Table 1. Trends of overall age-standardized incidence rates of lung cancer with joinpoint analyses in Japan and the United States

	Trend 1		Trend 2			Trend 3		Trend 4
	Years	APC (95% CI)	Years	APC (95% CI)	Years	APC (95% CI)	Years	APC (95% CI)
Japan (1975–2003)								
Males & females	1975–1984	2.8† (2.0, 3.6)	1984–1993	1.5† (1.0–2.1)	1993–2003	0.0 (−0.3, 0.3)		
Males	1975–1992	2.2† (1.9, 2.5)	1992–2003	−0.6† (−0.9, −0.2)				
Females	1975–1982	3.6† (1.5, 5.8)	1982–2003	1.1† (0.9, 1.4)				
USA (1973–2005)								
Males & females	1973–1981	2.9† (2.4, 3.4)	1981–1991	0.7† (0.3, 1.0)	1991–2003	−1.3† (−1.5, −1.1)	2003–2005	−3.1† (−6.2, 0.0)
Males	1973–1981	1.8† (1.3, 2.2)	1981–1991	−0.6† (−1.0, -0.3)	1991–2003	−2.2† (−2.5, −2.0)	2003–2005	−4.5† (−8.0, 0.9)
Females	1973–1978	7.5† (5.6, 9.5)	1978–1988	3.9† (3.3, 4.4)	1988–1997	0.7† (0.2, 1.2)	1997–2005	−0.7† (−1.2, −0.3)

Source: SEER-9 areas covering about 10% of the US population (States of Connecticut, Hawaii, Iowa, Utah, and New Mexico, and the metropolitan areas of San Fransisco-Oakland, Detroit, Atlanta, and Seattle-Puget Sound), and Japanese nine areas covering about 10% of the Japanese population (Prefectures of Yamagata, Niigata, Fukui, Shiga, Osaka, Okayama, Saga and Nagasaki, Hiroshima City and Nagasaski City).

Joinpoint analyses with up to three joinpoints were based on rates (per 100,000 persons) and were age adjusted to the world population. Joinpoint analysis used the Joinpoint Regression Program, version 3.3. April 1, 2008, National Cancer Institute.

APC is based on rates that were age standardized to the world population.

†APC is statistically significantly different from zero (two-sided $p < 0.05$, calculated using a *t*-test.)Abbreviations: APC: annual percent change; CI: confidence interval.

