larger, particularly for men (incidence: 26.3% for men, 4.0% for women, and 16.8% for men and women combined; mortality: 33.9% for men, 5.0% for women, and 22.1% for men and women combined). Second, we used age-specific smoking prevalence in the present study versus age-pooled prevalence in the previous one (*5*). When we used age-pooled prevalence in the present study, the PAFs were slightly larger (*e.g.* 64.5% *vs.* 61.7% for male lung cancer incidence), probably due to overestimation of smoking prevalence among the elderly. Thus, the PAFs in men decreased due to both a decline in smoking prevalence and pooling age. By contrast, in women, although the PAF of cancer incidence attributable to active smoking reduced from 5.0% (in 2005) (*5*) to 4.0% in the present study (in 2015), ever smoking prevalence increased from 12.3% (in 1990) (*5*) to 15.9% (in 2005). However, when we applied age-pooled prevalence to the calculation, the PAF became larger (*e.g.* 28.6% *vs.* 20.9% for female lung cancer incidence). The effects of increased smoking prevalence and age-pooling in women were therefore balanced out.

The PAFs of lung cancer incidence attributable to SHS exposure in the present study were slightly smaller than those in our previous estimates (1.3% *vs.* 1.6% for men, 8.7% *vs.* 12.6% for women) (*5*). The main reason is probably the decrease in the prevalence of SHS exposure, particularly at the workplace (men: 6.2% *vs.* 8% at home and 29.4% *vs.* 58% at workplace; women: 31.1% *vs.* 35% at home and 18.2% *vs.* 32% at workplace). Indeed, our PAF estimates were comparable to more recently published values (*32,33*). In April 2020, the revised Health Promotion Act came into force in Japan, by which indoor smoking at the workplace and in public places was partially banned. This legislative measure is expected to accelerate the decrease in SHS exposure, but the high prevalence of SHS exposure at home remains a major problem in Japan.

In men, our PAF estimates of active smoking in Japan were comparable to or larger than those in Western populations. According to recent publications, the PAF cancer incidence attributable to active smoking for men was 23.6% in United States (US) in 2014 (*34*), 17.7% in United Kingdom (UK) in 2015 (*35*), and 15.8% in Australia in 2010 (*36*) (corresponding value was 23.3% in the present study). This reflects the

higher male smoking prevalence in Japan, because the RR of lung cancer associated with active smoking was lower in Japanese than in Western populations (*e.g.* current smoking RR: 4.65 for men and 3.75 for women in Japan versus 8.96 for men and women in the UK study (*35*)). By contrast, in women, our PAF estimates of active smoking were smaller than those in Western populations (14.5% in US (*34*), 12.4% in UK (*35*), 10.1% in Australia (*36*) (corresponding value was 3.8% in the present study), reflecting the lower lung cancer RR and smaller female prevalence as well. The PAFs of active smoking reported in the Republic of Korea were comparable to our estimates (20.8% in men and 1.0% in women for cancer incidence) (*37*), probably because of similar values for RR and smoking prevalence.

The strength of this study is the representativeness of the data. The data for smoking prevalence and SHS exposure were based on national representative surveys. Most of the RRs used here were derived from the latest meta-analysis or pooled large-scale cohort studies in the Japanese populations. The selection of causally related cancers was also based on an up-to-date and comprehensive review of the literature of Japanese population.

This study has some potential limitations. First, some of the RRs we used were based on values that were not sufficiently adjusted for confounding factors (*i.e.* liver, laryngeal and kidney cancers) (*6*). In particular, the RRs of liver cancer which were unadjusted for hepatitis B and C virus infection need to be interpreted with caution. However, the pooled RRs we used were close to those reported in a study that adjusted for these infectious factors (*38*). The RR we used for SHS exposure at the workplace was also not derived from a domestic meta-analysis but based on a value reported in the U.S. Surgeon General Report (*39*). However, this comprehensive review showed that there were no substantial geographical variation in the RR of SHS at the workplace (*39*).

Second, we only included cancers that were evaluated as "causally related to tobacco smoke exposure" in comprehensive evaluation reports. There are many other cancers that may potentially have causal link to tobacco. In that sense, the PAFs presented here are conservative estimates, which could be increased by future accumulation of scientific evidence.

Third, we assumed a 10-year latency period from exposure to outcome. Although this assumption was also adopted by many recent studies of PAF estimates (*35,36,40*), latency from exposure to cancer occurrence is not well defined and could vary among cancers. We assumed that a longer lag time (15 years) resulted in larger PAF estimates for men, as stated above. Peto *et al.* proposed an alternative method that uses lung-cancer mortality as an indirect indicator of the accumulated hazards of smoking (*41*), which was adopted in the Global Bureau of Diseases Study (*1,42*). However, we previously confirmed that this difference in methodology did not lead to any substantial changes in PAF estimates (*6-8*).

Conclusion

We estimated that in Japan, 145,765 (15.2%) newly diagnosed cancer cases and 72,520 (19.6%) cancer deaths in 2015 were attributable to active smoking. For SHS exposure, 4,579 cancer cases (0.5%) and 2,667 cancer deaths (0.7%) in 2015 were attributed to SHS. This result reconfirms that tobacco is still a major cause of cancer in Japan.

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Burden of cancer attributable to consumption of alcohol in Japan in 2015

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Abstract: Alcohol can cause or contribute to the development of many non-communicable diseases, including cancer. We calculated the proportion of cancer incidence and mortality in 2015 attributable to alcohol consumption in 2005. Data on alcohol consumption, provided in *go*, a traditional Japanese alcohol measurement unit, was derived from the 2005 Japanese National Health and Nutrition Survey for each sex and age group, then converted into grams of ethanol per day. The optimal consumption of alcohol for the purpose of this study was determined to be none, based on a global assessment derived from previous observational studies that have looked at the association between alcohol consumption and cancer. Using standard formulas, population attributable fractions (PAFs) for all cancers positively associated with alcohol drinking - oral cavity, pharynx, esophagus, stomach, colorectum, liver, larynx, and female breast - were calculated for each sex and age group and aggregated to obtain the PAF among total cancer incidence and mortality. For Japan in 2015, 59,838 cases of cancer incidence and 23,929 cancer deaths were attributable to alcohol consumption. The estimated PAF for cancer incidence and mortality attributable to alcohol consumption was 6.2% and 6.5%, respectively. For both cancer incidence and mortality, the highest percentage of alcohol-attributable cancer sites was esophageal (54.0% for incidence, 52.3% for mortality). Avoidance of alcohol consumption would reduce the burden of alcohol on cancer in Japan.

***Keywords*:** cancer, alcohol, population attributable fraction, Japan

Introduction

Since 1998, alcohol consumption has been classified as a human carcinogen by the International Agency for Research on Cancer (IARC) (*1*). In the most updated review in 2010, the IARC concluded that alcohol consumption is a risk factor for cancers of the oral cavity, pharynx, larynx, esophagus, liver, colorectum, and breast (women only) (*2*). In addition to these cancer sites, the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) concluded that alcoholic drinks increase the risk of colorectal and stomach cancer in their latest report (*3*). The report also noted that there is no evidence of safe level of alcohol consumption (*3*).

Despite these established evidences, drinking patterns between countries and regions differ due to their cultural background. In this report, we examined the fraction of cancers occurring in 2015 attributable to alcohol consumption in Japan.

Materials and Methods

Cancers associated with alcohol

The IARC reconfirmed the consumption of alcohol as "group 1", carcinogenic to humans (*1,2,4,5*). For this study, we selected cancer sites associated with the consumption of alcoholic beverages that IARC reports found sufficient evidence for a positive association, and for which relative risk estimates were available. The cancer sites included in this study were oral cavity, pharynx, esophagus, stomach, colorectum, liver, larynx, and breast (women only).

Prevalence of exposure to alcohol

The latent period between 'exposure' to alcohol and the appropriate increase in risk of these cancers has not been well established. We assumed that this would be 10 years on average, and therefore examined the

effects of cancer incidence and mortality in 2015 from non-optional levels of alcohol consumption in the year 2005.

We used data from the Japanese National Health and Nutrition Survey (JNHNS) from 2005 (*6*). JNHNS targets household members aged at least one year old in all households within 300 districts (10 districts per prefecture; 15 districts for Tokyo) selected through stratified random sampling, which totaled about 5,000 households and 15,000 participants in November of 2005. The survey provides the proportions of individuals (by sex and age group) consuming different quantities of alcohol per day in *go*. In Japan, one unit of alcohol is measured by a traditional measurement, "*go*", which assumes 23g of ethanol for 180mL of sake, 10g ethanol for 30mL of whiskey or brandy, 6g ethanol for 60mL of wine, or 23g of ethanol for 633mL of beer, for ages 20 and over. Table 1 summarizes the sex- and age-group-specific proportion of alcohol drinkers (1-3 times/month or more) and average consumption amount of alcohol (g of ethanol/day) in Japanese in 2005.

Theoretical minimum risk exposure level

The optimum level of alcohol consumption was considered to be none, based on previous observational studies that looked at the association between alcohol consumption and cancer and found that cancer risk increases with increased consumption of alcohol.

Cancer incidence and mortality in Japan in 2015

Cancer incidence data in 2015 were estimated using the annual estimate of cancer incidence in 2013 by the Monitoring of Cancer Incidence in Japan (*7*). This was done using an age and period spline model, a type of model which is used for short-term projections of cancer incidence in Japan (*8*). The sex- and age-specific incidence data for target cancers were coded in accordance with the International Statistical Classification of Diseases and Related Health Problems, 10th edition (ICD-10), using morphology codes of the International Classification of Disease for Oncology, 3rd edition (ICD-O-3).

The data on cancer mortality statistics from 2015 were based on the vital statistics of Japan (*9*). We obtained sex- and age-specific mortality data by cause of death from available data sources from the Health, Labour, and Welfare Statistics Association (*10*), and used 4-digit ICD-10 codes to classify the cause of death.

Estimation of relative risks

Table 2 shows the increase in risk associated with alcohol consumption. The estimates derived from the studies listed below have been adjusted for potential major confounders.

Relative risks (RR) for esophagus, breast, and liver cancers were derived from epidemiological studies included in the WCRF/AICR's report (*3*). RR for oral, pharynx, larynx were derived from a published Japanese population-based cohort study (*11*). The RR for stomach cancer were estimated using a pooled analysis of Japanese studies (*12,13*). The RR for colorectal cancer was derived from a pooled analysis of five Japanese cohorts (*14*).

The risk for oral, pharynx, and larynx cancers was calculated in comparison to those who never drank.

Table 1. Sex- and age-group specific proportion of alcohol drinkers and average consumption amount of alcohol (g of ethanol/day) in Japanese in 2005

Age at exposure (2005)	Men		Women	
	Proportion of drinkers* (%)	Average intake (g/day) (Excess from 0 g/day)	Proportion of drinkers* (%)	Average intake (g/day) (Excess from 0 g/day)
0 - 4	0.0	0.0	0.0	0.0
5 - 9	0.0	0.0	0.0	0.0
10 - 14	0.0	0.0	0.0	0.0
15 - 19	0.0	0.0	0.0	0.0
20 - 24	60.3	15.9	52.4	10.1
25 - 29	66.2	21.1	49.0	13.0
30 - 34	68.1	31.5	52.1	14.8
35 - 39	71.9	30.4	50.8	17.3
40 - 44	75.8	33.7	49.1	16.0
45 - 49	78.7	33.9	47.5	14.5
50 - 54	79.8	34.2	41.9	15.1
55 - 59	78.7	34.2	36.4	12.8
60 - 64	75.7	31.3	31.6	12.2
65 - 69	72.3	28.6	25.4	11.0
70 - 74	70.2	24.0	19.4	7.8
≥ 75	57.9	20.2	15.0	7.8
Total	71.7	29.5	36.9	13.4

Data source: The National Health and Nutrition Survey, Japan, 2005 *Drinker: Frequency of drinking 1-3 times/month or more.

Table 2. Increase in risk associated with alcohol consumption

Cancer type	Studies	RR reference group	RR (95% CI)	Increase in risk per gram alcohol per day
Oral cavity, pharynx, larynx	Lu *et al.* (2018) (*11*)	Never	1.50 (1.02 - 2.22)	N/A
Esophagus	Ishiguro *et al.* (2009) (*24*)*	10g per day	1.34 (1.25 - 1.55)	0.02927
Stomach	Meta-analysis of six Japanese studies*	10g per day	1.03 (1.00 - 1.06)	0.00296
Liver	Ohishi *et al.* (2008) (*13*)*, Shimazu *et al.* (2012) (*12*)	10g per day	1.14 (0.90 - 1.44)	0.00677
Colorectal	Mizoue *et al.* (2008) (*14*)*	15g per day	1.07 (1.06 - 1.09)[b]	0.0131
Breast[a]	Suzuki *et al.* (2010) (*25*)*	10g per day	1.05 (0.98 - 1.14)	0.0131

*Included in the WCRF/AICR report (*3*). [a]Calculated for women only. [b]Adjusted for 10g per day. Abbreviations: RR = relative risk; CI = confidence interval; WCRF/AICR = World Cancer Research Fund, American Institute for Cancer Research

Table 3. Proportion (%) of cancer in 2015 attributable to alcohol consumption in Japan

Cancer Site (ICD-10)	Incidence			Mortality		
	Men	Women	Both sexes	Men	Women	Both sexes
Oral cavity and pharynx (C00 ─ C14)	26.8	12.9	22.5	26.6	10.5	21.9
Esophagus (C15)	58.7	28.3	54.0	57.4	26.7	52.3
Stomach (C16)	5.6	2.1	4.5	5.4	2.0	4.2
Colorectum (C18-C20)	18.1	7.2	13.4	17.3	6.6	12.4
Liver (C22)	31.9	12.7	25.2	30.8	11.8	24.3
Larynx (C32)	27.0	13.5	26.0	26.1	6.5	25.1
Breast (C50)		6.4	6.4		5.8	5.8
Total	8.3	3.5	6.2	8.8	3.0	6.5

For esophagus, breast, liver, and stomach cancers, risk was calculated based on that for 10g of ethanol intake per day. The risk of colorectal cancer was presented for 15g of ethanol intake per day, but was adjusted to that for 10g of ethanol intake per day. The increase in risk for an increase of one gram of ethanol consumption per day was calculated, based on a log-linear relationship between exposure and risk of cancer onset. The increased risk for one gram of increased ethanol consumption was calculated using the following formula:

$$Risk = exp^{[\ln(\text{risk per gram of ethanol}) \times \text{average exposure level}]}$$

Estimation of population attributable fractions (PAFs)

PAFs were calculated for each gender and age group. For cancers of the oral cavity, pharynx, and larynx, which compared the risk of ethanol consumption with never drinkers, PAFs were calculated according to the formula (*15*):

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

where P refers to the proportion of those who were drinkers in the total population.

For the remaining cancers, for which the risk was calculated based on the risk for 10g of ethanol consumption per day, PAFs were calculated using the following formula (*16*):

$$\text{PAF} = \frac{(Risk - 1)}{Risk}$$

Cancer site-specific PAF was multiplied by the number of incident cases or mortality of the site-specific cancer to obtain a site-specific number of attributable cancer incidence and mortality.

By summing these site-specific numbers of attributed cases of cancer incidence and mortality, we obtained the attributed number of total cancer incidence and mortality. Total cancer PAF was then obtained by dividing the number of attributed total cancer incidence and mortality by the number of observed total cancer incidence and mortality.

Results

In Japan in 2005, 72% of male and 37% of female adults drank alcohol 1 to 3 times per month or more. The proportion peaked at nearly 80% among men aged 45-59 and around 50% in women aged 20-44. Average daily ethanol consumption was 29.5g in men and 13.4g women (Table 1).

Table 3 summarized the estimated PAF of cancer incidence and mortality in 2015 attributed to consumption of alcohol in Japan. The estimated cancer cases attributed to alcohol consumption were 8.3% for men and 3.5% for women, or 6.2% of cancers overall,

and the estimated cancer deaths were 8.8% for men, 3.0% for women, and 6.5% overall.

Cancers of the liver (25.2%), oral cavity and pharynx, larynx, and esophagus had the highest proportion of alcohol-attributed cases (22.5% for cancers of the oral cavity and pharynx, 26.0% of the larynx, and 54.0% of esophagus). Although fractions for cancers of the stomach (4.5%), colorectum (13.4%), and breast (6.4%) were much lower, the number of cases of alcohol-attributable cancers was high. Detailed results on cancer incidence for each cancer, sex and age-group are shown in Table S1 (online data, *https://www.ghmopen.com/site/supplementaldata.html?ID=33*).

The results of cancer mortality were similar to that of cancer incidence attributable to alcohol consumption. Cancers of aero-digestive sites also accounted for highest percentages of alcohol-attributed mortality (21.9% of cancers of the oral cavity and pharynx, 25.1% of cancers of larynx, and 52.3% of cancers of the esophagus Similar to cancer incidence attributable to alcohol consumption, there were a gender difference in the mortality of aero-digestive cancers. Deaths attributable to alcohol consumption for four of the cancers for men were about twice of those attributable for women (oral cavity and pharynx: 26.6% for men, 10.5% for women; larynx: 26.1% for men, 11.8% for women; esophagus: 57.4% for men, 26.7% for women; and stomach: 5.4% for men, 2.0% for women). Detail results on cancer mortality for each cancer, sex and age-group were shown in Table S2 (online data, *https://www.ghmopen.com/site/supplementaldata.html?ID=33*).

Discussion

In this study, we estimated that 59,838 (6.2%) newly diagnosed cancer cases and 23,929 (6.5%) cancer deaths in 2015 could be attributed to consumption of alcohol from 2005 in Japan. PAFs were highest for the oral cavity and pharynx, larynx, and esophagus, for both cancer incidence and mortality.

Our results are comparable to those of previous studies. A previous Japanese estimate for 2005 showed cancer incidence and mortality attributable to alcohol consumption of 6.3% and 6.2%, respectively (*17*). A Canadian study (*18*) published in 2019 found 5.2% of alcohol-associated cancer cases were attributable to alcohol consumption. A United Kingdom study (*19*) published in 2011 showed 4.0% of alcohol-associated cancer cases were attributable to alcohol consumption. These numbers are lower than those of our study. The difference in findings between Japan and Western countries could be explained in part by genetic differences. Mutation of the aldehyde dehydrogenase 2 gene (*ALDH2*) is one of the most common hereditary disorders, affecting over 8% of the world population (*20*). Prevalence is highest in East Asians, including Japanese (*21,22*). *ALDH2* deficiency leads to greater exposure to acetaldehyde, a possible carcinogenic metabolite of alcohol (*23*). This genetic difference may have resulted in the stronger association between alcohol consumption and cancer we found (*14*).

There are several limitations to the study. The calculation of PAF depends on the accuracy of self-reported alcohol consumption. Further, the number of recently published epidemiological studies on alcohol consumption and cancer in Japan from which risk estimates could be obtained is limited. Therefore, it is possible that our PAF estimate may have been underestimated.

Conclusion

Alcohol consumption was attributed to 6.2% of cancer incidence, and 6.5% of cancer mortality, respectively. The results of this study may provide useful evidence for reducing the cancer burden in Japan.

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Burden of cancer attributable to excess bodyweight and physical inactivity in Japan in 2015

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Abstract: Overweight and obesity are known contributors to many non-communicable diseases, including cancer, and affect over one-tenth of the global population. One way to maintain a healthy weight and reduce the risk for cancer is through increased physical activity. We estimated the fraction of cancer incidence and mortality in 2015 attributable to excess bodyweight as well as lack of physical activity among the Japanese population. The optimal body-mass index (BMI) for the purposes of this study was determined to be less than 23 kg/m^2. Mean BMI for each sex and age group was calculated using measured weight and height data extracted from the 2005 Japanese National Health and Nutrition Survey (JNHNS). For the data on physical activity, we extracted the answers from the same survey from a question regarding whether the respondent did regular exercise. Population attributable fractions (PAFs) for each cancer positively associated with excess bodyweight - esophageal adenocarcinoma, stomach (cardia), colorectum, liver, gallbladder, pancreas, female breast (pre- and post- menopausal), ovary, endometrium, advanced prostate and kidney - and for those positively associated with physical inactivity - colorectum, female breast and endometrium - were calculated for each sex and age group and aggregated to obtain the PAF among total cancer incidence and mortality. Excess bodyweight was attributable to 0.7% of cancer incidence and mortality, while lack of regular exercise was attributable to 1.3% of cancer incidence and 0.8% of cancer mortality. Around 1% of cancer incidence and mortality in Japan in 2015 are attributable to excess bodyweight and physical inactivity.

***Keywords*:** cancer, excess bodyweight, physical inactivity, population attributable fraction, Japan

Introduction

The World Health Organization (WHO) defines overweight (body-mass index (BMI) greater than or equal to 25) and obesity (BMI 30 or over) as abnormal or excessive fat accumulation that may impair health (*1*). Since 1975, worldwide obesity has nearly tripled. In 2016, more than 1.9 billion adults aged 18 years or over were overweight- of these, over 650 million (13% of the global population) were obese (*1*). Overweight and obesity are known to be major risk factors for non-communicable diseases (*1*). In 2016, the International Agency for Research on Cancer (IARC) reaffirmed that overweight and obesity increase risk for cancers of the colon, rectum, gastric cardia, liver, gallbladder, pancreas, kidney, and esophageal adenocarcinoma, with positive dose-response relationships (*2*). The same report also noted positive associations between adult obesity and postmenopausal breast cancer and endometrial cancer (*2*).

The fundamental cause of excess bodyweight is an energy imbalance between calories consumed and calories expended. One of the ways to maintain a healthy bodyweight is through exercise. Regular physical activity is essential for optimal health. Exercising regularly has significant benefits, even at a modest level, including lower cancer incidence (*3*). The World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR) have reported that there is a probable association between physical inactivity and risk of cancers of colon, breast and endometrium (*3*).

Here, we estimated the fraction of cancer incidence and mortality in 2015 attributable to excess bodyweight and physical inactivity in the Japanese population.

Materials and Methods

Cancers associated with excess bodyweight and physical inactivity

For the purposes of this study, we selected cancer sites associated with overweight and obesity, and physical activity, for which IARC or WCRF/AICR found sufficient evidence to indicate a positive association, and with data available on relative risk. The cancer sites included in this study are the esophagus (adenocarcinoma), stomach (cardia), colorectum, liver, gallbladder, pancreas, breast, endometrium, ovary, prostate (advanced), and kidney for excess bodyweight; and colorectum, breast, and endometrium for physical inactivity.

Prevalence of excess bodyweight and physical inactivity estimates

Data on the prevalence of excess bodyweight were obtained from the Japanese National Health and Nutrition Survey (JNHNS) from 2005 (*4*). This survey reports mean BMI by age group and sex. BMI was calculated using measured weight and height in kg/m^2. Table 1 shows the sex- and age-group-specific prevalence of excess bodyweight in Japanese derived from the 2005 JNHNS. In 2005, mean BMI slightly exceeded 23 in men aged between 30 and 70 and women aged between 55 and 74.

Similarly, we used data from the 2005 JNHNS to determine physical activity level in the Japanese population. The survey provides data on the proportion of people (by sex and age group) who answered "yes" to a question regarding whether they do regular exercise. Table 2 shows the sex- and age-group-specific prevalence derived from 2005 JNHNS of those who do regular exercise in Japanese. Among men, the proportion who answered yes to whether they got regular exercise was highest in the 70-74 years age group, but in the 65-69 years age group among women.

The duration of the latent period between 'exposure' to excess bodyweight, physical inactivity and an appropriate increase in the risk of cancers has not been well established. We assumed that 10 years would be sufficient time for latency between exposure and outcome, and therefore examined the effects of cancers occurring in 2015 due to sub-optimal bodyweight and physical activity in the year 2005.

Theoretical minimum risk exposure level

The optimal BMI in Japan for the purposes of this study was determined to be less than 23 kg/m^2. Because mean BMI across all sex- and age-specific categories was below 25 kg/m^2, the PAF of excess body weight would be 0 if the definition of excess overweight were BMI ≥ 25 kg/m^2. Moreover, there has been controversy when applying international criteria for obesity to Asian populations; in response, the WHO expert consultation recommended a new overweight category of BMI ≥ 23 kg/m^2 and obesity of BMI ≥ 25 kg/m^2 (*5*). Accordingly, as a practical solution to estimating the PAF of excess bodyweight in a Japanese population, we defined the optimal BMI as less than 23 kg/m^2. The optimal amount of physical exercise in Japan for the purposes of this study was defined as regular exercise.

Cancer incidence and mortality in Japan in 2015

Cancer incidence data in 2015 were estimated using the annual estimate of cancer incidence in 2013 by the Monitoring of Cancer Incidence in Japan (*6*) by an age and period spline model. This type of model is used for short-term projections of cancer incidence in Japan (*7*).

Table 1. Sex- and age-group-specific prevalence of excess bodyweight in Japanese in 2005

Men			Women		
Age at exposure (2005)	Average body-mass index (BMI) (kg/m^2)	Excess from BMI 23 kg/m^2	Age at exposure (2005)	Average body-mass index (BMI) (kg/m^2)	Excess from BMI 23 kg/m^2
0 - 4	16.0	0	0 - 4	15.8	0
5 - 9	16.2	0	5 - 9	15.9	0
10 - 14	18.6	0	10 - 14	18.6	0
15 - 19	21.3	0	15 - 19	20.9	0
20 - 24	22.0	0	20 - 24	20.4	0
25 - 29	22.9	0	25 - 29	20.6	0
30 - 34	23.4	1.43	30 - 34	21.1	0
35 - 39	23.7	0.73	35 - 39	21.5	0
40 - 44	24.0	1.01	40 - 44	22.2	0
45 - 49	24.1	1.05	45 - 49	22.6	0
50 - 54	23.9	0.90	50 - 54	22.9	0
55 - 59	23.6	0.61	55 - 59	23.1	0.10
60 - 64	23.8	0.77	60 - 64	23.3	0.29
65 - 69	23.8	0.83	65 - 69	23.6	0.57
70 - 74	23.5	0.49	70 - 74	23.2	0.21
≥ 75	22.7	0	≥ 75	22.9	0

Data source: The National Health and Nutrition Survey, Japan, 2005.

Table 2. Sex- and age-group-specific prevalence of Japanese who do regular exercise, 2005

Men		Women	
Age at exposure (2005)	Proportion of those who answered "yes" to regular exercise in the population (%)	Age at exposure (2005)	Proportion of those who answered "yes" to regular exercise in the population (%)
0 - 4	0.0	0 - 4	0.0
5 - 9	0.0	5 - 9	0.0
10 - 14	0.0	10 - 14	0.0
15 - 19	0.0	15 - 19	0.0
20 - 24	24.5	20 - 24	17.6
25 - 29	19.9	25 - 29	17.3
30 - 34	15.4	30 - 34	14.2
35 - 39	18.0	35 - 39	17.3
40 - 44	19.2	40 - 44	17.0
45 - 49	20.7	45 - 49	25.4
50 - 54	20.4	50 - 54	26.9
55 - 59	24.9	55 - 59	30.6
60 - 64	38.8	60 - 64	37.2
65 - 69	46.4	65 - 69	40.2
70 - 74	46.7	70 - 74	38.7
≥ 75	38.0	≥ 75	28.4

Data source: The National Health and Nutrition Survey, Japan, 2005.

The sex- and age-specific incidence data for the target cancers were coded in accordance with the International Statistical Classification of Diseases and Related Health Problems, 10th edition (ICD-10), using the morphology codes of the International Classification of Disease for Oncology, 3rd edition (ICD-O-3).

The statistical data on cancer mortality from 2015 were based on the vital statistics of Japan (*8*). We obtained sex- and age-specific mortality data by cause of death from an available data source provided by the Health, Labour, and Welfare Statistics Association (*9*). Similarly to the cancer incidence data, 4-digit ICD-10 codes were used to classify the cause of death.

Due to a lack of information in these statistics, we regarded the number of case of esophagus adenocarcinoma as 5% of total esophageal cancer. For prostate cancer, 30% of prostate cancer incidence and all for prostate cancer mortality were regarded as advanced cancer.

Estimation of relative risks

The relative risk (RR) estimates associated with excess weight (BMI ≥ 23 kg/m^2) and physical activity are shown in Tables 3 and 4, respectively. We prioritized meta-analyses or pooled analyses published for Japanese populations, followed by Asian populations, then studies from other nations. RRs from our own meta-analyses or a single study were used if there was not enough evidence or if no preceding meta-analysis was available. If no Japanese data were available, WCRF/AICR's summary RR was used.

For BMI, RRs for esophageal, gastric cardia, kidney, gallbladder, liver, prostate, colorectal, and post-menopausal breast cancers were derived from epidemiological studies included in the WCRF/AICR reports (*3*). For the risk of ovarian cancer, a Japanese study (*10*) published in 2012 was used as a reference. For endometrial cancer, the summary RR of a Japanese study included in the WCRF/AICR (*11*) and a study published in 2019 (*12*) was used. For pancreatic cancer, the results of a pooled analysis of nine Japanese studies was used (*13*).

Increase in risk for a 1-unit increase in BMI was calculated based on the assumption that the relationship between exposure and risk factor is log-linear. Accordingly, the following equation was used:

$$Risk = exp^{[\ln(\text{risk per 1 BMI unit})\times(\text{Excess BMI}-23)]}$$

For physical activity, many previous studies that looked at the effect of physical activity on cancer risk presented their results in categories of activity (such as high/medium/low, or in quantiles). In this study, consistent with the available data, we categorized the population into two - those who do regular exercise (three or more days/week for breast cancer; three or more hours/day for colorectal cancer; and three or more times/week for endometrial cancer) and those who do not. The RR for all of cancer sites (post-menopausal breast cancer, colorectal, and endometrial (*14*)) were derived from the WCRF/AICR (*3*).

Estimation of population fractions (PAFs)

For excess bodyweight, PAFs were calculated for each sex and age group according to the formula (*15*):

$$\text{PAF} = \frac{(Risk - 1)}{Risk}$$

Table 3. Relative risk associated with overweight and obesity

Cancer type	Study	BMI unit for calculated risk (kg/m^2)	RR (95% CI)
Esophageal adenocarcinoma[a]	Summary RR from WCRF-CUP (*3*)	5	1.48 (1.35 - 1.62)
Cardia gastric cancer[**]	Kuriyama *et al.* (2005) (*11*)[*]	5	1.41 (0.85 - 2.34)
Kidney cancer	Summary RR of three Japanese studies[*] (*11,23,24*)	5	1.35 (1.02 - 1.79)
Gallbladder cancer	Summary RR of three Japanese studies[*] (*11,24,25*)	5	1.30 (0.86 - 1.96)
Liver cancer	Summary RR of four Japanese studies[*] (*11,24,26,27*)	5	1.36 (0.95 - 1.93)
Pancreas	Koyanagi *et al.* (2018) (*13*)	1	1.00 (0.95-1.05)
Advanced prostate cancer[c]	Summary RR of two Japanese studies[*] (*24,28*)	5	1.44 (1.07 - 1.92)
Ovarian cancer[d]	Weiderpass *et al.* (2012) (*10*)	1	1.00 (0.94 - 1.08)
Endometrial cancer[d]	Summary RR of Kuriyama *et al.* (2005) (*11*)[*] and Kawachi *et al.* (2019) (*12*)	5	1.39 (1.13 - 1.70)
Post-menopausal breast cancer	Wada *et al.* (2014) (*29*)[*]	5	1.28 (1.16 - 1.40)
Colorectal cancer	Summary RR of Yamamoto *et al.* (2010) (*30*)[*] and Matsuo *et al.* (2012) (*31*)	5	1.24 (1.20 - 1.29)

[*]Included in WCRF/AICR. [a]Considered as 5% of all esophageal cancer. [b]Calculated by excluding unknown cases. [c]Calculated for men only; all death cases are considered as advanced. [d]Calculated for women only. Abbreviations: BMI = body mass index; RR = relative risk; CI = confidence interval; WCRF/AICR = World Cancer Research Fund, American Institute for Cancer Research.

Table 4. Relative risk associated with physical activity

Cancer type	Study	Reference group	Decrease in risk due to physical activity
Breast	Suzuki *et al.* (2011) (32)[*]	≥ 3 days/week	0.83 (0.64 - 1.45)
Colorectal	Lee *et al.* (2007) (33)[*]		
Men		≥ 3 hours/day	0.82 (0.65 - 1.05)
Women		≥ 3 hours/day	1.06 (0.78 - 1.45)
Endometrial[a]	Hirose *et al.* (1996) (34)[*]	≥ 3 times/week	0.60 (0.38 - 0.93)

[*]Included in WCRF/AICR. [a]Calculated for women only. Abbreviations: RR = relative risk; CI = confidence interval; WCRF/AICR= World Cancer Research Fund, American Institute for Cancer Research.

For physical inactivity, PAFs were calculated using the formula (*16*):

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

where P refers to the proportion of those who are physically inactive in the total population.

By summing these site-specific attributed numbers of cancer incidence and mortality, we obtained the attributed number of total cancer incidence and mortality. Total cancer PAF was then obtained by dividing the number of attributed total cancer incidence and mortality by the number of observed total cancer incidence and mortality.

Results

The estimated PAF of cancer incidence and mortality in 2015 attributed to excess bodyweight and lack of physical activity is summarized in Table 5.

Excess bodyweight: For cancer incidence, the site with the highest PAF value was esophageal adenocarcinoma for men (5.5%) and liver for women (1.2%). For cancer mortality, the site with the highest PAF attributed to overweight was esophageal adenocarcinoma for both men and women (5.0% for men, 1.2% for women). In total, overweight was attributed to 0.7% of all cancer incidence and mortality (1.0% in men and 0.3% in women).

Physical inactivity: Physical inactivity attributed the most to the cancer incidence of colorectal for men (6.8%) and endometrium for women (14.7%). The trend remained the same for cancer mortality, although the PAF was slightly increased for both sexes (7.2% of colorectal cancer for men, and 16.9% of endometrium cancer for women). In total, physical inactivity was attributed to 1.3% of all cancer incidence (1.0% for men, 1.6% for women) and 0.8% of cancer mortality (0.9% for men, 0.8% for women).

Detailed results for each cancer, sex, and age-group are shown for excess bodyweight in Tables S1-S2 (online data, *https://www.ghmopen.com/site/supplementaldata.html?ID=34*) and for lack of physical activity in Tables S3-S4 (online data, *https://www.ghmopen.com/site/supplementaldata.html?ID=34*)

Discussion

Several previous estimates of the fraction of cancer in Japan attributable to excess bodyweight and physical inactivity have been published. In 2005, Kuriyama *et al.* (*11*) reported PAFs attributable to overweight and

Table 5. Proportion (%) of cancer in 2015 attributable to excess bodyweight (Body-mass index (BMI) ≥ 23 kg/m^2) and physical inactivity in Japan

Variables	Incidence			Mortality		
	Men	Women	Both sexes	Men	Women	Both sexes
Excess bodyweight (Body-mass index (BMI) ≥ 23 kg/m^2)						
Esophagus (C15)	0.4	0.1	0.3	0.2	0.1	0.2
Esophagus adenocarcinoma (C15)	5.5	1.2		5.0	1.2	
Stomach (C16)	0.4	0.1	0.3	1.1	0.2	0.8
Cardia gastric cancer (C16.0)	4.6	1.2		3.8	0.9	
Colorectum (C18-C20)	2.8	0.7	1.9	2.5	0.6	1.6
Liver (C22)	4.0	1.2	3.0	3.6	1.1	2.8
Gallbladder (C23)	3.1	0.9	1.8	2.7	0.8	1.6
Pancreas (C25)	0.0	0.0	0.0	0.0	0.0	0.0
Breast (C50)		0.4	0.4		0.6	0.6
Endometrium (C54)		0.6	0.6		1.0	1.0
Ovary (C56)		0.0	0.0		0.0	0.0
Advanced prostate (C61)	1.4		1.4	3.0		3.0
Kidney (C64)	3.1	1.0	2.5	2.5	0.9	1.9
Total	1.0	0.3	0.7	1.0	0.3	0.7
Physical inactivity						
Colorectum (C18-C20)	6.8	0.0	3.9	7.2	0.0	3.9
Breast (C50)		5.0	5.0		5.6	5.6
Endometrium (C54)		14.7	14.7		16.9	16.9
Total	1.0	1.6	1.3	0.9	0.8	0.8

obesity of -0.2% for men and 4.5% for women. In 2012, Inoue *et al.* (*17*) attributed overweight (BMI ≥ 25 kg/m^2) to 0.8% of cancer incidence and 0.5% of cancer mortality among men, and 1.6% and 1.1% among women. The same study found that physical inactivity, defined as the lack of three metabolic equivalents (METs) per day, attributed 0.6% of cancer incidence and 0.4% of cancer mortality in men, and 0.4% and 0.3% in women. These numbers slightly differ to our findings, namely that PAFs were lower in men than women, due to the different definition of physical inactivity and data source between these estimates.

In an international setting, a recent report from Canada (*18*) calculated that country's current burden of cancer attributable to excess bodyweight (BMI ≥ 25 kg/m^2) to be 3.1%. Brown *et al.* estimated that overweight and obesity were attributable to 6.3% of all cancers in the United Kingdom (UK) (*19*). The greater number of attributable cases in Europe and Northern America may be explained by the larger proportion of overweight and obesity in these populations. In the UK, 36% and 28% of the population are considered to be overweight and obese, respectively, in 2019 (*20*); while in Canada, over 61% were overweight or obese in 2015 (*21*). On the other hand, the prevalence of obesity among Japanese adults in 2018 is 3.8% (4.1% in men and 3.6% in women) (*22*), suggesting a possible gap in the obesity burden between Japan and Western countries. According to 2018 National Health and Nutrition Survey (*22*), the prevalence of overweight and obesity among the Japanese population has not changed statistically in the past decade. As long as Japan can maintain the current trend, the cancer burden attributable to excess bodyweight will continue to be marginal. Although physical inactivity was associated with an increase of certain types of cancer, the overall contribution was small, perhaps due to insufficient exposure level. Furthermore, lifestyle factors such as physical inactivity are associated with other factors such as poor diet and high bodyweight. Given that most cancers are have a multifactorial etiology, a multivariate estimation of the PAF would provide a better estimation of the burden.

There are several limitations to this study. Our cut-off for excess bodyweight was defined as a BMI of 23 and over, due to practicality of estimation for Japanese. This cut-off differs to the WHO overweight standard (BMI of 25 and over), which is often used in studies from other nations. The PAF of physical inactivity was calculated using a binominal category only, and the definition of regular exercise differed for each cancer site. This prevented us from being able to directly compare our results to previous studies. As evidence was insufficient, some of the RRs used for this study were not derived from a Japanese population. Additionally, many RRs used to calculate PAF were derived from a single cohort study. This may have led to over- or underestimation of the risk. When more data is available, it will be necessary to update the evidence by re-calculating these PAFs using RRs from meta-analyses or pooled analyses.

Despite the limitations listed above, these estimates have major implications for Japan's national health policy for cancer prevention and control strategies. Although the current Japanese obesity rate is low, policymakers and public health agencies must be prepared to intervene if necessary.

Conclusion

Our analysis provides evidence for the current burden of cancer attributable to excess bodyweight and physical inactivity. Excess bodyweight and physical inactivity contributed to 0.7% and 1.3% of cancer incidence, and 0.7% and 0.8% of cancer mortality, respectively. The results of this study may provide useful evidence for appropriately reducing the cancer burden in Japan.

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Burden of cancer attributable to infection in Japan in 2015

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Abstract: Population attributable fraction (PAF) offers a means to quantify cancer burden that is attributable to a specific etiological factor. To better characterize the current cancer burden due to infection in the Japanese population, we estimated the PAF for cancer incidence and mortality in 2015 that could be attributable to infectious agents, including Helicobacter pylori (*H. pylori*), Hepatitis B and C (HBV/HCV), Human papillomavirus virus (HPV), Epstein-Barr virus, and human T-lymphotropic virus type 1. We estimated the PAFs for each infectious agent on the basis of representative data on prevalence and risk-outcome associations assuming a latency period of 10 years. Overall, 16.6% of cancer cases in 2015 in Japan were attributable to the infectious agents included in this analysis. The estimated PAF was slightly higher in men (18.1%) than in women (14.7%). The highest proportion of cancer deaths attributable to infectious agents was observed for *H. pylori* infection, followed by HBV/HCV, and HPV infection. Our findings corroborated with previous estimates that *H. pylori* and HBV/HCV infections were the two most important infectious agents in the Japanese population. Strategies focusing on eradication of infectious agents among infected individuals or primary prevention through vaccination could decrease the burden of infection-related cancers.

***Keywords*:** cancer, infection, population attributable fraction, Japan

Introduction

Cancer became the leading cause of death in Japan in 1981. The number of total cancer deaths increased continuously thereafter, in parallel with aging of the population, to reach 370,346 deaths in 2016. Lung, colorectal, stomach, pancreas, and liver cancers have constituted the five leading causes of cancer death in recent years (*1*). This mortality pattern reflects the high burden of cancers of the digestive system in the Japanese population.

Infectious agents are known to play a role in cancer etiology. The International Agency for Research on Cancer (IARC) has classified at least six viruses as Group 1, *ie.* carcinogenic in humans, namely Epstein-Barr virus (EBV), Kaposi sarcoma-associated herpesvirus/human herpesvirus 8 (KSHV/HHV8), Human papillomavirus (HPV), Hepatitis B virus (HBV), Hepatitis C virus (HCV), human T-lymphotropic virus type 1 (HTLV-1) and *Helicobacter pylori* (*H. pylori*). Persistent infection with these pathogens is causally linked to several types of cancer, including liver, stomach, cervical cancers (*2*).

Population attributable fraction (PAF), which is calculated based on prevalence estimates and relative risk (RR) for exposure-outcome associations, provides a quantitative appraisal of the impact of etiological factors on cancer incidence and mortality (*3*). In the case of infectious agents, PAF indicates the proportion of cancer cases or deaths that would not have occurred if no one in the population had been infected. An estimated 13% of global cancer incidence was attributable to infectious agents in 2018, with PAFs varying according to geographic region and development status (*4*). In a 2005 PAF estimation in Japan, tobacco smoking had the highest PAF (30% for incidence and 35% for mortality) in men, followed by infectious agents (23% for incidence and 23% for mortality) (*5*), whereas infectious agents had the highest PAF (18% for incidence and 19% for mortality) in women.