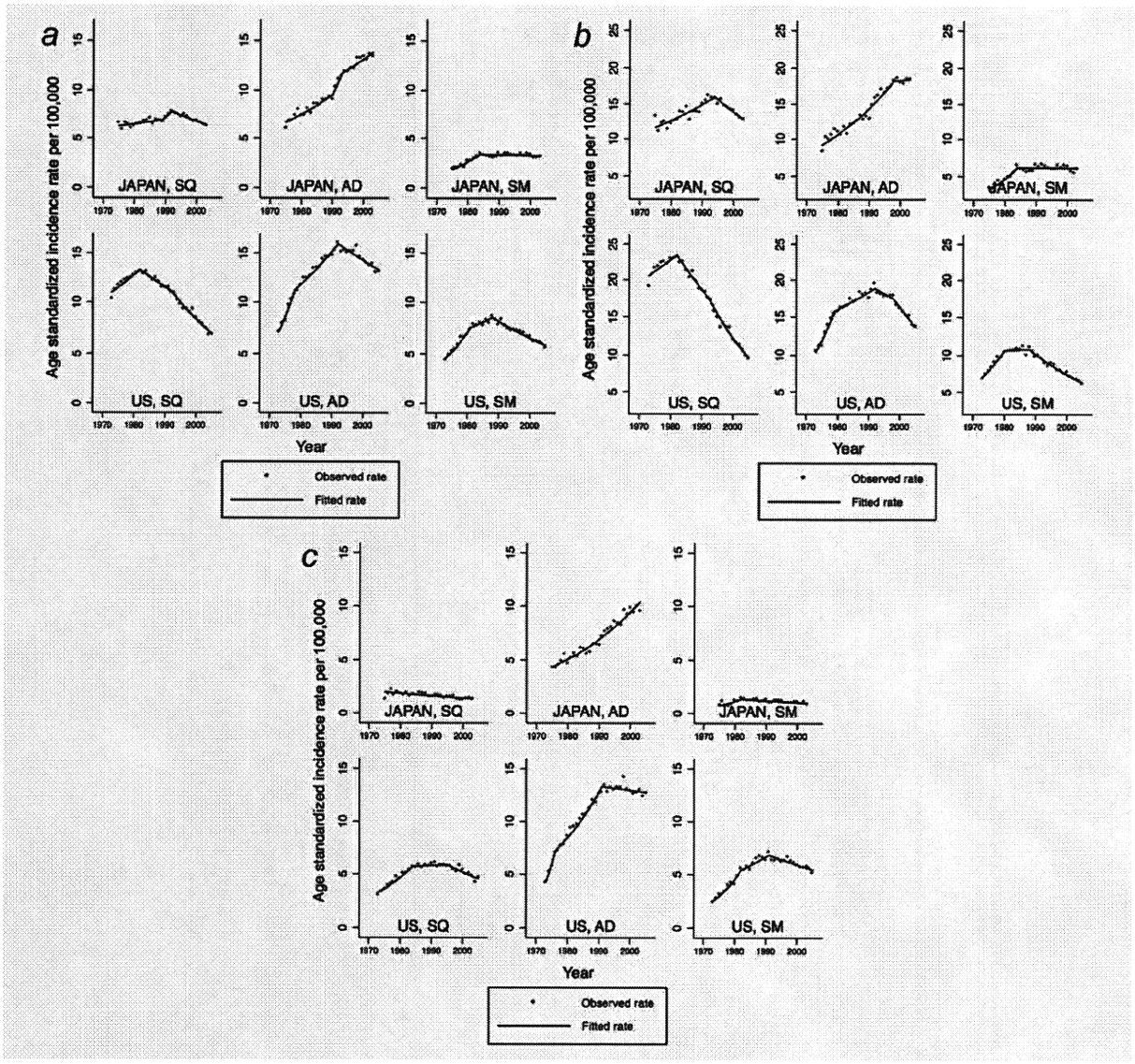

Figure 3. Joinpoint analysis of the age-standardized incidence rates (ASR) of lung cancer by histologic type among individuals in Japan and the United States. (*a*) Males and females combined Joinpoint analyses of the histology-specific ASR of lung cancer among individuals in Japan and in the United States are presented for (*a*) males and females combined, (*b*) males, (*c*) females. SQ, AD and SM indicate squamous cell carcinoma, adenocarcinoma and small cell carcinoma, respectively.

We used STATA version 10.1 (STATA Corporation, College Station, TX) for all analyses except the joinpoint regression analysis, for which we used the Joinpoint Regression Program version 3.3 (US National Cancer Institute, Bethesda, MD).

The Brown University Research Protections Office ruled that this study did not involve human subjects.

Results

Figure 1 illustrates temporal trends in annual nonfilter and filter cigarette consumption per capita in Japan and the United States. The sharp increase in filter cigarette consumption and sharp decrease in nonfilter consumption began in the 1960s and 1950s in the United States and Japan, respectively. Compared with the United States, the shift in consumption from nonfilter to filter cigarettes occurred more rapidly in Japan, with the share of filter cigarettes during this period rapidly reaching 99%. Further, the sharp increase in total consumption owed largely to increasing filter cigarette consumption. Filter cigarette consumption then generally continued to be flat until the late 1990s, when it began to

Table 2. Trends of age-standardized rates of lung cancer with joinpoint analyses by sex and histological group in Japan and the United States

Histology	Trend 1		Trend 2		Trend 3		Trend 4	
	Years	APC (95% CI)	Years	APC (95% CI)	Years	APC (95% CI)	Years	APC (95% CI)
Males & Females combined								
Japan (1975–2003)								
Squamous cell carcinoma	1975–1989	0.7† (0.2, 1.2)	1989–1992	4.4 (−3.3, 12.7)	1992–2003	−1.9† (−2.3, −1.4)		
Adenocarcinoma	1975–1990	2.4† (1.8, 3.0)	1990–1993	7.1 (−1.1, 15.9)	1993–2003	1.7† (1.1, 2.2)		
Small cell carcinoma	1975–1984	6.7† (4.2, 9.2)	1984–2003	0.2 (−0.6, 0.2)				
USA (1975–2003)								
Squamous cell carcinoma	1973–1982	2.1† (1.4, 2.8)	1982–1992	−1.7† (−2.4, −1.1)	1992–2005	−3.6† (−4.0, −3.2)		
Adenocarcinoma	1973–1978	9.4† (6.6, 12.3)	1978–1992	2.5† (2.4, 3.0)	1992–2005	−1.4† (−1.8, −1.0)		
Small cell carcinoma	1973–1981	6.4† (5.3, 7.6)	1981–1988	1.8† (0.4, 3.1)	1988–2005	−2.2† (−2.4, −1.9)		
Males								
Japan (1975–2003)								
Squamous cell carcinoma	1975–1994	1.7† (1.3, 2.1)	1994–2003	−2.4† (−3.1, −1.6)				
Adenocarcinoma	1975–1998	3.0† (2.7, 3.4)	1998–2003	0.2 (−1.6, 1.9)				
Small cell carcinoma	1975–1984	7.4† (4.4, 10.6)	1984–2003	−0.0 (−0.5, 0.5)				
USA (1973–2005)								
Squamous cell carcinoma	1973–1982	1.5† (0.7, 2.3)	1982–1992	−2.8† (−3.5, −2.1)	1992–2005	−4.5† (−4.9, −4.0)		
Adenocarcinoma	1973–1979	7.2† (5.7, 8.8)	1979–1992	1.4† (1.0, 1.8)	1992–1998	−1.3† (−2.6 – −0.0)	1998–2005	−3.3† (−4.1, −2.6)
Small cell carcinoma	1973–1980	6.2† (4.7, 7.7)	1980–1988	0.2 (−0.9, 1.3)	1988–2005	−3.1† (−3.4, −2.8)		
Females								
Japan (1975–2003)								
Squamous cell carcinoma	1975–2003	−1.4† (−1.8, −1.0)						
Adenocarcinoma	1975–2003	3.2† (2.9, 3.5)						