The validity of PAF estimates depends on prevalence estimates and relative risk for exposure-outcome associations, which may change over time. In particular, the prevalence of *H. pylori* infection in asymptomatic individuals in Japan has markedly changed over a short

period of time (*6*). To better characterize the current cancer burden due to infection, we estimated the PAF of cancer incidence and mortality in 2015 that was attributable to selected infectious agents in the Japanese population.

Material and Methods

Cancers associated with infection

The target cancers and infectious agents were selected based on the assessment of the carcinogenicity of biological agents by the IARC Monograph Working Group (*2*). Cancers included in the present study were gastric, gastric non-Hodgkin lymphoma (NHL), liver, cervix uteri, penis, vulva, anus, oral cavity, oropharynx, nasopharynx, Birkitt lymphoma, and adult T-cell lymphoma (ATL). These were selected because they each had sufficient evidence of a supporting role of infectious agents in their causation. Parasitic agent (*Clonorchis sinensis, Opisthorchis viverrini, and Schistosoma haematobium*)- and human immunodeficiency (HIV)-related cancers were excluded because exposure to these pathogens in the Japanese population is rare.

Cancer incidence and mortality in Japan in 2015

Cancer incidence data in 2015 were estimated using the annual estimate of cancer incidence in 2013 by the Monitoring of Cancer Incidence in Japan (MCIJ) (*7*), as determined by an age and period spline model. These models are used for short-term projection of cancer incidence in Japan (*8*). The sex- and age-specific incidence data for target cancers were coded in accordance with the International Statistical Classification of Diseases and Related Health Problems, 10th edition (ICD-10), using the morphology code of the International Classification of Disease for Oncology, 3rd edition (ICD-O-3).

The data on cancer mortality from 2015 were based on the vital statistics of Japan (*1*). We obtained sex- and age-specific mortality data by cause of death from an available data source provided by the Health, Labour, and Welfare Statistics Association (*9*). As with the cancer incidence data, 4-digit ICD-10 codes were used to classify cause of death.

Prevalence of exposures

Assuming a latency period of 10 years between infection and cancer occurrence, we extracted the best-available data on the prevalence of infectious agents in the Japanese population in 2005. Because of a clear cohort effect observed for the prevalence of *H. pylori* infection, we previously estimated prevalence by birth year from 1908 to 2003 in a systematic review and meta-regression analysis of studies conducted in Japan (*6*). Based on these results, we obtained the corresponding prevalence data by sex and 5-year age group for the year 2005. To capture representative data on the prevalence of HBV and HCV in the general population, we referred to the pooled prevalences of HBsAg and anti-HCV by sex and birth year that were estimated by combining three large cohorts in Japan: first-time blood donors, participants in screening programs initiated by local governments, and individuals who underwent a comprehensive medical checkup (Ningen dock) (*10*). Estimated prevalence by birth year was converted to prevalence of HBV or HCV by 5-year age group in 2005. Because prevalence data were not available for individuals born before 1930 or after 1986, we assumed that these individuals had the same estimated prevalence as the next or preceding birth cohort (1931-1935 and 1981-1985), respectively. As with previous studies, the prevalence of HPV infection was assumed to be 100%, based on the fact that HPV DNA virus can be detected in all cervical cancer cases (*4,11*). For EBV and HTLV, we quoted the prevalence data from previously published literature (*4*), because very few data were available for Japanese subjects.

Estimation of relative risk

The majority of previous PAF studies used an RR of 5.9 for the association between *H. pylori* and non-cardia gastric cancer, as determined by a previous meta-analysis involving 12 case-control studies on this topic (*12*). However, this risk estimate might be an underestimation given that several studies using more sensitive measurement methods, such as western blot, demonstrated much stronger associations, with odds ratios (ORs) ranging from 10.6 to 21.4 (*13*). Furthermore, in a 2015 meta-analysis of the *H. pylori*-stomach cancer association in Japanese subjects, the RR for individuals who had both *H. pylori* infection and gastric atrophy was 15-fold greater than that of those with neither *H. pylori* infection nor gastric atrophy (*14*). Therefore, we used an RR of 15 for the calculation of PAF for both men and women. For gastric cardia cancer, we adopted an RR of 2.0, obtained from a meta-analysis of studies conducted in Asian countries, including Japan (*15*).

Concerning the RR of liver cancer associated with HBV or HCV infection, no data from meta-analyses of studies involving Japanese are yet available. We therefore adopted results from the Japan Public Health Center-based Prospective Study, a nationally representative cohort study. RR was 35.8 (95% CI: 20.4-62.7) for HCV-infected subjects and 16.1 (95% CI: 7.6-33.9) for HBV-infected subjects. These estimates were comparable to those reported in a 2015 meta-analysis which showed an OR of 45.3 (95% CI: 25.4-80.6) for HCV infection and 38.9 (95% CI: 19.8-38.4) for HBV infection (*16*).

With respect to RR estimates for EBV and HTLV-1, we adopted the corresponding data from a synthesis

analysis of the global burden of cancer attributable to infections in 2012 (*4*).

Estimation of PAF

For *H. pylori*, HBV, and HCV, PAF was calculated using Levin's formula (*4*):

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

where *RR* is relative risk and *P* indicates the prevalence of infectious agents in the general population.

Regarding the contribution of HTLV-1 to adult T-cell lymphoma and the contribution of HPV to cervical cancer, infection is thought to be necessary for carcinogenesis, and thus the PAF was assumed to be 100%; all of these cancers could be attributed to persistent infections among exposed subjects (*4*). For other HPV-related cancer sites and EBV-related cancers, PAF was calculated using the prevalence of each infectious agent in cases only and RRs associated with the infection (*4*):

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

where *Pc* is prevalence among cases.

The number of cancer incidence or mortality in 2015 attributable to a single infectious agent was calculated by multiplying total cancer incidence or mortality in that year by PAF.

Results

Table 1 lists the prevalence of *H. pylori* and HBV/HCV infections by sex and 5-year age group in the general population in 2005. Notably, prevalence increased with age for both infections.

Table 2 shows the PAFs of cancer incidence and mortality attributable to infectious agents. HIV was not included in the present study because of a lack of relevant data. Overall, we estimated that 16.6% of cancer incidence and 17.7% of cancer mortality in 2015 in Japan were attributable to infectious agents. The PAF estimates were slightly higher in men than in women for both cancer incidence (18.1% *vs.* 14.7%) and mortality (18.5% *vs.* 16.5%). Among infection-induced cancers, the PAF estimates for cancer incidence ranged from 4.3-100% in men, with the highest PAF noted for HTLV-1 (100% for ATL), followed by *H. pylori* (89% for stomach non-cardia cancer), HPV (88% for anal cancer), and EBV (80% for nasopharynx cancer). In women, the PAF estimates ranged from 4.3-100%, with the highest PAFs observed for HPV (100% for cervical cancer and 88% for anal cancer), followed by *H. pylori* (90% for stomach non-cardia cancer) and EBV (80% for nasopharynx cancer) (Table 2) (Table S1 and S3, online data, *https://www.ghmopen.com/site/supplementaldata.html?ID=35*). Similar PAF estimates were obtained for cancer mortality (Tables 2), (Table S2 and S4, online data, *https://www.ghmopen.com/site/supplementaldata.html?ID=35*).

For site-specific cancers, the number of cancer incidence attributable to infection was highest for stomach cancer, followed by liver cancer. Among infectious agents, *H. pylori* contributed the largest proportion of attributable cancer incidence, accounting for approximately 12.0% (14.3% in men and 8.9% in women) of all incident cases in Japan in 2015 (Table S1, online data, *https://www.ghmopen.com/site/supplementaldata.html?ID=35*). HBV and HCV contributed 2.8% (3.1% in men and 2.4% in women) of attributable cancer incident cases (Table S3, online data, *https://www.ghmopen.com/site/supplementaldata.html?ID=35*). HPV contributed 1.5% of cancer cases in

Table 1. Estimated prevalence for major infectious agents by sex and 5-year age group in the Japanese population in 2005

Age at exposure (2005)	*H. pylori*	HBV	HCV
Men			
0 - 4	5.7	0.3	0.1
5 - 9	8.0	0.3	0.1
10 - 14	13.0	0.3	0.1
15 - 19	17.4	0.3	0.1
20 - 24	22.0	0.3	0.1
25 - 29	26.4	0.5	0.2
30 - 34	31.4	0.7	0.3
35 - 39	37.6	0.9	0.5
40 - 44	44.7	1.1	1.0
45 - 49	51.7	1.3	1.2
50 - 54	56.6	1.4	1.2
55 - 59	59.9	1.5	1.5
60 - 64	62.5	1.5	1.9
65 - 69	65.0	1.2	2.7
70 - 74	66.8	1.0	4.9
≥ 75	67.5	1.0	4.9
Women			
0 - 4	5.7	0.2	0.2
5 - 9	8.0	0.2	0.2
10 - 14	13.0	0.2	0.2
15 - 19	17.4	0.2	0.2
20 - 24	22.0	0.2	0.2
25 - 29	26.4	0.4	0.2
30 - 34	31.4	0.6	0.3
35 - 39	37.6	0.6	0.5
40 - 44	44.7	0.7	0.8
45 - 49	51.7	0.9	1.0
50 - 54	56.6	1.1	1.2
55 - 59	59.9	1.3	1.5
60 - 64	62.5	1.3	2.0
65 - 69	65.0	1.1	2.9
70 - 74	66.8	1.2	4.5
≥ 75	67.5	1.2	4.5

Abbreviations: *H. pylori* = *helicobacter pylori*; HBV = hepatitis B virus; HCV = hepatitis C virus.

Table 2. PAF of cancer incidence and mortality attributable to infectious agents in Japan in 2015

Agent	Cancer site	ICD-10	Prevalence in cases (PAF)	Obs. cases	Attrib. cases	Obs. deaths	Attrib. deaths
Men							
H. pylori	Stomach cancer	C16	-	91,883	78,078	30,809	27,009
	Gastric NHL	5% of C82-C85, C96	74	760	561	328	243
HBV/HCV	Liver cancer	C22	-	28,222	16,823	19,008	11,922
HPV	Penis	C60	51	412	210	141	72
	Anus	C21	88	521	458	209	183
	Oral cavity	C02-C06	4.3	6,409	276	1,844	79
	Oropharynx	C01, C09-C10	46	2,688	1,236	824	379
EBV	Nasopharynx	C11	80	581	465	224	179
	Birkitt Lymphoma	C837	30	170	51	36	11
	Hodgkin Lymphoma	C81	56	805	444	102	57
HTLV-1	ATL	C915	100	912	879	446	446
Total				549,241	99,481	219,508	40,580
% of cancers					18.1		18.5
Women							
H. pylori	Stomach cancer	C16	-	42,203	35,822	15,870	14,050
	Gastric NHL	5% of C82-C85, C96	74	629	464	257	190
HBV/HCV	Liver cancer	C22	-	15,087	9,663	9,881	6,714
HPV	Cervix uteri	C53	100	11,253	11,253	2813	2,813
	Vulva	C51	48	867	416	262	126
	Vagina	C52	78	363	279	151	118
	Anus	C21	88	472	415	202	178
	Oral cavity	C02-C06	4.3	4,544	195	1,467	63
	Oropharynx	C01, C09-C10	46	514	236	169	78
EBV	Nasopharynx	C11	80	277	222	75	60
	Birkitt Lymphoma	C837	30	138	41	19	6
	Hodgkin Lymphoma	C81	56	446	249	58	32
HTLV-1	ATL	C915	100	663	638	506	506
Total				408,572	59,893	150,838	24,935
% of all cancers					14.7		16.5
Both sexes							
Total				957,813	159,374	370,346	65,515
% of all cancers					16.6		17.7

women, while other infectious agents, such as EBV and HTLV, contributed less than 1% of attributable cancer incident cases.

Discussion

Based on the best available data, we estimated that 16.6% of cancer incident cases were attributable to six infectious agents in Japan in 2015. Unlike other developed countries, in which infection contributes to only a small proportion of cancer etiology (*3,4,17*), infectious agents, particularly *H. pylori* and HBV/HCV, are still responsible for a high proportion of cancer burden among some Eastern Asian countries, including Japan (*18*).

The overall PAF estimate in the present study was slightly lower than that reported for 2005 in an earlier study (*5*). One possible reason is the difference in prevalence data used to estimate PAF. The earlier study used the prevalence of *H. pylori* and HBV/HCV infections in cases. However, given the dynamic changes in *H. pylori* and HBV/HCV infections across various age groups, we used prevalence data by 5-year age group in the general population extracted from our previous systematic review and meta-regression of studies targeting Japanese populations (*6,10*). Another difference is that the RR used to calculate PAF was higher in the present study than in our previous study (15.0 *vs.* 5.9). Methodological differences aside, our slightly lower PAF estimates suggest a relatively decrease in the contribution of infectious agents to cancer, albeit that confirmation of this finding awaits further study.

We estimated that approximately 90% of non-cardia gastric cancers were attributed to *H. pylori* infection in the Japanese population. This result is similar to the updated IARC PAF estimate. Recognizing the possible underestimation of PAF in their previous study, in which prevalence data were obtained from serologic antibody tests, the IARC group presented an updated PAF of 89.0% for gastric cancer associated with *H. pylori* infection based on prevalence data from immunoblot (western blot) assay, which provides greater sensitivity in detecting anti-*H. pylori* antibodies than ELISA (*13*). Collectively, these findings reinforce the dominant role of *H. pylori* in the etiology of non-cardia gastric cancer. Less consistent, however, is the role of *H. pylori* in proximal and gastrointestinal junction gastric adenocarcinomas, which share a common pathogenesis with distal cancers but are distinct

from them (*19*). While *H. pylori* has been shown to be positively associated with both distal gastric cancer and proximal and gastroesophageal junction cancers in East Asian countries, including China and Japan (*20,21*), no significant associations have been observed in Western populations (*22*). Here, to our knowledge for the first time, we estimated that 38% of gastric cardia cancers were attributable to *H. pylori* infection in the Japanese population. However, cautious interpretation is warranted because of the inconsistent definition of gastric cardia cancer across studies, and quality of population-based cancer registry data.

Chronic infection with HBV or HCV is a major risk factor for liver cancer worldwide. Overall, our study showed that 59.6% of incident cases and 62.7% of deaths were attributed to either HBV or HCV infection in 2015. This estimate is comparable to the worldwide estimate of 60%, but is much higher than that in other developed countries (*23*). Interestingly, the prevalence of HBV and HCV infections and their contributions to liver cancer etiology exhibit remarkable geographical variation (*23*). HBV infection is the dominant cause of liver cancer in the majority of Asian countries, including China and Korea (*22*), whereas only 16% of liver cancer cases and deaths were attributable to HBV infection in Japan, as shown in our study. On the other hand, our data showed that HCV is a predominant cause of liver cancer in Japan, with approximately 46% of cases attributable to it. One striking feature is that the prevalence of anti-HCV peaked in individuals born between 1931 and 1935, who also showed high mortality rates of live cancer (*10*). Unsafe healthcare-related injections and blood transfusion were thought to have contributed to the wide transmission of HCV in this birth cohort (*10*). With the improvement in medical care since the 1950s, the prevalence of HCV has continuously decreased in successive younger generations, and was estimated to be 0.13% in the 1981-1985 birth cohort (*10*).

HPV is one of the most important infectious agents for a wide range of cancers, accounting for 4.6% of new cancer cases in 2012 (*4*). According to National Cancer Registry data, 11,283 women were newly diagnosed with cervical cancer in 2016. HPV infection would have contributed to all these incident cases if we assume a PAF of 100%. Notably, cervical cancer is the second leading cause of cancer-related deaths for women between the ages of 20 and 39 (*24*), suggesting that early detection is important in reducing the burden for this age group. In addition to cervical cancer, high-risk HPV also contributes to a varying fraction of head and neck, anal, penile, vulvar and vaginal cancers in men and women, with the PAF estimates ranging from 4.3% to 100%.

One strength of our study is that we used the best available, nationwide representative data to estimate PAFs due to infectious agents for Japanese subjects. In particular, by using population data by sex and 5-year age group, we were able to capture the dynamic changes occurring in the prevalence of *H. pylori* and hepatitis infection, two key etiologic factors responsible for a high proportion of cancer incidence and mortality in the Japanese population. We also highlight several methodological weaknesses that should be addressed to allow better interpretation and application of our PAF estimates. First, uncertainties remain concerning PAF estimates for EBV and HPV, because prevalence or risk factor data mostly came from studies involving Western populations. Second, given the varied latent periods between exposure and outcome used to estimate PAFs in the previous studies, we assumed it to be 10 years in the present study. In the case of *H. pylori*-induced gastric cancer, a cascade of carcinogenic processes for intestinal-type gastric cancer has been established; the process - starting from *H. pylori*-induced gastritis, then moving to gastric atrophy, intestinal metaplasia, dysplasia, and finally to malignant tumor - may take more than 10 years (*25*). Although the latency of 10 years adopted in our study may be too short, analysis using a latency of 15 years yielded similar results (data not shown). Third, assuming independent causes of mortality, we did not take possible interactions between infectious agents into account. However, the proportion of co-infections with HBV and HCV was 0.1% in a previous population-based cohort study (*16*), and the PAF estimate was 1.8% for co-infections with HBV and HCV in our earlier study (*5*). These findings suggest that the exclusion of coinfection with HBV and HCV in the present study might not have introduced serious bias.

From a practical point of view, PAF estimates are most useful in informing public health interventions when the exposure-disease association is recognized as causal and the exposure can be avoided through primary prevention. This notion fits well with pathogen-related cancers. Elimination of pathogens or vaccination could theoretically result in a marked decrease in disease outcomes. For example, the HBV vaccination program introduced in 1986 contributed to a decrease in age-adjusted mortality rates of liver cancer in childhood in Japan (*26*). For *H. pylori* infection, a population-wide "test-and-treat" strategy may be cost-effective and worthy of implementation in a country like Japan, which has both a high incidence of gastric cancer and high prevalence of *H. pylori* (*27*). The success of this implementation might also expedite a reduction in gastric cancer incidence/mortality, eventually making it a rare cancer. Despite the demonstrated safety and effectiveness of HPV vaccine, vaccination uptake plummeted in Japan shortly after it was introduced in 2013 due to anecdotal reports of adverse effects, such as complex regional pain and postural orthostatic tachycardia syndrome (POTS), in a small proportion of girls who had been vaccinated (28). Concerns have

been raised about a possible increase in the incidence of HPV-related diseases, including cervical cancer, if the current suspension of the vaccination program continues.

Conclusion

An estimated 16.6% of cancer incidence and 17.7% of cancer mortality were attributable to infection in Japan in 2015. Our findings corroborate the previous estimate that *H. pylori* and HBV/HCV still remain the two most important infectious agents in the Japanese population. Strategies focusing on the eradication of infectious agents among infected individuals or primary prevention through vaccination could decrease the burden of infection-related cancers. As dynamic changes in exposure prevalence occur over time, continued efforts to estimate the PAF due to infection is important for public health regulation.

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Burden of cancer attributable to insufficient vegetable, fruit and dietary fiber consumption in Japan in 2015

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Abstract: Consumption of vegetables, fruit and dietary fiber is closely associated with cancer incidence and mortality in the population, especially under conditions of insufficient consumption. We estimated the fraction of cancer incidence and mortality in 2015 attributable to insufficient consumption of vegetables, fruit and dietary fiber in the Japanese population. Consumption of vegetables, fruit and dietary fiber in grams per day, by sex and age group, is available for 2005 from the Japanese National Health and Nutrition Survey. Optimal consumption of vegetables and fruits for this study was assumed to be over 350g and 100g/day, respectively. Optimal consumption of dietary fiber was defined by age group according to the Dietary Reference consumption for Japanese. Population attributable fractions (PAFs) were estimated for each sex and age group according to a standard formula, and aggregated to obtain the PAF among total cancer incidence and mortality. Insufficient consumption of vegetables, fruit, and dietary fiber contributed 0.2%, 0.1% and 1.0% of all cancer incidence, and 0.2%, 0.1% and 0.9% of cancer mortality, respectively. The results of this study may provide useful evidence in reducing the cancer burden attributable to insufficient consumption of vegetables, fruit and dietary fiber in Japan.

***Keywords*:** cancer, vegetable and fruit, dietary fiber, population attributable fraction, Japan

Introduction

In 2018, the World Cancer Research Fund and American Institute for Cancer Research confirmed that consumption of non-starchy vegetables and fruit together was a probable protective factor for colorectal cancer (*1*). Individually, consumption of non-starchy vegetables was classified as a "limited-suggestive" protective factor for cancer of the oral cavity, pharynx, larynx, nasopharynx, esophagus, lung, and breast. Consumption of fruits was classified as a limited-suggestive protective factor for cancer of the esophagus and lung. Consumption of citrus fruits was classified as a limited-suggestive protective factor for cancer of the stomach (*1*). Foods containing dietary fiber were classified as a convincing protective factor of colorectal cancer. Consumption of these plant-source foods together might substantially influence cancer incidence and mortality in the population; specifically, when consumption level is insufficient.

The population attributable fraction (PAF) for all-cause cancer associated with insufficient vegetable and fruit consumption has previously been estimated for several countries, including Australia (*2*), Brazil (*3*), Germany (*4*), and the United Kingdom (*5*). The results indicated that while the risk attributed to insufficient consumption varied among countries, it was not low in any. Additionally, PAF for all cancer associated with inadequate dietary fiber consumption was estimated for Australia (*2*) and Germany (*4*). Because dietary consumption is a modifiable factor, identifying the proportion of cancers attributed to this factor could have important implications for cancer prevention strategies.

We previously reported that the fractions of cancer attributable to insufficient consumption of vegetables and fruit in 2005 in Japan were 0.4% and 0.8%, respectively (*6*). PAFs were the same for incidence and mortality. In the present report, we updated this to the fraction of cancer incidence and mortality in Japan for 2015, and also estimated the fraction attributed to dietary fiber consumption.

Materials and Methods

Cancers associated with insufficient vegetables, fruit and dietary fiber

The WCRF/AICR classified consumption of non-starchy vegetables and fruits together as a probable protective factor for colorectal cancer (*1*). Individually, consumption of non-starchy vegetables was classified as a limited-suggestive protective factor for cancer of the oral cavity, pharynx, larynx, nasopharynx, esophagus, lung, and breast. Consumption of fruits was classified as a limited-suggestive protective factor for cancer of esophagus and lung. Consumption of citrus fruits was classified as a limited-suggestive protective factor for cancer of the stomach. In addition, non-starchy vegetables and fruit in the aggregate were classified as a probable protective factor for aerodigestive cancer and some other cancers.

Foods containing dietary fiber were classified as probable protective factors of colorectal cancer (*1*). Therefore, we applied the target cancers associated with vegetables, fruit and dietary fiber identified by this evaluation, namely those which showed sufficient evidence for a positive association with vegetables, fruit and dietary fiber, and for which relative risk estimates in Japan were available, namely stomach, lung and colorectal cancer.

Theoretical minimum risk exposure level

The optimal consumption of vegetables and fruits in Japan for this purpose was defined as over 350 and 100 g/day, respectively. These values were based on goals established for the National Health Promotion Movement in the 21st Century (*7*). The optimal consumption of dietary fiber was defined by age group according to the Dietary Reference Consumption for Japanese (*8*).

Prevalence of vegetables, fruit and dietary fiber consumption

The latent period - the interval between "exposure" to insufficient consumption and the increase in risk of cancer - is unknown. For the purpose of this study, the latent period between being "exposed" to insufficient consumption and the consequent increase in cancer was assumed to be 10 years. The 2015 fraction of avoidable cancers calculated for this study is therefore based on an estimate of insufficient consumption in 2005.

The data on vegetable, fruit and dietary fiber consumption by sex and age group were derived from the Japanese National Health and Nutrition Survey (JNHNS) from 2005 (*9*), taking the 3-year mean of individual year data for 2004-2006 obtained from the Ministry of Health, Labour, and Welfare, Japan with permission.

Sex and age group-specific consumption of vegetables, fruit and dietary fiber in g/day by the Japanese population in 2005, as derived from the JNHNS, are shown in Table 1. The optimal consumption levels and the deficit from each for the estimation of PAF are given by sex and 5-year age group.

Cancer incidence and mortality in Japan in 2015

Cancer incidence data in 2015 were estimated using the annual estimate of cancer incidence in 2013 by the Monitoring of Cancer Incidence in Japan (*10*). We used an age and period spline model. This type of model is used for short-term projections of cancer incidence in Japan (*11*). The sex- and age-specific incidence data for target cancers were coded in accordance with the International Statistical Classification of Diseases and Related Health Problems, 10th edition (ICD-10), using the morphology code of the International Classification of Disease for Oncology, 3rd edition (ICD-O-3).

The data on cancer mortality statistics from 2015 were based on the vital statistics of Japan (*12*). We obtained sex- and age-specific mortality data by cause of death from available data sources from the Health, Labour, and Welfare Statistics Association (*13*), and used 4-digit ICD-10 codes to classify the cause of death.

Estimation of relative risks

Risk estimates for the association between site-specific cancer and consumption of vegetable, fruit and dietary fiber are summarized in Table 2. We used relative risk of the highest consumption (quartile or quintile) for the point estimate of risk, with the lowest respective category (first quartile or quintile) as reference. Relative risk for the association between stomach cancer and vegetable consumption was sourced from a pooled analysis of four Japanese cohorts (*14*). Because a decrease in risk with higher consumption of vegetables was observed only for the distal subsite of stomach cancer, we limited this research to distal stomach cancer only, which nevertheless accounted for 95% of total stomach cancer cases. Relative risk for the association between fruit consumption and lung cancer was sourced from a pooled analysis of four Japanese cohorts (*15*). Relative risk for the association between highest consumption of dietary fiber and colon cancer was sourced from a published analysis by Wakai *et al.* (*16*) using the method by Levin *et al.* (*17*). The risk for a deficit of one gram in decreased consumption was calculated using the following formula:

$$Risk = exp^{[\ln(\text{risk per gram of deficit}) \times \text{average exposure level}]}$$

where gram of deficit is 3-year mean of individual data by age group derived from the JNHNS.

Estimation of population attributable fractions (PAFs)

Table 1. Sex and age group-specific consumption of vegetables, fruit and dietary fiber in g/day in Japan in 2005

	Vegetables			Fruit			Dietary fiber		
Age at exposure (2005)	Mean consumption (g/day)	Optimal consumption (g/day)	Deficit from optimal consumption (g/day)	Mean consumption (g/day)	Optimal consumption (g/day)	Deficit from optimal consumption (g/day)	Mean consumption (g/day)	Optimal consumption (g/day)	Deficit from optimal consumption (g/day)
Men									
0 - 4	137	350	213	109	100	0	8.4	-	0.0
5 - 9	196	350	154	108	100	0	11.9	11.5	0.0
10 - 14	258	350	92	108	100	0	14.9	15.0	0.1
15 - 19	253	350	97	110	100	0	14.0	19.5	5.5
20 - 24	240	350	110	72	100	28	12.5	20.0	7.5
25 - 29	268	350	82	68	100	32	13.5	20.0	6.5
30 - 34	276	350	74	53	100	47	13.6	20.0	6.4
35 - 39	255	350	95	52	100	48	13.1	20.0	6.9
40 - 44	260	350	90	67	100	33	13.5	20.0	6.5
45 - 49	284	350	66	79	100	21	14.4	20.0	5.6
50 - 54	296	350	54	80	100	20	14.8	20.0	5.2
55 - 59	316	350	34	117	100	0	16.4	20.0	3.6
60 - 64	337	350	13	144	100	0	17.6	20.0	2.4
65 - 69	336	350	14	156	100	0	17.7	20.0	2.3
70 - 74	329	350	21	163	100	0	17.6	19.0	1.4
≥ 75	307	350	43	150	100	0	16.3	19.0	2.7
Women									
0 - 4	137	350	213	114	100	0	8.2	-	0.0
5 - 9	195	350	155	111	100	0	11.5	11.0	0.0
10 - 14	261	350	89	115	100	0	14.3	14.5	0.2
15 - 19	245	350	105	109	100	0	12.9	17.5	4.6
20 - 24	231	350	119	82	100	18	12.3	18.0	5.7
25 - 29	243	350	107	79	100	21	12.7	18.0	5.3
30 - 34	237	350	113	79	100	21	12.6	18.0	5.4
35 - 39	240	350	110	73	100	27	12.7	18.0	5.3
40 - 44	240	350	110	86	100	14	13.0	18.0	5.0
45 - 49	274	350	76	110	100	0	14.7	18.0	3.3
50 - 54	292	350	58	137	100	0	15.6	18.0	2.4
55 - 59	312	350	38	162	100	0	16.7	18.0	1.3
60 - 64	317	350	33	172	100	0	17.3	18.0	0.7
65 - 69	322	350	28	181	100	0	17.5	18.0	0.5
70 - 74	313	350	37	167	100	0	16.6	19.0	2.4
≥ 75	285	350	65	153	100	0	15.2	19.0	3.8

Table 2. Summary of risk estimates for the association between consumption of vegetables, fruit, and dietary fiber and site-specific cancer

Exposure	Cancer site	Studies	Reference group	Estimated risk for the highest (quartile of quintile) consumption
Vegetable	Stomach	Shimazu *et al.* (2014) (*14*)		
	Men		First quintile	0.78 (0.63 - 0.97)
	Women		First quintile	0.89 (0.62 - 1.29)
Fruit	Lung	Wakai *et al.* (2015) (*15*)		
	Men		First quintile	0.88 (0.66 - 1.16)
	Women		First quintile	
Dietary fiber	Colon	Wakai *et al.* (2007) (*16*)		
	Men		First quartile	0.52 (0.28 - 0.96)
	Women		First quartile	0.64 (0.36 - 1.13)

PAFs were calculated for each sex and age group according to the formula:

$$\mathrm{PAF} = \frac{(Risk - 1)}{Risk}$$

The number of attributable cancers was then totaled across all sex and age categories to show a percentage of the total number of all incident cases and deaths of cancer in Japan in 2015.

Results

Sex and age group-specific consumption of vegetables,

fruit and dietary fiber among Japanese people in 2005 is shown in Table 1. The deficit from optimal consumption to mean vegetable intake was high in younger generations (up to 40-44 years-old) and decreased for both sexes thereafter. A similar tendency was seen for fruit, but the decrease was observed slightly later for men (55-59 years-old). The deficit from optimal consumption to mean dietary fiber intake was highest among 20-24-year-olds.

Risk estimates for the association between consumption of vegetables, fruit, and dietary fiber and site-specific cancer in Japan are summarized in Table 2. For vegetables, the estimated risk of stomach cancer was 0.78 for men and 0.89 for women. We used these values to calculate PAF. For fruit, the estimated risk of lung cancer was 0.88 for men and women; while for dietary fiber, the estimated risk of colon cancer was 0.52 for men and 0.64 for women.

The estimated PAF of cancer incidence and mortality in 2015 attributed to insufficient vegetable, fruit and dietary fiber consumption in Japan is summarized in Table 3. Insufficient consumption of vegetables was attributed to 1.7% (1.8% in men and 1.3% in women) of gastric cancer incidence, and to 0.2% (0.3% in men and 0.1% in women) of total cancer incidence. Insufficient consumption of fruits was attributed to 0.5% (0.7% in men and 0.2% in women) of lung cancer incidence, and to 0.1% (0.1% in men and 0.02% in women) of total cancer incidence. Insufficient consumption of vegetables was attributed to 1.3% (1.3% in men and 1.2% in women) of mortality from gastric cancer, and to 0.2% (0.2% in men and 0.1% in women) of total cancer mortality. Insufficient consumption of fruits was attributed to 0.4% (0.5% in men and 0.1% in women) of mortality from lung cancer, and to 0.1% (0.1% in men and 0.01% in women) of total cancer mortality.

Insufficient consumption of dietary fiber was attributed to 10.5% (13.6% in men and 7.1% in women) of colon cancer incidence, and to 1.0% (1.2% in men and 0.8% in women) of total cancer incidence. It was attributed to 10.2% (12.4% in men and 7.9% in women) of mortality from colon cancer, and to 0.9% (1.0% in men and 0.9% in women) of total cancer mortality.

Detailed results for each cancer, sex, and age-group are shown for insufficient vegetable and fruit consumption in Tables S1-S2 (online data, *https://www.ghmopen.com/site/supplementaldata.html?ID=36*) and for insufficient fiber consumption in Tables S3-S4 (online data, *https://www.ghmopen.com/site/supplementaldata.html?ID=36*).

Discussion

In this report, we estimated the proportion and absolute number of cancer incidence and mortality in Japan in 2015 that was attributable to insufficient vegetable, fruit and dietary fiber consumption. According to the results from a large prospective cohort study or pooled/meta-analysis of cohort studies in Japan, insufficient consumption of vegetables, fruit and dietary fiber was attributed to stomach cancer, lung cancer, and colon cancer, respectively. The results indicate that insufficient consumption of vegetables and fruit contributed 0.1-0.2% of both total cancer incidence and mortality. In addition, insufficient dietary fiber consumption contributed approximately 1% of total cancer incidence and mortality.

In a previous study which estimated the effects of 16 risk factors on cause-specific mortality (*18*), the number of cancer deaths attributable to low fruit and vegetable consumption was 3.8 in thousands, similar to that of our study. In that study, the risk of low consumption of vegetables and fruit was relatively minor, at only one-third that of high dietary sodium consumption, the highest dietary risk factor for cancer in Japan. Further, low dietary fiber consumption was not included.

In contrast, several previous estimates of the fraction of cancer attributable to insufficient consumption of vegetables, fruits and dietary fiber have been published

Table 3. Proportion (%) of cancer in 2015 attributable to insufficient consumption of vegetable, fruit, and dietary fiber in Japan

Items	Incidence			Mortality		
	Men	Women	Both sexes	Men	Women	Both sexes
Insufficient vegetable consumption						
Stomach (C16)	1.8	1.3	1.7	1.3	1.2	1.3
Total cancer (C00 - C96)	0.3	0.1	0.2	0.2	0.1	0.2
Insufficient fruit consumption						
Lung (C33 - C34)	0.7	0.2	0.5	0.5	0.1	0.4
Total cancer (C00 - C96)	0.1	0.0	0.1	0.1	0.0	0.1
Insufficient vegetable and fruit consumption						
Total cancer (C00 - C96)	0.4	0.2	0.3	0.3	0.1	0.2
Insufficient dietary fiber consumption						
Colon (C18)	13.6	7.1	10.5	12.4	7.9	10.2
Total cancer (C00 - C96)	1.2	0.8	1.0	1.0	0.9	0.9

from Western countries. PAFs of all cancer attributed to vegetables and fruits combined for all cancer cases were 4.7% in the UK in 2010 (*5*) and 2.1% in Germany in 2018 (*4*). In Australia in 2010, PAFs of all cancer attributed to insufficient fruits and vegetables were 1.4% and 0.3%, respectively (*2*). In France, PAFs of all cancer in 2015 attributed to insufficient fruits and vegetables were 1.4% and 0.5%, respectively (*19*). Compared to these percentages, the PAF of all cancer in Japan in the present study is rather low.

According to the National Health and Nutrition Survey, average consumption of vegetables by Japanese increased until the mid-1990s, and has since then maintained a steady level between 260-300g/day for about two decades (*20*). On the other hand, stomach cancer decreased rapidly during this period, both in incidence and mortality. If these trends continue, the burden of all cancer attributed to insufficient consumption of vegetables in the future will be even lower than now. In contrast, average consumption of fruit in Japan decreased drastically up to the 2000s, to around 120g/day, and has since continued to decrease slowly (*20*). Considering the increasing trend of lung cancer in Japanese women, all cancers attributed to the low consumption of fruit might increase in the future. Consumption of dietary fiber, on the other hand, has remained at approximately 15g/day for the past two decades (*20*). Foods which make the greatest contribution to the total consumption of dietary fiber include not only fruits and vegetables, but also grains. Since the incidence of colon cancer is increasing in Japanese women, all cancers attributable to insufficient dietary fiber consumption might increase in the future.

There are a few limitations to this study. First, the methodology used to estimate dietary consumption differed. We adopted the mean consumption levels from the results of 1-day dietary records collected in the National Nutrition Survey to take advantage of representative data. Among the various methods available, dietary records also have the advantage of accurately estimating the quantity of consumption. On the other hand, relative risks were estimated using FFQs, which are designed for ranking by consumption level. Moreover, levels of consumption in categories such as quintiles may vary in the meta- and pooled analyses. Our present analysis was based on the hypothesis of a dose-response association between exposure and outcome; however, the differences in cut-off point caused by the different methods might have resulted in error if this hypothesis was not applicable to dietary consumption. Secondly, the RR used to calculate the PAF for insufficient dietary fiber consumption was derived from a single study. This may have led to the over- or underestimation of risk. When additional data are available, re-calculation of the PAF using RR from a meta-analysis or pooled analysis will be essential for updating the evidence.

Despite the limitations, these estimates have major implications for Japan's national health policy for cancer prevention and control strategies.

Conclusion

Our analysis provides evidence for the current burden of cancer attributable to insufficient consumption of vegetables, fruit and dietary fiber. Insufficient consumption of vegetables, fruit, and dietary fiber contributed 0.2%, 0.1% and 1.0% of all cancer incidence, and 0.2%, 0.1% and 0.9% of cancer mortality, respectively. These results may provide useful evidence in efforts to reduce the cancer burden in Japan.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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Burden of cancer attributable to air pollution in Japan in 2015

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Abstract: $PM_{2.5}$ is a major environmental health problem and a risk factor for lung cancer. Exposure to $PM_{2.5}$ has attracted growing public concern nationwide. Here, we aimed to estimate the cancer in 2015 attributable to $PM_{2.5}$ in Japan. Ambient air pollution level due to excess concentration of $PM_{2.5}$ was estimated using geophysically based satellite-derived $PM_{2.5}$ concentrations in 2005, with a spatial resolution of 0.5° × 0.5° longitude-latitude, and population data presented in a 1 km by 1 km grid. We used the WHO guideline value for $PM_{2.5}$ exposure (≤ 10 μg/m^3) as the optimal level of $PM_{2.5}$ exposure. By using relative risk from a large-scale cohort study in Japan, we estimated the population attributable fraction (PAF) for lung cancer, which is positively associated with $PM_{2.5}$, and aggregated the results to obtain the PAF among total cancer incidence and mortality. Population-weighted mean $PM_{2.5}$ level in 2005 was 14.9 μg/m^3. Approximately 95.7% of the population was exposed to levels above the WHO guideline value. Lung cancer attributable to $PM_{2.5}$ exposure corresponded to 11,922 cases and 7,264 deaths, which accounted for 9.7% and 9.8% of total lung cancer incidence and mortality, respectively, and 1.2% and 2.0% of total cancer incidence and mortality, respectively. Substantial geographic variation in $PM_{2.5}$-attributable incidence and mortality fractions was found, with cities in western Japan and metropolitan areas having a higher PAF than other municipalities. This study provides useful information to aid policy-makers and public health agencies in the efficient establishment of environmental cancer prevention policies.

***Keywords*:** cancer, air pollution, population attributable fraction, Japan

Introduction

Outdoor air pollution, often referred as ambient air pollution, is a major environmental health problem which affects people across all socioeconomic strata in low-, middle, and high-income countries. Types of ambient air pollution include gases (*e.g.*, carbon monoxide, sulfur dioxide, nitrogen oxides, ozone) and fine particulate matter (PM), notably $PM_{2.5}$ - particles less than 2.5 micrometers in diameter - and PM_{10}. In 2013, the International Agency for Research on Cancer (IARC) confirmed that outdoor air pollution, including $PM_{2.5}$, is carcinogenetic to humans (*1*), and the recent Global Burden of Disease (GBD) study (GBD 2017) found that $PM_{2.5}$ accounted for 5.3% of lung cancer mortality worldwide, and 5.5% in Japan (*2*).

Several countries and regions have reported mortality burdens attributable to $PM_{2.5}$ at a subnational level (*3-5*). In Taiwan, population attributable fractions (PAFs) for lung cancer were estimated to range from 4.7% to 17.4% in different counties (*6*). An earlier report from the US also revealed starkly localized geographic variation in this mortality burden (*7*). In addition to evaluation of the impact of $PM_{2.5}$ at the national level, a better understanding of geographic patterns in PAF at the subnational level will help policy-makers and public health agencies to improve the quality of public health practice. Nevertheless, few studies have focused on the PAF of cancer due to $PM_{2.5}$ at either the national or subnational level in Japan.

Here, we aimed to estimate cancer incidence and mortality attributable to ambient air pollution, with a special focus on $PM_{2.5}$ concentration, at the national and sub-national level (city level) in Japan.

Materials and Methods

Cancers associated with air pollution

IARC has classified particulate matter, a major component of outdoor air pollution, as carcinogenic to humans (Group 1), finding a consistent association of outdoor air pollution with lung cancer (*1*). Accordingly, we included lung cancer as the target cancer in the present estimate.

Theoretical minimum risk exposure level

For this study, we used the WHO guideline value for $PM_{2.5}$ exposure (10 μg/m^3) as reference (*8*). The latent period - the interval period between "exposure" to $PM_{2.5}$ above the reference and the increase in risk of cancer of the lung - is unknown. Based on previous epidemiological studies of exposure, we assumed a latent period of 10 years, and accordingly calculated the number of avoidable cancers in 2015 using the estimated $PM_{2.5}$ exposure in 2005.

Distribution of $PM_{2.5}$ exposure and population-weighted $PM_{2.5}$ exposure estimates

Because nationwide observation data of $PM_{2.5}$ were not available before 2009, when environmental quality standards for $PM_{2.5}$ were established in Japan, the distribution of $PM_{2.5}$ exposure and population-weighted $PM_{2.5}$ exposure was estimated using population and $PM_{2.5}$ concentrations data.

We obtained the population data from Japanese Census data in 2005 and 2000 (*9,10*). We used the population data in 2005 for the main analysis and that in 2000 for sensitivity analysis. The spatial distribution of population in 2005 is illustrated in Figure 1. The population data are presented in grids of 45 seconds longitude by 30 seconds latitude, which is also known as the Basic Grid Square (*11*). Each grid-square was given a unique ID computed on the basis of geographical position (latitude and longitude). The gridded data covered an area between 122°-154° east longitude and 20°- 46° north latitude.