decrease. In the United States, filter cigarette consumption peaked in the late 1970s.

Figure 2 and Table 1 provide the long-term trends in overall lung cancer incidence in Japan and the United States using the joinpoint regression analyses. For males and females combined, while the peak incidence has already occurred in the United States, with a downward trend beginning in 1991, the incidence for Japanese continues to be flat, followed by an upward trend until 1993. While the peak incidence for Japanese males occurred in 1992, the incidence for Japanese females continues to increase. Rates among Japanese males decreased by 0.6% per year from 1992 to 2003, after increasing by 2.2% annually from 1975 to 1992, and rates among Japanese females increased by 3.6% annually from 1975 to 1982 and by 1.1% after 1982. In the United States, peak incidence has already occurred in females in 1988, 7 years later than that in males. Among American males, rates decreased by 0.6% per year from 1981 to 1991 and by 2.2% per year from 1991 to 2005, after increasing by 1.8% annually from 1973 to 1978.

Figure 3 illustrates temporal patterns in ASR for selected histological types of lung cancer in Japan and the United States. For males and females combined (Fig. 3*a*), the peak incidence of SQ in Japanese occurred in 1992, 10 years later than that in the United States. In the United States, the rate of decline in SQ incidence significantly increased after 1992. While the incidence of AD continues to increase in Japan, peak incidence has already occurred in Americans, with a downward trend beginning in 1992. The incidence of AD in Japanese and Americans overtook the incidence of SQ in 1984 and 1976, respectively. For males (Fig. 3*b*), the peak incidence of SQs has already occurred in Japanese, with a downward trend beginning in 1994, 12 years later than that in the United States. While the incidence of AD for Japanese males leveled in 1998 after an upward trend, the peak incidence occurred in the US males, with a downward trend beginning in 1992. For females, the trends of SQ and AD in Japanese are different to those in Americans (Fig. 3*c*). In Japanese, the incidence for SQ continues to decrease and that for AD continues to increase. In contract, the peak incidences of SQ and AD have already occurred in 1982 and 1991 in the United States, respectively.

Table 2 provides the long-term trends in different histological groups of lung cancer incidence using the joinpoint regression analyses. For SQ, rates among Japanese increased by 0.7% annually from 1975 to 1989, were stable from 1989 to 1992, and then decreased by 1.9% from 1992 to 2003. Among Americans, rates increased by 2.1% annually from 1973 to 1982, then decreased by 1.7% from 1982 to 1992 and by 3.6% from 1992 to 2005. For AD, rates among Japanese increased by 2.4% annually from 1975 to 1990, were stable from 1990 to 1993 and then increased by 1.7% from 1993 to 2003. In contrast, rates among Americans increased by 9.4% annually from 1973 to 1978 and by 2.5% from 1978 to 1992 and then decreased by 2.2% from 1992 to 2005. In Japan,

Table 2. Trends of age-standardized rates of lung cancer with joinpoint analyses by sex and histological group in Japan and the United States (Continued)

	Trend 1		Trend 2		Trend 3		Trend 4	
Histology	Years	APC (95% CI)	Years	APC (95% CI)	Years	APC (95% CI)	Years	APC (95% CI)
Small cell carcinoma	1975–1982	8.7† (2.0, 15.7)	1982–2003	−1.6† (−2.3, −0.9)				
USA (1973–2005)								
Suamous cell carcinoma	1973–1984	5.3† (4.2, 6.3)	1984–1995	0.2 (−0.6, 1.1)	1995–2005	−2.5† (−3.3, −1.7)		
Adenocarcinoma	1973–1976	19.1† (9.5, 29.5)	1976–1991	4.2† (3.7, 4.7)	1991–2005	−0.3 (−0.7, 0.1)		
Small cell carcinoma	1973–1982	9.0† (7.2, 10.9)	1982–1991	2.7† (1.3, 4.1)	1991–2005	−1.6† (−2.1, 1.1)		