To assign exposure to $PM_{2.5}$, we used surface $PM_{2.5}$ concentrations estimated by the Atmospheric Composition Analysis Group (*12*). The provided data were estimates of annual mean exposure to $PM_{2.5}$ in 2005 and 2000, with a spatial resolution of 0.01° × 0.01° longitude-latitude. The group estimated $PM_{2.5}$ concentrations using information from satellite-, simulation- and monitor-based sources (*13*). A geographically weighted regression (GWR) model was used to correct discrepancies between the satellite-based estimated $PM_{2.5}$ and monitor-based $PM_{2.5}$ levels.

The $PM_{2.5}$ data used in this study covered an area between 122°-154° east longitude and 20°- 46° north latitude. As with the population data, the $PM_{2.5}$ data in 2005 were used for the main analysis and the $PM_{2.5}$ data in 2000 were used for sensitivity analysis.

To estimate annual average $PM_{2.5}$ concentrations at the national and city levels, we added the longitude-latitude coordinate code computed from the grid-ID to the population data, then linked the population and $PM_{2.5}$ concentration data using the longitude-latitude coordinate code as the matching key with the nearest neighbor matching method.

Next, city codes were assigned to each grid using the intersect tool (ArcToolbox/Analysis tools/Overlay) of the ArcGIS (ArcGIS Pro, version 2.5.2; ESRI Inc, Redlands, CA, USA) geographic information system. This tool can create geometric intersections of any number of feature layers. In this study, we created an intersection between the city layer and gridded data layer; where a grid intersected two or more cities, the grid contained the codes of all intersected cities. Finally, we calculated population-weighted $PM_{2.5}$ concentrations at the city level using following formula (*14*):

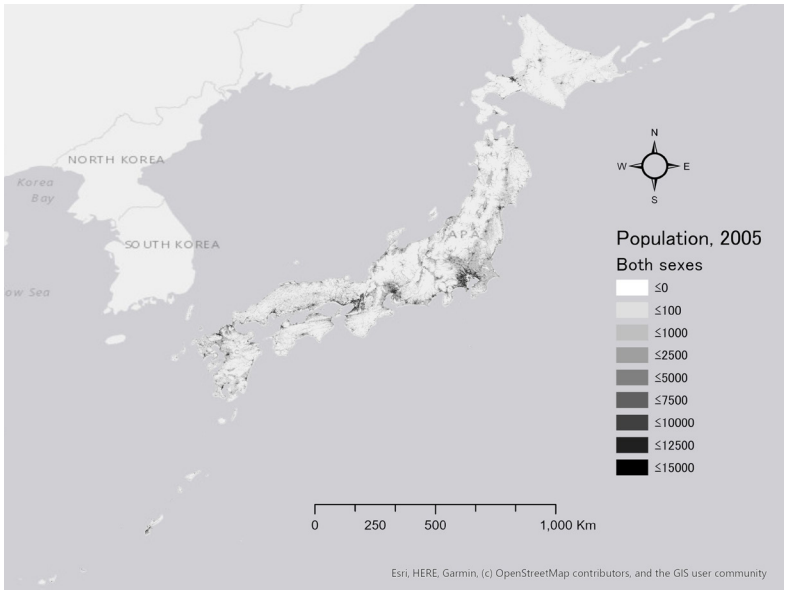

Figure 1. The spatial distribution of population in Japan in 2005, with a spatial resolution of 1km × 1km grid.

$$WPM_k = \sum_i^{N_k} PM_{ik} Pop_{ik} / Pop_k$$

$$Pop_k = \sum_i^{N_k} Pop_{ik}$$

where WPM_k is the population-weighted $PM_{2.5}$ concentration estimate in city k, N_k is the number of grid in city k, PM_{ik} is the $PM_{2.5}$ concentration in grid i in city k, Pop_k is the population in city k, and Pop_{ik} is the population in grid i in city k.

Cancer incidence and mortality in Japan in 2015

Cancer incidence data in 2015 were estimated using the annual estimate of cancer incidence in 2013 by the Monitoring of Cancer Incidence in Japan project (*15*). We used an age and period spline model. This type of model is often used for short-term projection of cancer incidence in Japan (*16*). The sex- and age-specific incidence data for target cancers were coded in accordance with the International Statistical Classification of Diseases and Related Health Problems, 10th edition (ICD-10), using the morphology code of the International Classification of Disease for Oncology, 3rd edition (ICD-O-3).

The data on cancer mortality statistics from 2015 were based on the vital statistics of Japan. We obtained sex- and age-specific mortality data at both the national (*17*) and city level (*18*) by cause of death from available data sources from the Health, Labour, and Welfare Statistics Association, with cause of death classified using 4-digit ICD-10 codes.

Estimation of relative risk

The relative risk (RR) of air pollution exposure on lung cancer was taken from a prospective population-based observational study (*19*), the Three-Prefecture Cohort study, which was conducted from 1983 to 2000 in three prefectures (Miyagi, Aichi, and Osaka) (*20*). The Three-Prefecture Cohort study had a long follow-up period and covered both high and low $PM_{2.5}$ concentration areas. Because RR in the study was reported in 10-unit increases in the average concentration of air pollutants (μg/m^3), we assumed a log-linear association to convert the RR per 10-unit increase using the following formula:

$$\beta = \ln(RR_{10unit})/10$$

$$RR_{x-x_0} = \exp(\beta(x - x_0))$$

where β is the parameter estimate for the association between lung cancer and the exposure of $PM_{2.5}$, RR_{10unit} is the RR per 10-unit increase in the average concentration of $PM_{2.5}$, and $RR_{x\text{-}x0}$ is the RR at exposure x compared to that with the reference exposure x_0. In our study, RRs of $PM_{2.5}$ on lung cancer incidence and mortality were assumed to be equal. Consequently, RR_{10unit} (95% confidence interval) of lung cancer, 1.26 (1.14-1.36) for men and 1.17 (0.98-1.39) for women, was used for estimation of PAF of cancer due to air pollution.

Estimation of population attributable fractions (PAFs)

For lung cancer, PAF at the national level was calculated by sex as:

$$PAF = \frac{\sum(p_x ERR_x)}{1 + \sum(p_x ERR_x)}$$

where p_x is the proportion of the population and ERR_x is the excess relative risk at $PM_{2.5}$ exposure level x.

The excess relative risk for each x level of $PM_{2.5}$ exposure was calculated using the following formula:

$$ERR_x = RR_{x-x_0} - 1 = \exp\big(\beta(x - x_0)\big) - 1$$

We used the WHO guideline value for $PM_{2.5}$ exposure (10 μg/m^3) as reference (*8*).

The number of lung cancer cases/deaths attributable to $PM_{2.5}$ was calculated by sex as:

$$ELC = LC \times PAF$$

where ELC is excess incidence/mortality of lung cancer and LC is lung cancer incidence/mortality.

The number of attributable cancers was then totaled across all sex and age categories to show the percentage of the total number of all incidence and mortality of cancer in Japan in 2015.

In addition, the PAF of mortality of lung cancer was estimated at the city level, using population-weighted $PM_{2.5}$ concentration by city. As we assumed that $PM_{2.5}$ levels were uniform within each city, that is *WPM*, PAF at city k, which is PAF at the city level, was calculated by sex as:

$$PAF_k = \frac{ERR_{WPM_k}}{1 + ERR_{WPM_k}}$$

Sensitivity analysis

In addition to the main analysis, the impact of $PM_{2.5}$ on cancer incidence and mortality was assessed using three alternative reference levels, namely the national

ambient air quality standards in Japan (15.0 μg/m^3) (*21*) and the USA (12.0 μg/m^3) (*22*), and a value which may be close to the background $PM_{2.5}$ concentration in Japan (4.0 μg/m^3), based on a previous estimated background concentration of about 4.4 μg/m^3 in Taiwan and surrounding oceanic regions (*23*). We also investigated the influence of time lag between $PM_{2.5}$ exposure and lung cancer incidence and mortality by using the population and $PM_{2.5}$ concentration data in 2000, which is 15-year time lag analysis.

Results

Fine particular matter exposure

The distribution of the population-weighted exposure to $PM_{2.5}$ in 2005 is shown in Figure 2. The 5th, 50th and 95th percentiles of population-weighted $PM_{2.5}$ levels in that year were 10.2, 15.1, 20.5 μg/m^3, respectively, and the population-weighted annual average exposure was 14.9 μg/m^3. Approximately 95.7% of the study population was exposed above the yearly average WHO guideline value of 10 μg/m^3, while 56.6% was above the Japan standard value of 15.0 μg/m^3.

The spatial distribution of population-weighted $PM_{2.5}$ concentrations at the city level in 2005 in Japan is shown in Figure 3. The Kanto region, including Tokyo and Kanagawa prefectures, and the Kansai region, including Osaka prefecture, had high $PM_{2.5}$ concentrations. Western Japan, including the Kyushu and Chugoku regions, also had higher $PM_{2.5}$ concentrations than other areas. In contrast, $PM_{2.5}$ concentrations were lower in northern Japan, such as the Hokkaido and Tohoku regions.

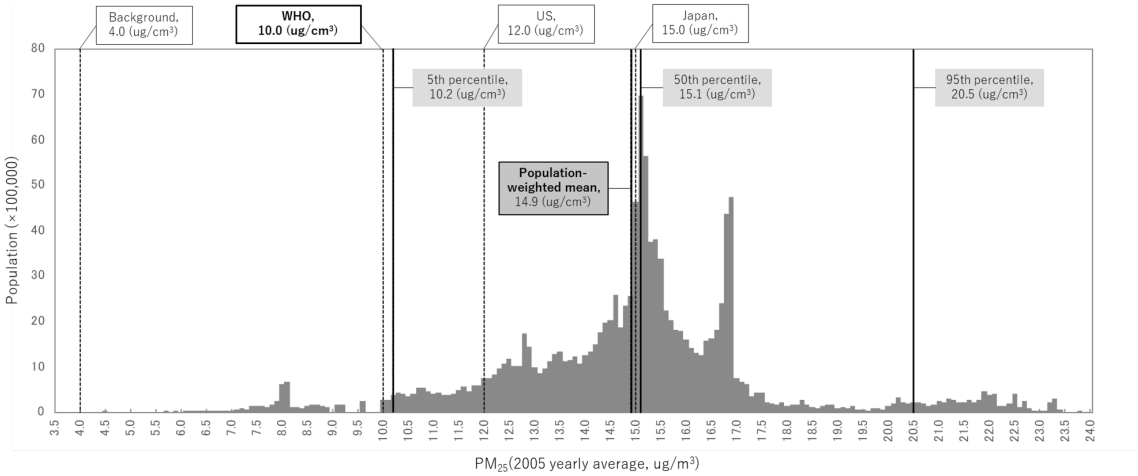

Figure 2. Distribution of exposures to $PM_{2.5}$ in Japan in 2005. Background: Expected value of background $PM_{2.5}$ concentration in Japan; WHO: WHO Air quality guideline values for annual average $PM_{2.5}$ concentrations; US: National Ambient Air Quality Standards for annual average $PM_{2.5}$ concentrations in the US; Japan: Environmental Quality Standards for annual average $PM_{2.5}$ concentrations in Japan.

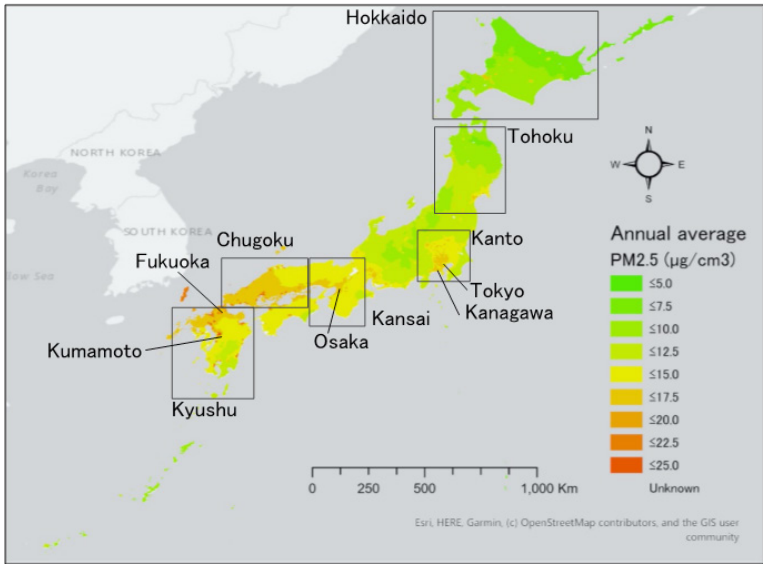

Figure 3. Annual average of population-weighted $PM_{2.5}$ concentrations at the city level in 2005 in Japan.

Cancer attributable to $PM_{2.5}$

Table 1 summarized the estimated PAF of cancer incidence and mortality in Japan in 2015 attributed to ambient air pollution ($PM_{2.5}$). Detailed results by sex and age group are shown in Tables S1 (incidence) and S2 (mortality) (online data, *https://www.ghmopen.com/site/supplementaldata.html?ID=40*). The estimated PAF was 9.7% (10.7% for men, 7.5% for women) of lung cancer incidence, corresponding to 11,922 cases (8,907 in men, 3,014 in women), and 9.8% (10.7% for men, 7.5% for women) of lung cancer mortality, corresponding to 7,264 deaths (5,682 in men, 1,582 in women). Accordingly, 1.2% of cancer incidence (1.6% in men, 0.7% in women) and 2.0% of cancer mortality (2.6% in men, 1.0% in women) in 2015 were due to excessive $PM_{2.5}$ exposure.

Figure 4 shows the geographic variation in PAF of lung cancer mortality associated with $PM_{2.5}$ exposure at the city level across Japan. Cities in western Japan had a higher PAF than other cities, with Kumamoto City in the Kyushu region having the highest PAF (26% for males, 19% for females). Estimated PAFs were also higher in cities in Tokyo, Kanagawa, and Osaka prefectures compared to other cities. On the other hand, PAF was lower in northern Japan, such as in the Hokkaido and Tohoku regions.

Figure 5 shows the number of lung cancer deaths attributable to $PM_{2.5}$ exposure at the city level across

Table 1. Proportion (%) of cancer in 2015 attributable to ambient air pollution ($PM_{2.5}$) in Japan

Factors	Cancer Incidence			Cancer Mortality		
	Men	Women	Both sexes	Men	Women	Both sexes
Lung (C33-34)						
Exceed 10 μg/cm^3 (WHO[a])	10.7	7.5	9.7	10.7	7.5	9.8
Exceed 12 μg/cm^3 (US[b])	6.9	4.8	6.2	6.8	4.8	6.2
Exceed 15 μg/cm^3 (Japan[c])	2.0	1.4	1.8	2.0	1.4	1.8
Exceed 4 μg/cm^3 (background[d])	22.0	15.8	20.0	22.0	15.7	20.2
Total cancer (C00-C96)						
Exceed 10 μg/cm^3 (WHO[a])	1.6	0.7	1.2	2.6	1.0	2.0

[a]WHO Air quality guideline values for annual average $PM_{2.5}$ concentrations; [b]National Ambient Air Quality Standards for annual average $PM_{2.5}$ concentrations in the US; [c]Environmental Quality Standards for annual average $PM_{2.5}$ concentrations in Japan; [d]Expected value of background $PM_{2.5}$ concentration in Japan.

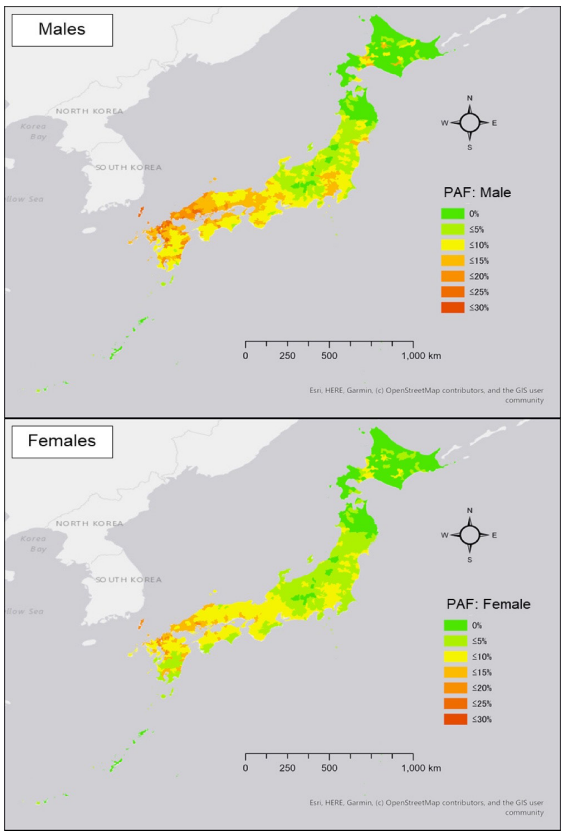

Figure 4. Spatial variations in the PAF (%) of lung cancer due to $PM_{2.5}$ at the city level by sex in Japan in 2015.

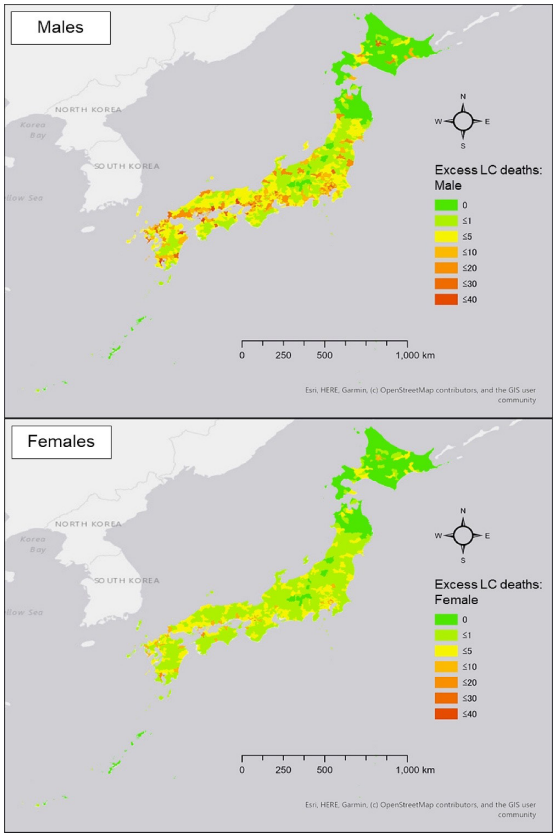

Figure 5. Spatial variations of the number of lung cancer deaths due to $PM_{2.5}$ at the city level by sex in Japan in 2015.

Japan. Cities in metropolitan areas, such as Tokyo and Osaka prefectures, tended to have a large number of deaths associated with $PM_{2.5}$. In the northern part of the Kyushu region and southern part of the Chugoku region also, many cities had a large number of deaths due to $PM_{2.5}$ exposure.

Sensitivity analysis

When the $PM_{2.5}$ reference level was replaced by the national ambient air quality standards in the US (12.0 μg/m^3) and in Japan (15.0 μg/m^3), the PAF for both sexes combined decreased to 6.2% and 1.8% for incidence and mortality, respectively. When the reference level for $PM_{2.5}$ was changed to 4.0 μg/m^3, which is regarded as consistent with the background concentration in Japan, PAF was 20% for both incidence and mortality. Results with the 15-year time lag analysis were similar to those with a 10-year time lag analysis.

Discussion

We estimated the cancer incidence and mortality attributed to ambient air pollution ($PM_{2.5}$) exposure in Japan in 2015 by applying GIS spatial analysis data. This is the first nationwide report of the PAF of cancer attributable to ambient air pollution in Japan and PAF of lung cancer mortality due to $PM_{2.5}$ at a sub-national level. We identified a large geographic variation in PAF, namely a higher ratio in the western part in Japan. Further, the large metropolitan areas around Tokyo and Osaka had a large number of excess attributable cases due to $PM_{2.5}$ exposure.

Cigarette smoking is the single biggest risk factor for lung cancer. In Japan, the PAF of lung cancer mortality caused by cigarette smoking in 2015 was about 60.9% for men and 18.3% for women (*24*). Although the PAF of lung cancer due to $PM_{2.5}$ was small compared to that due to cigarette smoking in men, it was about half as large as that due to cigarette smoking for women. Moreover, the PAF due to $PM_{2.5}$ was comparable to that due to secondhand smoking (SHS) for women (8.7%) and larger than that due to SHS for the total population (3.7%). In addition to the inclusion of tobacco control in indoor air policies, environmental approaches to air quality management are also important for cancer prevention, including lung.

The GBD 2015 study reported that lung cancer mortality attributable to $PM_{2.5}$ was about 6,800 deaths (males 4,700, females 2,000), or 8.7% of total lung cancer mortality in Japan (*25*). Our national-level estimates of PAF were higher than the GBD 2015 estimates. One reason is the year of $PM_{2.5}$ exposure data: the GBD study used $PM_{2.5}$ exposure and mortality data from the same year (2015), whereas we used $PM_{2.5}$ exposure data in 2005 and mortality in 2015. In other words, we assumed a 10-year time lag between $PM_{2.5}$ exposure and lung cancer mortality. In fact, several studies have reported that lung cancer has a long latency period (*26-28*). To our knowledge, however, uncertainties are still present in the time lag between $PM_{2.5}$ and lung cancer mortality. We therefore assumed that a time lag of 10 years accounted for longer-term exposure, as has also been done in previous studies (*29*). In Japan, average $PM_{2.5}$ concentrations in rural areas have leveled off, whereas those measured at the roadside have greatly decreased since 2000 (*30*). The GBD approach might therefore have provided lower attributable deaths due to $PM_{2.5}$. Another difference between the GBD and our present study is the choice of $PM_{2.5}$ reference level, which has a major impact on PAF estimation. The GBD study applied a uniform distribution between 2.4 μg/m^3 and 5.9 μg/m^3 as the reference level of $PM_{2.5}$ (*25*), whereas our main analysis was set to 10.0 μg/m^3. The reference level of 4.0 μg/m^3 in our sensitivity analysis is similar to the reference level applied in the GBD. Under this setting, our PAFs were much larger than those of the GBD study. The large differences in PAF were considered due to the differences in $PM_{2.5}$ exposure data.

Unlike the differences in $PM_{2.5}$ exposure data between the GBD and our present study, the differences between $PM_{2.5}$ concentrations in 2000 and 2005 in our study were small. Accordingly, replacement of the $PM_{2.5}$ concentration in 2005 with that in 2000 resulted in almost no change in PAF at the national level.

Our estimates revealed the geographic variation in the PAF of lung cancer due to $PM_{2.5}$ exposure in Japan. We found a high PAF in major metropolitan areas such as Tokyo, Kanagawa and Osaka. In our method, PAFs are thoroughly dependent on the population-weighted concentration of $PM_{2.5}$. Tokyo, Kanagawa and Osaka are among the most densely populated areas in Japan. These areas had higher $PM_{2.5}$ concentrations, mainly as a result of local industrial and traffic pollution (*31*). Accordingly, the PAFs were also relatively high in the major metropolitan areas. Moreover, Japan's 2005 census showed that 30% of the overall population was concentrated in the metropolitan areas (*32*). Therefore, trends in $PM_{2.5}$ in the area would have a substantial impact on the national estimates of PAF.

Higher concentrations of $PM_{2.5}$ and bigger PAF were also found in many parts of rural areas in western Japan. The main reason is $PM_{2.5}$ arising from foreign anthropogenic sources, especially from the Chinese mainland (*31,33-35*). In Japan, the main contributor to $PM_{2.5}$ differ according to region. Contributions from foreign anthropogenic sources were greater than those from domestic pollution in the Kyushu region (*33,35*).

China has a very large PAF compared to Japan, although variations in PAF have been assigned according to the setting of reference levels of $PM_{2.5}$ and the time lag between $PM_{2.5}$ exposure and lung

cancer mortality/incidence (*36-40*). One of the Chinese studies estimated that the PAF in China in 2015 was 23.9% overall (*38*). However, the study applied a high reference level of $PM_{2.5}$ (40 μg/m^3). If we use the same reference level as the Chinese study, the number of lung cancer deaths attributed to $PM_{2.5}$ would be zero in Japan because there were no areas which had a $PM_{2.5}$ concentration over 30 μg/m^3. A previous study in the Republic of Korea estimated that the PAF was 26.9% (95% CI: 15.5%-37.0%) by applying a uniform distribution between 2.4 μg/m^3 and 5.9 μg/m^3 as the reference level of $PM_{2.5}$ (*41*). The reference level of 4.0 μg/m^3 in our sensitivity analysis is similar to this level in the Korean study. Under this setting, the PAFs were slightly larger in the Korea than Japan. The larger PAFs in China and Korea were caused by exposure to higher $PM_{2.5}$ concentrations. Average concentrations in China, Republic of Korea and Japan were 66.2 μg/m^3, 30.4 μg/m^3 , and 14.3 μg/m^3 in 2005, respectively (*42*). The south and south-east Asia region had much higher concentrations of $PM_{2.5}$ than other Asian countries (*43*). Japan was considered to have smaller PAFs of $PM_{2.5}$ among Asian countries.

On the other hand, a recent study in Canada, where air pollution levels are much lower than in Japan, estimated that 2-6% of incident lung cancer cases in 2012 might have been attributable to $PM_{2.5}$ exposure by applying different reference levels of $PM_{2.5}$ (7.5 μg/m^3 and 3.18 μg/m^3, respectively) (*44*). In the GBD study, the fraction of lung cancer mortalities attributable to $PM_{2.5}$ was estimated to be 8.6% in Western Europe and 4.6% in the US (*25*). The health impact of $PM_{2.5}$ exposure in Japan is large compared to these European and North American countries.

One strength of the present study was that we used the estimated annual average of $PM_{2.5}$ concentration-based satellite-, simulation- and monitor-based concentrations. Agreement with the estimated data we used and ground-observed $PM_{2.5}$ concentrations were improved by applying the GWR model. Since establishment of the national ambient air quality standards in 2009 (*21*), the number of $PM_{2.5}$ monitoring stations in Japan has been increasing year by year (*45*). Nevertheless, there are still insufficient monitoring stations to monitor spatial distribution at the city level with ground-based monitoring alone (*46*). By using satellite-, simulation- and monitor-based concentration data, not only monitoring data alone, our analysis provided subnational information.

Another strength of the present study was that we used small grid-square level mortality data instead of city-level mortality data. Our analysis therefore provided national and subnational information that was more accurate than the previous estimate.

The RR used for the present study was based on a large-scale prospective cohort study from three prefectures in Japan. An advantage of this RR is that the large number of confounders (age, smoking status, pack-years, smoking status of family members, indoor charcoal or briquette braziers used for heating, and occupation) were directly adjusted using individual data.

On the other hand, the RR used for present study involves several uncertainties regarding the estimation of $PM_{2.5}$ concentration and time lag between $PM_{2.5}$ exposure and lung cancer outcome. However, the RR values from the analysis were generally comparable to those reported in previous studies conducted in the US and European countries (*28,47-49*).

This study has several limitations. First, our analysis did not account for cumulative $PM_{2.5}$ exposure. Adverse health effects are dependent not only on concentration but also on the length of $PM_{2.5}$ exposure. In Japan, more than two million people move across prefectural boundaries every year (*50*). Rates of inter-prefectural migration vary among prefectures. Migration has an effect on both the length of $PM_{2.5}$ exposure and cumulative $PM_{2.5}$ exposure. Adjustment for migration may improve the estimation of PAF and its distribution in Japan.

Second, we could not obtain individual measurements of exposure to ambient $PM_{2.5}$ in this analysis. Individuals also constantly move in time and space. To support health impact assessment, it is essential to develop a better understanding of individual exposure pathways in people's everyday lives by taking account of all environments in which people spend time.

Finally, smoking prevalence varies across prefectures in Japan, ranging in 2019 from 26.5% in Ehime to 35.8% in Saga (Japan total: 28.8%) (*51*). A previous meta-analysis reported the presence of smoking-related confounding bias in the RR of $PM_{2.5}$ on lung cancer, and suggested that never- and former smokers may have an elevated risk of lung cancer associated with $PM_{2.5}$ compared to current smokers (*52,53*). However, because we had no information on smoking prevalence among cities, we used the overall RRs adjusted for multiple covariates, including smoking status, instead of RRs by smoking status.

Conclusion

Our findings indicate that nearly 10% of lung cancer and 1-2% of total cancer were attributable to excess $PM_{2.5}$ exposure in Japan, with regional differences. This study provides useful information for policy-makers and public health agencies to aid the efficient development of their environmental cancer prevention policies.

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BRIEF REPORT

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Burden of cancer attributable to consumption of highly salted food in Japan in 2015

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Abstract: Salt consumption is high in most parts of the world, particularly among populations in Asia-Pacific region, including Japan. The recent portion of global deaths attributable to excess salt was largest among dietary exposures. We estimated the cancer in 2015 attributable to highly salted food in the Japanese population. Consumption of highly salted food in grams per day was available by sex and age group for 2005 from the Japanese National Health and Nutrition Survey. The optimal consumption of highly salted food for this study was assumed to be 0 g/day. Population attributable fractions (PAFs) for stomach cancer, which is positively associated with highly salted food intake in Japan, were estimated for respective sex and age groups according to a standard formula, and aggregated to obtain the PAF among total cancer incidence and mortality. In both sexes, 2.4% of cancer incidence and 2.2% of cancer mortality in 2015 were due to intake of highly salted food. Annually at least 22,000 total cancer cases in Japan could have been prevented by avoiding highly salted food.

***Keywords*:** cancer, highly salted food, population attributable fraction, Japan

Introduction

Cancer and cardiovascular disease are the leading causes of death in many parts of the world. High sodium consumption and salt-preserved foods are considered major dietary risk factors of cardiovascular diseases caused by high blood pressure (*1*) and some cancers (*2*). The World Health Organization (WHO) recommends keeping salt intake to less than 5 g/day to prevent these non-communicable diseases (NCDs) (*3*). The East Sub-Saharan African region is reported to have the lowest intake, with an average of 5 grams of salt per day (*4*). Most people in the world consume too much salt. Intake is highest in high income Asia-Pacific countries, including Japan, at an average of approximately 12 g/day as measured by 24-hour urinary excretion, and in Central Asia, at 13 grams of salt per day, in 2010 (*4*). The World Cancer Research Fund (WCRF)/American Institute for Cancer Research (AICR) reaffirmed in 2018 that salt-preserved foods increase risk for cancers of the stomach with a positive dose-response relationship (*2*). The latest estimate by the International Agency for Research on Cancer (IARC) describes stomach cancer as the fifth-most common cancer worldwide, with around 1,033,701 new cases globally in 2018 (*5*). Salt consumption in the Japanese population decreased by 1g at most in the 10 years between 2005 and 2015 (*6*). Despite global and domestic efforts, 2015 intake levels were still far from the WHO recommendation. At least 50% of salt in the diet appears to come from commercially processed foods with salt (*e.g.* salted-preserved fish or salted pickled vegetables). This remains the case even after salty seasonings such as soy sauce and miso - major sources of personal preference-based discretional sodium among Japanese - are excluded (*7*).

The fundamental etiology of stomach cancer by highly salted food intake is suggested to be as follows (*2*): high salt levels alter the viscosity of the mucous protecting the stomach, and intake of highly salted food may stimulate the colonization of H. *pylori*, the greatest known risk factor for stomach cancer. Highly salted food is not essential for optimal health in stomach cancer.

Here, we estimated the fraction of cancer incidence and mortality in 2015 attributable to highly salted food in the Japanese population.

Materials and Methods

Cancers associated with highly salted food

The WCRF/AICR reaffirmed that salt-preserved food increases risk for cancers of the stomach with a positive dose-response relationship (*2*). We therefore included these target cancers in the present evaluation; specifically, those with sufficient evidence for a positive association with highly salted food, and with available relative risk estimates in Japan, including stomach cancer.

Theoretical minimum risk exposure level

For this study, the optimal consumption of highly salted food in Japan was set at 0 g/day. The latent period - the interval period between "exposure" to highly salted food and the increase in risk of cancers of the stomach - is unknown. Based on previous epidemiological studies of exposure, we assumed a latent period of 10 years, and accordingly calculated the 2015 fraction of avoidable cancers using an estimate of highly salted food intake in 2005.

Prevalence of highly salted food consumption

The data on highly salted food consumption were derived from the Japanese National Health and Nutrition Survey (JNHNS) from 2005 (*8*). For this purpose, we used the 3-year mean of individual data for the years 2004-2006 provided by the Ministry of Health, Labour, and Welfare, Japan, with permission. Highly salted foods include pickled salty vegetables and salt-preserved fish. The survey presents mean consumption and its standard deviation by sex and age group. Table 1 shows the consumption of highly salted food per day by sex and age group for the Japanese population in 2005.

Table 1. Sex- and age-group-specific average consumption of highly salted food in Japan in 2005

Age at exposure (2005)	Highly salted food consumption (g/day)	
	Men	Women
0 - 4	7.2	7.8
5 - 9	10.0	10.5
10 - 14	13.5	16.1
15 - 19	20.3	20.4
20 - 24	21.8	20.4
25 - 29	25.5	19.6
30 - 34	26.7	20.4
35 - 39	27.2	20.5
40 - 44	30.9	23.5
45 - 49	36.9	29.6
50 - 54	38.9	32.4
55 - 59	43.6	37.8
60 - 64	49.0	39.8
65 - 69	49.1	44.8
70 - 74	50.7	43.3
≥ 75	46.8	41.6
Total	33.5	29.6

Cancer incidence and mortality in Japan in 2015

Cancer incidence data in 2015 were estimated using the annual estimate of cancer incidence in 2013 by the Monitoring of Cancer Incidence in Japan project (*9*). We used an age and period spline model. This type of model is used for short-term projection of cancer incidence in Japan (*10*). The sex- and age-specific incidence data for target cancers were coded in accordance with the International Statistical Classification of Diseases and Related Health Problems, 10th edition (ICD-10), using the morphology code of the International Classification of Disease for Oncology, 3rd edition (ICD-O-3).

The data on cancer mortality statistics from 2015 were based on the vital statistics of Japan (*11*). We obtained sex- and age-specific mortality data by cause of death from available data sources from the Health, Labour, and Welfare Statistics Association (*12*), using 4-digit ICD-10 codes to classify the cause of death.

Estimation of relative risk

The relative risk (RR) of stomach cancer in relation to highly salted food consumption was obtained from a meta-analysis of eight cohort studies (91% weight of combined results was sourced from four studies in Japan) conducted by the WCRF (*13*). This 2018 meta-analysis reported an RR of 1.09 (95% confidence interval: 1.05-1.13) per 20 g/day. We derived the increase in risk of stomach cancer for 1 g/day of highly salted food and average RR for the whole population based on the average highly salted food consumption, with an assumed log-linear relationship between highly salted food consumption and stomach cancer risk of:

$$Risk = exp^{[\ln(\text{risk per gram of highly-salted food intake}) \times \text{average exposure level}]}$$

Estimation of population attributable fractions (PAFs)

For stomach cancer, PAF was calculated for each sex and age group according to the standard formula (*14*):

$$\text{PAF} = \frac{(Risk - 1)}{Risk}$$

The number of attributable cancers was then totaled across all sex and age categories in order to show the percentage of the total number of all incidence and mortality of cancer in Japan in 2015.

Results and Discussion

The consumption of highly salted food among Japanese

people in 2005 is shown in Table 1. On average, across age categories, consumption was 33.5 g/day and 29.6 g/day for men and women, respectively. Consumption increased by age category up to 65-74 years for men (approximately 50 g/day) and women (approximately 45 g/day).

Tables 2 and 3 show the estimated number of incidence and mortality of stomach cancer in 2015 attributed to excessive consumption of highly salted food in 2005. Consumption of highly salted food was attributed to 17.7% of stomach cancer incidence for men and 15.4% for women. A similar trend was seen for stomach cancer mortality (18.1% for men, 15.8% for women). Likewise, consumption of highly salted food was attributed to 3.0% of total cancer incidence for men and 1.6% for women, and to 2.5% of total cancer mortality for men and 1.7% for women. Accordingly, in both sexes, 2.4% of cancer incidence and 2.2% of cancer mortality in 2015 were due to excessive intake of highly salted food. These results were not changed when the latent period was assumed to be 15 years (exposure mean calculated based on the 2000 National survey).

Our study suggests that 2.4% (22 thousand) of total cancer incidence and 2.2% (8 thousand) of cancer mortality in 2015 could have been prevented by avoiding highly salted food. Three PAFs of cancer were reported, based on inadequate salt intake, a reasonable optimal intake of ≤ 6 g/day (*15,16*), and a strict optimal

Table 2. Numbers and proportion of cancer cases in 2015 attributable to highly salted food consumption (> 0 g intake of highly salted food consumption)

Age at exposure (2005)	Age at outcome (2015)	Stomach cancer			Total cancers	
		PAF	Obs. cases	Attrib. cases	Obs. cases	Attrib. cases
Men						
0 - 4	10 - 14	0.03	1	0	410	0
5 - 9	15 - 19	0.04	3	0	519	0
10 - 14	20 - 24	0.06	13	1	682	1
15 - 19	25 - 29	0.08	36	3	974	3
20 - 24	30 - 34	0.09	88	8	1,595	8
25 - 29	35 - 39	0.10	231	24	2,962	24
30 - 34	40 - 44	0.11	682	74	6,281	74
35 - 39	45 - 49	0.11	1,476	163	10,557	163
40 - 44	50 - 54	0.12	2,867	357	17,827	357
45 - 49	55 - 59	0.15	4,937	726	29,272	726
50 - 54	60 - 64	0.15	9,056	1,398	53,238	1,398
55 - 59	65 - 69	0.17	15,599	2,672	91,095	2,672
60 - 64	70 - 74	0.19	16,743	3,189	96,962	3,189
65 - 69	75 - 79	0.19	16,081	3,065	93,375	3,065
70 - 74	80 - 84	0.20	13,054	2,560	77,034	2,560
≥ 75	≥ 85	0.18	11,015	2,010	65,753	2,010
Total		0.18	91,883	16,249	549,241	16,249
% of incident cases				17.7		3.0
Women						
0 - 4	10 - 14	0.03	1	0	351	0
5 - 9	15 - 19	0.04	6	0	531	0
10 - 14	20 - 24	0.07	18	1	914	1
15 - 19	25 - 29	0.08	48	4	1,791	4
20 - 24	30 - 34	0.08	120	10	3,780	10
25 - 29	35 - 39	0.08	277	22	7,759	22
30 - 34	40 - 44	0.08	605	51	14,970	51
35 - 39	45 - 49	0.08	912	77	19,397	77
40 - 44	50 - 54	0.10	1,300	125	22,922	125
45 - 49	55 - 59	0.12	1,853	222	26,467	222
50 - 54	60 - 64	0.13	3,104	404	36,091	404
55 - 59	65 - 69	0.15	5,182	778	50,521	778
60 - 64	70 - 74	0.16	5,834	920	49,841	920
65 - 69	75 - 79	0.18	6,358	1,117	49,967	1,117
70 - 74	80 - 84	0.17	6,704	1,142	50,482	1,142
≥ 75	≥ 85	0.16	9,881	1,623	72,222	1,623
Total		0.15	42,203	6,497	408,572	6,497
% of incident cases				15.4		1.6
Both sexes			134,087	22,746	957,813	22,746
% of incident cases				17.0		2.4

Abbreviations: Attrib. = Attributable; Obs. = observed; PAF = population attributable fraction.

Table 3. Numbers and proportion of cancer mortality in 2015 attributable to highly salted food consumption (> 0 g intake of highly salted food consumption)

Age at exposure (2005)	Age at outcome (2015)	Stomach cancer			Total cancers	
		PAF	Obs. deaths	Attrib. deaths	Obs. deaths	Attrib. deaths
Men						
0 - 4	10 - 14	0.03	0	0	52	0
5 - 9	15 - 19	0.04	0	0	86	0
10 - 14	20 - 24	0.06	8	0	112	0
15 - 19	25 - 29	0.08	19	2	153	2
20 - 24	30 - 34	0.09	30	3	260	3
25 - 29	35 - 39	0.10	66	7	521	7
30 - 34	40 - 44	0.11	141	15	1,225	15
35 - 39	45 - 49	0.11	256	28	2,035	28
40 - 44	50 - 54	0.12	524	65	3,923	65
45 - 49	55 - 59	0.15	992	146	7,622	146
50 - 54	60 - 64	0.15	2,199	339	16,179	339
55 - 59	65 - 69	0.17	4,108	704	29,367	704
60 - 64	70 - 74	0.19	4,939	941	34,860	941
65 - 69	75 - 79	0.19	5,504	1,049	37,820	1,049
70 - 74	80 - 84	0.20	5,710	1,120	40,650	1,120
≥ 75	≥ 85	0.18	6,312	1,152	44,515	1,152
Total		0.18	30,809	5,571	219,508	5,571
% of cancer deaths				18.1		2.5
Women						
0 - 4	10 - 14	0.03	0	0	55	0
5 - 9	15 - 19	0.04	3	0	61	0
10 - 14	20 - 24	0.07	5	0	64	0
15 - 19	25 - 29	0.08	13	1	170	1
20 - 24	30 - 34	0.08	52	4	394	4
25 - 29	35 - 39	0.08	75	6	763	6
30 - 34	40 - 44	0.08	141	12	1,623	12
35 - 39	45 - 49	0.08	211	18	2,484	18
40 - 44	50 - 54	0.10	279	27	3,841	27
45 - 49	55 - 59	0.12	436	52	5,501	52
50 - 54	60 - 64	0.13	803	105	9,146	105
55 - 59	65 - 69	0.15	1,352	203	14,322	203
60 - 64	70 - 74	0.16	1,617	255	16,783	255
65 - 69	75 - 79	0.18	1,991	350	20,329	350
70 - 74	80 - 84	0.17	2,739	467	25,876	467
≥ 75	≥ 85	0.16	6,153	1,011	49,345	1,011
Total		0.16	15,870	2,510	150,838	2,510
% of cancer deaths				15.8		1.7
Both sexes			46,679	8,081	370,346	8,081
% of cancer deaths				17.3		2.2

Abbreviations: Attrib. = Attributable; Obs. = observed; PAF = population attributable fraction.

intake of ≤ 0.5 g/day (*17*). These were a PAF of 1.6% of cancer incidence in 2005 for Japanese (*15*), 0.5% of cancer incidence in 2010 for the UK (*16*), and 14,000 cancers cases (4%) among 335,000 deaths of total cancer in 2007 for Japanese (*17*). The difference in consumption of highly salted foods, such as pickled vegetables, and stomach cancer incidence between Japanese or Asian countries and Western countries suggests the presence of a burden gap between Japan and Western countries (*7,18*). Exposure prevalence in the present study was estimated based on the intake of highly salted food rather than of salt, from the suggestion that the intake of highly salt-concentrated preserved foods confers a greater risk of stomach cancer than that of whole salt (*19*). Similarly, the 2018 WCRF report summary for stomach cancer was updated to describe exposure to highly salted food, from salt intake in the preceding 2007 report (*13*). A further strength of our present study is that exposures (mean intake) were calculated for individual survey-derived age classes, compared to a representative mean for all ages based on household surveys in the previous 1990 estimation. This improvement was permitted by a change in data collection methods in the 1995 JNHNS, and revealed higher mean intake for older age classes, with higher stomach cancer incidence and mortality (*8*).

This study has some potential limitations. In a meta-analysis of salt-preserved foods and digestive cancers,

only a single large study from Japan showed positive associations between intake of salt-preserved fish or salt-preserved fish roe and risk of colorectal cancer (*19*). Therefore, the PAF of highly salted food was calculated for stomach cancer only, which may have led to an underestimation of risk. Also, we used an RR of 1.09 per 20 g increment in this estimation based on a meta-analysis for salted vegetables in the WCRF 2018 report (*2*), because this meta-analysis included nearly all the published Japanese studies and clearly defined the exposure. A meta-analysis by Kim *et al.* of pickled vegetables and stomach cancer in Japanese and Korean populations reported an RR of 1.28. That study included observational case-control and cohort studies for highest *vs.* lowest intake in quantitative amounts or combined frequency (*20*). The WCRF 2018 report included another meta-analysis of stomach cancer estimates, with an RR of 1.70 for unspecified highly salted food, including salty confectionary and foods deep boiled in soy sauce (*tsukudani*) (*2*). PAFs of highly salted food for cancers may be slightly larger than the present results if other detailed food items were used for mean exposure calculation. Carcinogenesis by highly salted food intake may be confounded by other factors, such as H. *pylori* infection. Given that stomach cancer has a multifactorial etiology, a multivariate estimation of PAF would provide a better estimation of the burden.

Allowing for these limitations, these estimates have major implications for Japan's national health policy for cancer prevention and control strategies. In a previous study of the burden of non-communicable disease death, including death due to cardiovascular disease and cancers, assessed for dietary factors in Japan, the burden for cardiovascular disease attributable to salt intake was larger than that for cancer, with corresponding numbers of 19,000 and 14,500, respectively (*17*). In the global burden of death attributable to behavioral, environmental, occupational, and metabolic risk factors, the major portion for diet risks, and the portion due to excess salt was largest among dietary exposures such as fruit or vegetables (*21*). The current Japanese salt intake level is highest in the world. Policymakers and public health agencies must invest in and implement interventions to reduce salt intake and diets with highly salted foods to control the burden of non-communicable diseases in Japan, including cancers.

Conclusion

Our analysis provides evidence for the current burden of cancer attributable to intake of highly salted foods. In 2015, at least 22,000 cancer cases in Japan could have been prevented by avoiding highly salted foods. The results of this study may provide useful evidence to reduce the cancer burden in Japan.

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BRIEF REPORT

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Burden of cancer attributable to excess red and processed meat consumption in Japan in 2015

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Abstract: The International Agency for Research on Cancer has evaluated red meat as probably carcinogenic and processed meat as carcinogenic to humans. The World Cancer Research Fund and American Institute for Cancer Research concluded there is convincing evidence that consumption of processed meat increases the risk of colorectal cancer. We estimated the number and fraction of cancer incidence and mortality in 2015 that could be attributed to excess red and processed meat consumption in 2005 among the Japanese population. Data on the consumption of red and ptocessed meat, in g/day, by sex and age group, is available for 2005 from the Japanese National Health and Nutrition Survey. For the present study, the optimal consumption of red meat in Japan was considered as less than 500 g/week, or 71.4 g/day, and 0 g/day for processed meat. Population attributable fractions (PAFs) were calculated for each sex and age group according to a standard formula, and aggregated to obtain the PAF among total cancer incidence and mortality. We found that 0.01% and 0.4% of cancer incidence was attributable to red and processed meat consumption, respectively, while 0.0002% and 0.3% of cancer mortality was attributable to red meat and to processed meat consumption. Based on the current evidence, monitoring red and processed meat consumption may not contribute to reducing cancer incidence and mortality in Japan.

***Keywords*:** cancer, red meat, processed meat, population attributable fraction, Japan

Introduction

Lifestyle factors, including diet, are key determinants of cancer risk (*1*). The International Agency for Research on Cancer (IARC) has rated red meat as probably carcinogenic (Group 2a) and processed meat as carcinogenic to humans (Group 1) (*2*). An expert report by the World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR) titled Food, Nutrition, Physical Activity and Prevention of Cancer concluded there was strong evidence that the consumption of processed meat - defined as meat preserved by smoking, curing, salting, or the addition of chemical preservatives - and of red meat increase the risk of colorectal cancer (*3*). The report recommended limiting weekly consumption to no more than about three portions (350-500 g/week). It also reported that consumption of processed meat was associated with a limited-suggestive increase in risk for nasopharynx, esophagus, lung, stomach, and pancreatic cancer (*3*).

Potential mechanisms by which red and processed meat may effect cancer risk derive from high cooking temperatures: heme iron may catalyze lipid peroxidation, leading to tissue damage (*4,5*) and the formation of carcinogenic *N*-nitroso compounds (*6-8*). Cooking meat at high temperatures also induces the formation of heterocyclic aromatic amines and polycyclic aromatic hydrocarbons, which might also contribute to carcinogenesis of various sites (*9-12*).

Globally, red and processed meat have been linked to an increased risk of colorectal cancer incidence (*3,13*). National-level estimates of the burden for all cancers due to red and processed meat were 2.3% in Australia (*14*), 2.4% in Germany (*15*), and 2.7% in the UK (*16*). In the Japanese setting, red meat was not included in former studies of PAF for cancer (*17*) or non-communicable diseases (*18*) due to relatively low consumption compared to Europe and the US. The 2013 Japanese National Health and Nutrition Survey (JNHNS) (*19*) reported that an individual's average

daily red and processed meat consumption was 63 g and 13 g, respectively - among the lowest in the world (*19-21*). The Japan Public Health Center-based Prospective Study (JPHC Study) (*13*) found no significant association between processed meat consumption and risk of colorectal cancer for Japanese men and women, but did find a significantly increased risk for red meat in the highest level consumption group, suggesting the possibility of a risk difference between Japan and Europe or North America. A Japanese meta-analysis reported a significant risk of colorectal cancer (*22*) with red meat and a non-significant risk with processed meat, providing the rationale for the present study.

In this report, we estimated the number and fraction of cancer incidence and mortality in 2015 that could be attributed to excess red and processed meat consumption in 2005 among the Japanese population.

Materials and Methods

Cancers associated with red and processed meat

IARC rated red meat as probably carcinogenic (Group 2a) and processed meat as carcinogenic to humans (Group 1) (*2*). Additionally, the WCRF and AICR concluded there was strong evidence that the consumption of processed meat, as well as red meat, increases the risk of colorectal cancer (*3*). In the present study, therefore, we evaluated target cancers identified by this evaluation to be associated with red and processed meat. We included colorectal cancer, which showed sufficient evidence for a positive association with red and processed meat and for which relative risk estimates were available in Japan.

Theoretical minimum risk exposure level

For the purpose of this study, we considered the optimal consumption of red meat in Japan - defined as beef, pork, ham, sausage, other animal meat such as mutton, and organ meat such as tripe - was less than 500 g/week. In the present study, 1/7 of 500 g/week, or 71.4 g/day, was adopted as a theoretical minimum risk exposure level. In addition, we considered the optimal consumption of processed meat, defined as ham and sausage, as 0 g/day (*23*).

Prevalence of excess red and processed meat estimates

The latent period, as in the interval between "exposure"to red and processed meat and the increase in the risk of cancer of the colon is unknown. The average follow-up period of the six cohorts included in the systematic review by Pham *et al.* (*22*) was 13 years. For the present study, we assumed that a mean latency of 10 years would be sufficient, and therefore calculated the 2015 fraction of avoidable cancers due to red and processed meat consumption in 2005.

The data on red and processed meat consumption by sex and age group were derived from the JNHNS from 2005 (*24*). For this purpose, we used the 3-year mean of individual datas for 2004-2006, obtained from the Ministry of Health, Labour, and Welfare, Japan, with permission.

Cancer incidence and mortality in Japan in 2015

We estimated cancer incidence data in 2015 using the annual estimate of cancer incidence in 2013 by the Monitoring of Cancer Incidence project in Japan (*25*). We used an age and period spline model, a type used for short-term projection of cancer incidence (*26*). The sex- and age-specific incidence data for target cancers were coded using the International Statistical Classification of Diseases and Related Health Problems, 10th edition (ICD-10), with the morphology code of the International Classification of Disease for Oncology, 3rd edition (ICD-O-3).

The data on total and colon cancer mortality statistics from 2015 were obtained from Japan's vital statistics (*27*). We obtained sex- and age-specific mortality data by cause of death from available data sources from the Health, Labour, and Welfare Statistics Association (*28*). Similar to the cancer incidence data, we used the 4-digit ICD-10 codes to classify the cause of death.

Estimation of relative risk

The relative risk (RR) for colorectal cancer associated with consumption of red and processed meat was sourced from a meta-analysis of Japanese cohort and case-control studies (Table 1) (*22*). First, colon and rectal cancers were considered separately. However, rectum was excluded as the RR was lower than 1.00. Consequently, we estimated PAF for only colon cancer applying the meta-analysis RR value of cohort studies. We used estimated risk (95% confidence interval) of colon cancer for the highest quintile of consumption by 1.20 (1.00-1.44) and 1.18 (0.92-1.53) for red meat and processed meat, respectively (*22*). Increase in the risk by an increment of 1 g/day of red and processed meat consumption, respectively, was calculated, based on an assumption that the relationship between exposure and colon cancer risk is log-linear. The following equation was used for red and processed meat consumption, respectively, and the risk of colon cancer:

$$Risk = exp^{[\ln(\text{risk per gram of red and processed meat}) \times \text{average exposure level}]}$$

Estimation of population attributable fractions (PAFs)

PAF was calculated for each sex and age group according to the formula:

Table 1. Summary of risk estimates for the association between red and processed meat consumption and site-specific cancer

Exposure	Theoretical minimum risk exposure level	Cancer type	Estimated risk for the highest quintile of consumption	*Ref.*
Red meat	< 500 g/week or < 71.4 g/day	Colon	1.20 (1.00 - 1.44)	Pham *et al.* (*22*)
Processed meat	0 g/day	Colon	1.18 (0.92 - 1.53)	Pham *et al.* (*22*)

Table 2. Sex- and age-group-specific consumption of red and processed meat, in g/day in Japan in 2005

Age at exposure (2005)	Red meat		Processed meat	
	Mean consumption (g/day)	Excess from 71.4 g/day	Mean consumption (g/day)	Excess from 0 g/day
Men				
0 - 4	34.93	0.00	10.3	10.3
5 - 9	54.66	0.00	13.0	13.0
10 - 14	79.99	8.56	15.8	15.8
15 - 19	106.92	35.49	22.5	22.5
20 - 24	88.76	17.33	16.9	16.9
25 - 29	90.13	18.70	18.1	18.1
30 - 34	88.87	17.44	17.9	17.9
35 - 39	81.45	10.03	14.9	14.9
40 - 44	80.58	9.15	17.0	17.0
45 - 49	76.47	5.04	15.0	15.0
50 - 54	69.84	0.00	12.3	12.3
55 - 59	67.06	0.00	12.5	12.5
60 - 64	59.93	0.00	11.0	11.0
65 - 69	48.35	0.00	8.7	8.7
70 - 74	43.69	0.00	7.8	7.8
≥ 75	34.42	0.00	7.0	7.0
Total	67.54	0.00	13.3	13.3
Women				
0 - 4	33.44	0.00	9.7	9.7
5 - 9	50.61	0.00	11.8	11.8
10 - 14	65.68	0.00	14.3	14.3
15 - 19	78.25	6.82	18.4	18.4
20 - 24	61.06	0.00	13.3	13.3
25 - 29	60.79	0.00	12.9	12.9
30 - 34	58.12	0.00	13.5	13.5
35 - 39	58.51	0.00	12.4	12.4
40 - 44	60.00	0.00	13.3	13.3
45 - 49	56.96	0.00	11.5	11.5
50 - 54	49.84	0.00	10.1	10.1
55 - 59	49.81	0.00	10.3	10.3
60 - 64	41.82	0.00	7.6	7.6
65 - 69	37.98	0.00	7.5	7.5
70 - 74	36.43	0.00	7.5	7.5
≥ 75	27.93	0.00	5.3	5.3
Total	49.53	0.00	10.5	10.5

Red meat: beef, pork, ham, sausage, other meat such as mutton, and organ meat; processed meat: ham and sausage consumption; and excess, reported as mean g/day.

$$\mathrm{PAF} = \frac{(Risk - 1)}{Risk}$$

The number of attributable cancers was then totalled across all sex and age categories, in order to show the percentage of the total number of all cancer incidence and mortality recorded in Japan in 2015.

Results and Discussion

Table 2 shows the age- and sex-stratified red and processed meat mean consumption, in g/day, and the excess over 71.4 g/day for red meat and over 0 g/day for processed meat for the Japanese population, derived from the JNHNS in 2005. Red and processed meat consumption in all categories peaked in the

Table 3. Proportion (%) of cancer in 2015 attributable to excess red and processed meat consumption in Japan

Factors	Incidence			Mortality		
	Men	Women	Both sexes	Men	Women	Both sexes
Red meat						
Colon (C18)	0.1	0.0	0.1	0.1	0.0	0.0
Total cancer (C00-C96)	0.0	0.0	0.0	0.0	0.0	0.0
Processed meat						
Colon (C18)	4.3	3.3	3.8	4.0	3.0	3.0
Total cancer (C00-C96)	0.4	0.4	0.4	0.3	0.3	0.3

15-19-year age group. In men, the trend of excess consumption continued until age 49 for red meat and continued until the oldest age group for processed meat. Japanese women overall consumed less red meat than men. While only 15-19-year-old women consumed red meat in excess, women of all age categories consumed processed meat in excess.

The estimated PAF of cancer incidence and mortality in 2015 attributed to red and processed meat consumption in Japan is summarized in Table 3.

Table S1 (online data, *https://www.ghmopen.com/site/supplementaldata.html?ID=39*) shows the PAF of cancer incidence in Japan in 2015 due to red and processed meat consumption in 2005. Excess red meat consumption was attributable to 0.01% of total cancer incidence in Japan (0.01% in men and 0.0001% in women). Excess processed meat consumption attributed to 0.4% of total cancer incidence in Japan (0.4% for both men and women). Table S2 (online data, *https://www.ghmopen.com/site/supplementaldata.html?ID=39*) shows the PAF of cancer mortality in 2015 attributed to red and processed meat consumption in Japan in 2005, where excess red meat consumption attributed to 0.0002% of total cancer mortality (0.01% in men and 0.0002% in women) and the excess processed meat consumption attributed to 0.3% of total cancer mortality (0.3% for both men and women).

Additionally, using a similar approach as an Australian study (*14*), we performed a sensitivity analysis by changing the cut-off to 0 g/day instead of 71.4 g/day for red meat consumption. The PAFs were 0.6% (0.6% for both men and women) for cancer incidence and 0.5% (0.5% in men and 0.6% women) for cancer mortality.

In summary, our study suggests that 0.01% and 0.4% of cancer incidence may be attributable to red and processed meat consumption, respectively, while 0.0002% and 0.3% of cancer mortality may be attributable to red meat and to processed meat consumption, respectively. The results do not greatly differ from the theoretical minimum risk exposure level of zero. Regarding RR, an IARC monograph reported 17% increased risk for every 100 g/portion of red meat eaten daily (*2*). This is not substantially different from the RR used in this study (13% and 14% for every 100 g of meat consumption among men and women, respectively), based on a meta-analysis of Japanese studies (*22*).

Colorectal cancer incidence and mortality trends in Japan follow a different pattern compared to Europe and the United States (*27*). This difference may be due higher consumption of fish and less meat among Japanesean (*21*).

A recent 2016 review of cancer attributable to modifiable factors by Whiteman *et al.* (*29*) provides an insufficient overview of the global situation for red and processed meat, and includes only two reports, from Australia (*14*) and the UK (*16*). In the UK study, the theoretical minimum risk exposure level for red meat was nil (*16*), and thus was stricter than our study cut off. The study reported that 2.7% of all cancers were attributable to red and processed meat. The Australian study found men aged 19 years and older that consumed 121 g/day of red meat and 64 g/day of processed meat accounted for 2.3% of all cancers (*14*), with a theoretical minimum risk exposure level of zero. In addition to these studies, a 2018 German study reported that 2.4% of all cancers were attributable to red meat, with a theoretical minimum risk exposure level of 500 g red meat/week and 0 g processed meat/week (*15*). Red and processed meat is not as popular or heavily consumed in Japan as in Western countries, resulting in the low attributed PAF in Japan. Therefore, policies to control red and processed meat consumption will likely not be effective to reduce cancer incidents and mortality in Japan.

Conclusion

Our analysis provides evidence for the relatively small burden of cancer attributable to red and processed meat consumption in Japan. From the results, 0.01% and 0.4% of cancer incidence, and 0.0002% and 0.3% of cancer mortality is attributable to red and processed meat consumption, respectively. These findings may provide critical evidence for the priority ranking of programs aimed to reduce the cancer burden in Japan.

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BRIEF REPORT

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Burden of cancer attributable to exogenous hormone use in Japan in 2015

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Abstract: Exogenous female hormone use has not been as popular in Japan as in western populations. Here, we estimated the population-attributable fraction (PAF) of cancers in Japan in 2015 attributed to exogenous female hormone use. We used the most recent prevalence data for oral contraceptives (OC) and hormone replacement therapy (HRT), available from a large-scale population-based cohort study started in 2011-2016. For the purpose of this study, optimal usage of exogenous hormones was considered to be none. PAF was calculated for each age group using a standard formula. Overall, a negligible fraction, 0.4% of cancer incidence and 0.2% of cancer mortality in Japanese women was attributable to exogenous hormone use (OC use and HRT), and 0.2% of cancer incidence and 0.1% of cancer mortality overall when both sexes combined. The relatively low prevalence of exogenous hormone use in Japan compared to Western countries may explain the low fraction of cancer attributable to exogenous hormones among Japanese women.

***Keywords*:** cancer, exogenous hormone use, oral contraceptives, hormone replacement therapy, population attributable fraction, Japan

Introduction

In 2007, the International Agency for Research on Cancer (IARC) published a monograph on carcinogenic risk to humans that concluded that combined oral-progestogen contraceptives (OC) are carcinogenic to humans (*1*), particularly for cancers of the breast, cervix, and liver. On the contrary, however, there is also convincing evidence that these agents may act as protective factors for cancer of the endometrium and ovary.

The same review by IARC also concluded that, with regard to hormone replacement therapy (HRT), there is sufficient evidence in the association between combined estrogen-progestogen menopausal therapies and cancer of the breast (*1*). The finding of increased breast cancer risk associated with HRT has mainly been found among current users. Combined estrogen-progestogen menopausal therapy was considered to be carcinogenic to humans if progestogens are taken for less than 10 days per month; however, the risk for endometrial cancer was inversely associated with the number of days per month that progestogens are added to the regimens.

The usage of hormonal preparations in Japan has always been low. Despite the popularity of using HRT in the US and European nations, in 2011-2016, only 2.4% and 4.8% of women aged 40-74 had reported ever use of any type of OC and HRT, respectively, based on recent cohort study data in Japan (*2*).

In this report, we explore the population-attributable fractions (PAF) of cancers in Japan in 2015 attributed to exogenous female hormone use.

Materials and Methods

Cancers associated with exogenous hormone use

IARC has confirmed the usage of both OC (combined estrogen-progestogen) and HRT (combined estrogen-progestogen menopausal therapy) as Group 1, carcinogenic to humans (*3*). For the purpose of this study, we chose sites associated with OC and HRT for which IARC has found sufficient evidence for positive associations using available data on relative

risk. The cancer sites included in this report are breast, endometrium, and ovary.

Theoretical minimum risk exposure level

PAF of cancers associated with exogenous hormone use is the proportion of cancers diagnosed in a certain period in a population that could possibly have been prevented if no one in the population used OC or HRT. Accordingly, the optimal exposure to exogenous hormone use in this study was defined as no use. Analyses were conducted based on the type of exogenous hormone used (OC use or HRT).

Prevalence of exposure to hormonal use

No latent period was assumed in relation to female hormonal use, as current and recent users of female hormones are thought to be at the highest risk. To obtain Japanese data from a study or survey as close to 2015 as possible, we used data from the Japan Public Health Center-based Prospective Study for the Next Generation (JPHC-NEXT) (*4*) for both OC and HRT use. These data were based on a self-administered questionnaire given at baseline, which included exogenous hormone use. The generally healthy women ($n \approx 60{,}000$) were asked if they had ever used OC and HRT. The baseline summary for OC and HRT use was reported (*2*). We further obtained age group-specific data from the research group for the purpose of this study. Since the JPHC-NEXT study includes participants aged 40-74, we assumed that the prevalence of OC use by those aged under 40 years was equal to that of those aged 40-44, and that the prevalence of HRT use by those aged over 75 was equal to that those aged 70-74.

Table 1 shows the proportion of the Japanese women with recent OC use and HRT by age group.

Cancer incidence and mortality in 2015

Cancer incidence data in 2015 were estimated using the annual estimate of cancer incidence in 2013 by the Monitoring of Cancer Incidence in Japan (*5*) using an age and period spline model, which are used as a short-term projection method for cancer incidence in Japan (*6*). The sex- and age-specific incidence data for target cancers were coded based on the International Statistical Classification of Diseases and Related Health Problems, 10th edition (ICD-10), using the morphology code of the International Classification of Disease for Oncology, 3rd edition (ICD-O-3).

The data on cancer mortality statistics from 2015 were based on the vital statistics of Japan (*7*). We obtained sex- and age-specific mortality data by cause of death from an available data source from the Health, Labour, and Welfare Statistics Association (*8*). Similarly to the cancer incidence data, 4-digit ICD-10 codes were used to classify the cause of death.

Estimates of relative risk of exposure to exogenous hormonal use

Given that previous studies on exogenous hormone use and cancer risk conducted in Japanese women were limited, we used results from global meta-analyses as described below.

OC use

Breast cancer: In 1996, the Collaborative Group on Hormonal Factors in Breast Cancer (*9*) conducted an analysis of global epidemiological evidence on the association between use of OC and breast cancer risk. The relative risks associated with current and former use of OC (estrogen and progesterone) showed that OC use lead to a slight increase in risk.

Table 1. Proportion of exogenous hormone use with oral contraceptives (OC) and hormone replacement therapy (HRT) in Japan

Age at exposure and outcome (2015)	Proportion of oral contraceptive (OC) usage in the population (%)	Proportion of hormone replacement therapy (HRT) usage in the population (%)
10 - 14	0.0	0.0
15 - 19	0.0	0.0
20 - 24	3.5	0.0
25 - 29	3.5	0.0
30 - 34	3.5	0.0
35 - 39	3.5	0.0
40 - 44	3.5	1.3
45 - 49	2.8	3.4
50 - 54	2.4	6.3
55 - 59	0.0	6.5
60 - 64	0.0	5.9
65 - 69	0.0	5.9
70 - 74	0.0	4.8
75 - 79	0.0	4.8
80 - 84	0.0	4.8
≥ 85	0.0	4.8

Data source: Reference (*2,4*)

Table 2. Summary of risk estimates of site-specific cancers associated with exogenous hormone use for the present analysis

Factors	Cancer type	Studies	Reference group	Increase in risk
Oral contraceptive use	Breast	Collaborative Group on Hormonal Factors in Breast Cancer (1996) (*9*)	Never	1.07 ± 0.02*
	Endometrium	Collaborative Group on Epidemiological Studies on Endometrial Cancer (2015) (*10*)	Never	0.69 (0.66 - 0.73)
HRT use	Ovary	Collaborative Group on Epidemiological Studies of Ovarian Cancer (2008) (*11*)	Never	0.73 ± 0.02**
	Breast	Kim *et al.* (2018) (*18*)	Never	1.33 (1.24 - 1.44)
	Ovary	Meta-analysis of the result of prospective studies from Collaborative Group on Epidemiological Studies on ovarian Cancer (2015) (*19*)	Never	1.22 (1.06 - 1.38)

*Standard deviation. **Standard error.

Endometrial cancer: In 2007, IARC concluded that there is strong evidence that the use of estrogen-progestogen OC has a protective effect against carcinogenicity in the endometrium (*1*). Based on their review of four cohorts and 21 case-controls, risk for endometrial cancer among women who had taken these medications, and the reported risk reduction generally correlated with the duration of use and persisted for at least 15 years after cessation of use. A more recent meta-analysis published in 2015 (*10*) echoed these previous findings, although the risk reduction was marginally smaller.

Ovarian cancer: A 2007 review by IARC concluded that OC use had a protective effect against ovarian cancer among women (*1*). Not only was risk reduction associated with the duration of OC use, its protective effect persisted over two decades. An analysis conducted by the Collaborative Group on Epidemiological Studies of Ovarian Cancer in 2008 (*11*) showed that ever users of OC had 27% risk reduction compared to never users.

HRT

Breast cancer: The magnitude of the risk of HRT for risk of breast cancer has now been well established, mainly through studies conducted in the United States, Europe, and the UK (*12-16*). In the Million Women Study (*17*), compared to never users, the RR of current HRT users was 1.66 (95% Confidence Interval (CI): 1.58-1.75), while among past HRT users the risk did not differ from never users. For the present study, we derived HR for breast cancer from a meta-analysis conducted by Kim *et al.* (*18*) conducted in 2018, which reported the pooled HR of 23 prospective cohort studies and two randomized controlled trials to be 1.33 (95% CI: 1.24-1.44).

Ovarian cancer: The RRs of ovarian cancer by duration of HRT use in current and past users was obtained from a meta-analysis of individual participant dataset (*19*). We further conducted a meta-analysis of these RRs to obtain a summary RR of HRT use in ovarian cancer.

Table 2 shows a summary of the studies used in this estimate to derive RRs.

Estimation of population attributable fractions (PAFs)

PAF was calculated using the standard formula (*20*):

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

Where *P* refers to the prevalence of hormonal usage by age. For the PAF estimation, we included age 20-54 for OC use and age 40 and over for HRT use. The numbers of attributable cancers were then totalled across age categories to show a percentage of the total number of all incidence and mortality of cancer in Japan in 2015.

Results and Discussion

Table 1 shows the proportion of exogenous hormone use among Japanese women around 2015 by age group. Around 3% in the age 20-54 group was using OC and around 5% of the population aged 40 and over was using HRT.

Table 2 shows a summary of risk estimates for each of the cancer sites associated with exogeneous hormone use. For the present study, we included breast cancer for OC use and breast and ovarian cancer for HRT use.

The estimated PAF of cancer incidence and mortality in 2015 attributed to exogenous hormone use (OC use and HRT), individually and aggregated in Japan is summarized in Table 3. In the Japanese setting, only breast cancer incidence and mortality were attributable to OC use, with 62 incident cases and 5 deaths. Accordingly, the overall PAF for OC use was 0.02% for cancer incidence and 0.003% for cancer mortality in Japanese women. Likewise, breast and ovarian cancer were attributed to recent HRT, accounting for 1,391 cases and 274 deaths. Overall PAF for the HRT was 0.3% for cancer incidence and 0.2% for cancer mortality. In total, 0.4% of all cancer incidence and 0.2% of all cancer mortality in Japanese women in 2015 were attributable to exogenous hormone use, and 0.2% of total cancer incidence and 0.1% of total cancer

Table 3. Proportion (%) of cancer in 2015 attributable to exogenous hormone use in Japan

Factors	Incidence		Mortality	
	Women	Both sexes	Women	Both sexes
Oral contraceptive use (OC)				
Breast (C50)	0.1		0.04	
Endometrium (C54)	0.0		0.0	
Ovary (C56)	0.0		0.0	
Total cancer (C00-C96)	0.02		0.003	
Hormone replacement therapy (HRT)				
Breast (C50)	1.5		1.6	
Ovary (C56)	1.0		1.1	
Total cancer (C00-C96)	0.3		0.2	
Exogenous hormone use (OC and HRT)				
Breast (C50)	1.6	1.2	1.6	1.6
Endometrium (C54)	0.0	0.0	0.0	0.0
Ovary (C56)	1.0	1.0	1.1	1.1
Total cancer (C00-C96)	0.4	0.2	0.2	0.1

mortality when both sexes were combined. Detailed results for each cancer, sex, and age group are shown for in Tables S1-S2 (online data, *https://www.ghmopen.com/site/supplementaldata.html?ID=37*).

In this study, we estimated the impact of exogenous hormone use on cancer incidence and mortality among Japanese women in 2015. We found that 0.4% of all cancer incidence and 0.2% of all cancer mortality were attributable to exogenous hormone use by Japanese women. Our findings (0.02% for OC, 0.3% for HRT among Japanese women) are lower than those from recent studies in Australia for 2010 (*21-23*) and in the UK for 2015 (*24*), where PAFs among overall cancers in women in Australia were 0.3% for OC use and 1.1% for HRT use, and 0.5% and 0.8% in the UK, respectively. The low prevalence data for OC and HRT use in Japan applied in this study may explain the low PAF of cancer attributable to exogenous hormones. Published data on the prevalence of exogenous hormone use in Japanese are limited. In the present study we used the most recent prevalence data for OC and HRT usage from the baseline data of a large-scale cohort study obtained in 2011-2016, which reflect recent exposure level to exogenous hormone use in the general Japanese population. The Japan Nurses' Health Study (JNHS) reported the prevalence of OC and HRT use among female nurses by cross-sectional survey between 2001-2007 (*25*), in which the lifetime prevalence of exogenous hormone use was 6.0% for OCs and 13.8% for HRT, albeit that these are relatively high compared with other studies focusing on general Japanese populations (*2,26*). According to the recent estimates from the United Nations that showed the estimated prevalence of contraceptive use among women of reproductive age (15-49) in 2019, the estimated prevalence of use of the pill was 2.9% in Japan (*27*), which accorded with our referenced data. We applied the prevalence data closest to the year 2015, and in the general population. More accurate estimates for risk would allow a better understanding of the impact of usage of exogenous hormones on cancer burden among Japanese women.

Conclusion

Our estimate found an overall negligible fraction, 0.4% of cancer incidence and 0.2% for cancer mortality in Japanese women, was due to exogenous hormone use (OC use and HRT). The low fraction of cancer attributable to exogenous hormones among Japanese women may be explained by the relatively low prevalence of exogenous hormone use in Japan compared with Western countries.

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BRIEF REPORT

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Burden of cancer attributable to never breastfeeding in Japan in 2015

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Abstract: We estimated the population attributable fraction (PAF) of cancers in Japan attributed to never breastfeeding in 2015. The data on breastfeeding in Japan were derived from two sources. Data on women aged younger than 40 were obtained from the Longitudinal Survey of Babies in the 21st Century (LSB21); those for women aged 40 to 69 was derived from the Japan Public Health Center-based Prospective Study for the Next Generation (JPHC-NEXT). For the present study, the optimal frequency of breastfeeding was a history of ever breastfeeding. The PAF was calculated for each age group using a standard formula. Overall, 0.3% of total cancer incidence and 0.1% of total cancer mortality in Japanese women were attributable to never breastfeeding. The high prevalence of women who breastfed children may explain the lower fraction of cancer attributable among Japanese women compared to studies from other parts of the world.

***Keywords*:** cancer, breastfeeding, population attributable fraction, Japan

Introduction

The Continuous Update Report (CUP) on Food, Nutrition, Physical Activity and Prevention of Cancer by the World Cancer Research Fund (WCRF) and American Institute for Cancer Research (AICR) concluded that there is probable evidence for an association between breastfeeding and decreased risk of breast cancer (*1*). In 2002, the Collaborative Group on Hormonal Factors in Breast Cancer showed that for every year of breastfeeding, the risk of breast cancer decreases by 4.3% (*2*). On the other hand, the association between breastfeeding and cancer risk of female reproductive organs is unknown. There is a limited or suggestive evidence for an association between breastfeeding and increased risk for ovarian cancer (*1*). While that report also discussed evidence for endometrial cancer, it was considered too limited to allow the drawing of a conclusion (*1*).

Here, we estimated the population-attributable fractions (PAF) of cancer incidence and mortality in Japan in 2015 attributed to never breastfeeding.

Materials and Methods

Cancers associated with breastfeeding

We defined the PAF of cancers associated with breastfeeding as the proportion of cancers diagnosed in a certain period in a population that could possibly have been prevented if everyone in the population ever breastfed children. In this study, we included cancers that were discussed in the WCRF/AICR CUP project (*1*). The cancer sites included in this estimate were breast, endometrium, and ovary.

Theoretical minimum risk exposure level

The optimum level of breastfeeding was considered as a history of ever breastfeeding.

Prevalence of breastfeeding

The latent period between cancer onset and breastfeeding is unknown. Therefore, for this study, we decided the optimal exposure to breastfeeding is a history of ever breastfeeding. Since 2001, the Japanese Ministry of Health, Labour and Welfare (MHLW) has been implementing a survey, called the Longitudinal Survey of Babies in the 21st Century (LSB21), with the aim of developing strategies to combat the declining fertility rate in Japan (*3*). The LSB21 surveyed families from all over Japan with newborns delivered between the

10th and 17th of January or July of 2001. The baseline questionnaire was sent to all of the families six or seven months after the baby was born. Follow-up questionnaires were then sent annually. Each participating child's birth records were linked with the Japanese vital statistics, which includes information such as birth length and weight, gestational age, sex and parental age.

For the history of breastfeeding, LSB21 obtained this information from the baseline questionnaire. The question asked whether the mother breast fed, formula fed, or both, in addition to the duration (ranging from zero to seven months). For people aged 40 and over, we used data from the Japan Public Health Center-based Prospective Study for the Next Generation (JPHC-NEXT), launched in 2011 (*4*). JPHC-NEXT is population-based cohort study being conducted in seven prefectural areas all over Japan. Self-administered questionnaires about lifestyle were provided to all residents aged 40 to 74 at the time of the baseline survey. The questionnaire asked female participants if they had ever breastfed their child, and if they answered yes, the duration. Table 1 shows the proportion of women who were breastfeeding in 2005.

Cancer incidence and mortality in 2015

Cancer incidence in 2015 was estimated using the annual estimate of cancer incidence in 2013 by the Monitoring of Cancer Incidence in Japan (*5*). Estimation was done using an age and period spline model, a type of analysis which is used for short-term projection of cancer incidence in Japan (*6*). The sex- and age-specific incidence data for target cancers were coded in accordance with the International Statistical Classification of Diseases and Related Health Problems, 10th edition (ICD-10), using the morphology code of the International Classification of Disease for Oncology, 3rd edition (ICD-O-3).

Table 1. Staining Intensity of ALM and SSM lesions

Age at exposure (2005)	Proportion of ever breastfeeding (%)	
	Ever (%)	Never (%)
0 - 4	0	100
5 - 9	0	100
10 - 14	0	100
15 - 19	0	100
20 - 24	94	6
25 - 29	94	6
30 - 34	94	6
35 - 39	94	6
40 - 44	94.4	5.6
45 - 49	93.5	6.5
50 - 54	91.2	8.8
55 - 59	90.4	9.6
60 - 64	90.6	9.4
65 - 69	92.1	7.9
70 - 74	92.1	7.9
≥ 75	92.1	7.9

The data on cancer mortality from 2015 were based on the vital statistics of Japan (*7*). We obtained sex- and age-specific mortality data by cause of death from an available data source from the Health, Labour, and Welfare Statistics Association (*8*). Similar to the cancer incidence data, 4-digit ICD-10 codes we used to classify the cause of death.

Estimates of relative risk of history of breastfeeding

Table 2 shows a summary of relative risk estimates used in the present estimate, in which relative risk (RR) was measured compared to women who had no history of breastfeeding. The estimates, derived from the studies listed, were adjusted for potential major confounders. For breast (*9*) and ovarian cancer (*10*), the RRs were derived from a Japanese-based cohort study among women who were parous. For the risk of endometrial cancer, the RR was derived from a meta-analysis consisting of 15 studies, including three Japanese studies (*11*).

Since RRs for ever breastfeeding compared with never were estimated for the target cancers, we calculated the reciprocal of each RR to obtain the RR for never breastfeeding versus ever.

Estimation of population attributable fractions (PAFs)

PAF was calculated using the standard formula (*12*):

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

Where P refers to the prevalence of never breastfeeding by age. The numbers of attributable cancers were then totalled across age categories, in order to show a percentage of the total number of all cancer incidence and mortality in Japan in 2015.

Results and Discussion

Table 1 shows the proportion of Japanese women with ever and never experience of breastfeeding in 2005 by age group. Among women aged 20 and over, over 90% have breastfed at least once. In comparison to women who had no history of breastfeeding women who breastfed had the following RR: breast 0.86 (0.65-1.15) (*9*), ovarian 1.00 (0.5-1.90) (*10*), and 0.88 (0.72-1.06) (*11*) (Table 2).

The estimated PAF of cancer incidence and mortality in 2015 attributed to never breastfeeding in Japan is summarized in Table 3. Detailed results for each cancer, sex, and age-group are shown for in Tables S1-S2 (online data, *https://www.ghmopen.com/site/supplementaldata.html?ID=38*). In the Japanese setting, the only breast

Table 2. Summary of risk estimate of site-specific cancers associated with breastfeeding for the present analysis

Factors	Cancer type	Studies	Reference group	Decrease in risk
Breastfeeding	Breast	Iwasaki *et al.* (2007) (9)	Never	0.86 (0.65 - 1.15)
	Ovarian	Weiderpass *et al.* (2012) (10)	Never	1.00 (0.5 - 1.90)
	Endometrium	Zhan *et al.* (2015) (11)	Never	0.88 (0.72 - 1.06)

Table 3. Proportion (%) of cancer in 2015 attributable to never breastfeeding in Japan

Factors	Incidence		Mortality	
	Women	Both sexes	Women	Both sexes
Breast (C50)	1.3		1.3	
Endometrium (C54)	1.1		1.1	
Ovary (C56)	0.0		0.0	
Total cancer (C00-C96)	0.3	0.1	0.1	0.1

cancer incidence and mortalities attributable to never breastfeeding were of breast and endometrium, with about 1% of incidence and mortality for each (breast: 1,066 attributable cases, 176 attributable deaths; endometrium: 165 attributable cases, 22 attributable deaths). Overall, in 2015, there were 1,231 cases and 202 deaths attributable to a history of never breastfeeding in 2005. Accordingly, the overall PAF for never breastfeeding was 0.3% for cancer incidence and 0.1% for cancer mortality in Japanese women.

In this report, we used RRs calculated for cancers in relation to never breastfeeding on the number of cancer incidence and mortality among Japanese women in 2015. We estimated that 1,231 cancer incident cases (0.30% of total cancer incidence) and 202 cancer deaths (0.13% of total cancer mortality) in 2015 could be attributed to never breastfeeding. These estimates are relatively low compared to results from the United Kingdom (UK) (1.5%) (*13*) but similar to the results from Australia (0.5%) (*14*).

With regard to breast cancer risk, these UK and Australian studies (*13,14*) found that 4.7% and 1.7% of cases were attributable to breastfeeding, respectively. These numbers are higher than our present finding (1.3%). This could be attributable to the difference in the proportion of women who have breastfed, as well as in the duration of breastfeeding used for calculation. In the UK (*13*) and Australia (*14*), 52-66% and 83% of women had initiated breastfeeding upon the birth of a child in 2000 and 2001, respectively. Compared to these two Western studies, over 90% of all Japanese women included in the study had breastfed. Further, the definition used as a history of breastfeeding differed - while the UK and Australia studies had clear definitions of what was considered breastfeeding, our study defined a history of breastfeeding as a history of ever breastfeeding. The result from Australian study suggested that breastfeeding for less than 12 months is associated with an increased risk of cancer. Given these methodological differences, it is difficult to make direct comparisons between these previous and our present studies.

The protective effect of breastfeeding on breast cancer is not direct, but likely an indirect cause, such as due to lactation. According to the CUP project, the reduction in breast cancer may result from the hormonal influence of the associated period of amenorrhea and infertility (*1*). A longer lactation period leads to a reduced number of menstrual cycles throughout life, altering the cumulative exposure to sex hormones, which are known risk factor for post-menopausal breast cancer. The exfoliation of breast tissues during lactation, as well as the apoptosis of epithelial cells after the breastfeeding period is over, might eliminate cells with DNA damage and mutations, leading to lower breast cancer risk (*1*).

A more accurate history of lactation history estimates for risk would allow a better understanding of the impact of possible protective factors of breastfeeding on cancer burden among Japanese women.

Conclusion

Our estimate found an overall 0.3% of total cancer incidence and 0.1% of total cancer mortality in Japanese women was attributable to never breastfeeding. The high prevalence of women who breastfed may explain the lower fraction of cancer attributable among Japanese women compared to studies from other parts of the world.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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Hayakawa K, Kutsuna S, Kawamata T, *et al*. SARS-CoV-2 infection among returnees on charter flights to Japan from Hubei, China: a report from National Center for Global Health and Medicine. Glob Health Med. 2020; 2:107-111.

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Shalev AY. Post-traumatic stress disorder: Diagnosis, history and life course. In: Post-traumatic Stress Disorder, Diagnosis, Management and Treatment (Nutt DJ, Davidson JR, Zohar J, eds.). Martin Dunitz, London, UK, 2000; pp. 1-15.

Example 4 (Sample web page reference):
World Health Organization. The World Health Report 2008 – primary health care: Now more than ever. *http://www.who.int/whr/2008/whr08_en.pdf* (accessed March 20, 2021).

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