Source: SEER-9 areas covering about 10% of the US population (States of Connecticut, Hawaii, Iowa, Utah, and New Mexico, and the metropolitan areas of San Fransisco-Oakland, Detroit, Atlanta, and Seattle-Puget Sound), and Japanese nine areas covering about 10% of the Japanese population (Prefectures of Yamagata, Niigata, Fukui, Shiga, Osaka, Okayama, Saga and Nagasaki, Hiroshima City and Nagasaki City).
Joinpoint analyses with up to three joinpoints were based on rates (per 100,000 persons) and were age adjusted to the world population. Joinpoint analysis used the Joinpoint Regression Program, version 3.3.April 1, 2008, National Cancer Institute.
APC is based on rates that were age standardized to the world population.
†APC is statistically significantly different from zero (two-sided $p < 0.05$, calculated using a *t*-test.)
Abbreviations: APC: annual percent change; CI: confidence interval.

Table 3. The relationship between cigarette consumption and lung cancer incidence by histologic type in Japan and the United States

	SQ			AD		
Type of cigarette	Lag time τ^*	$\hat{\beta}_2^{SQ}$ ($\times 10^{-3}$)†	95% CI ($\times 10^{-3}$)	Lag time τ^*	$\hat{\beta}_2^{AD}$ ($\times 10^{-3}$)†	95% CI ($\times 10^{-3}$)
Japan						
Nonfilter	30	0.464‡	(0.164, 0.764)	24	−1.099‡	(−1.767 to −0.431)
Filter	30	−0.340‡	(−0.518, −0.162)	25	1.946‡	(1.297–2.594)
United States						
Nonfilter	20	0.455‡	(0.319, 0.591)	17	0.353	(−0.020 to 0.757)
Filter	25	−0.268‡	(−0.383–0.152)	15	3.183‡	(1.955–4.411)

*τ is defined as the lag between lung cancer incidence and cigarette consumption; CI, confidence interval. $^\dagger\beta_2$ is the coefficient for cigarette consumption in the model of $Y(t^+) = \beta_0 + \beta_1 Y(t) + \beta_2 X(t^+ - \tau) + \varepsilon$ ‡Statistically significantly different from zero (two-sided $p < 0.05$, calculated using a t-test).

rates for small cell carcinoma increased by 6.7% annually from 1975 to 1984, then leveled off thereafter. In contrast, rates in the United States increased by 6.4% annually from 1973 to 1981 and by 1.8% from 1981 to 1988, and then began to decrease thereafter.

Because sex-specific data on cigarette consumption by cigarette design were not available on public, we examined the relationship between cigarette consumption and lung cancer incidence by histologic type in males and females combined. Table 3 summarizes the statistical relationship between them using multiple regression analyses. The models in Table 3 did not violate assumptions of normality and uncorrelatedness. Among Japanese, the trend in nonfilter consumption was positively associated with the incidence of SQ ($\hat{\beta}_2^{SQ}$, 0.464×10^{-3}, 95% confidence interval (CI), [0.164×10^{-3}, 0.764×10^{-3}], $p = 0.006$) with the appropriate time lag of 30 years, and the trend in filter cigarette consumption was positively associated with AD incidence ($\hat{\beta}_2^{AD}$, 1.946×10^{-3}, 95%CI, [1.297×10^{-3}, 2.594×10^{-3}], $p < 0.001$) with the appropriate time lag of 25 years. Similarly, among Americans, the trend in nonfilter consumption was positively associated with SQ incidence ($\hat{\beta}_2^{SQ}$, 0.364×10^{-3}, 95%CI, [0.109×10^{-3}, 0.619×10^{-3}], $p = 0.008$) with the appropriate time lag of 20 years, while the trend in filter consumption was positively associated with AD incidence ($\hat{\beta}_2^{AD}$, 3.142×10^{-3}, 95%CI, [1.923×10^{-3}, 4.361×10^{-3}], $p < 0.001$) with the appropriate time lag of 15 years. The negative association between trends in nonfilter cigarette consumption and AD and between trends in filter consumption and SQ among Japanese and Americans reflect the shift in market share from nonfilter to filter cigarettes.

Discussion

AD has replaced SQ as the most frequent histologic type of lung cancer in both Japan and the United States. This increase in AD incidence in both the countries is also associated with the introduction of filtered cigarettes and the substantial increase in filter cigarette consumption. The decrease in nonfilter cigarette consumption due to the shift in market share from nonfilter to filter cigarette is associated with the decrease in the incidence of SQ. To our knowledge, these empirical observations, using population-based data from two distinct countries, are the first to support the long-held hypothesis that smoking filtered *vs.* nonfiltered cigarettes leads to separate presentations of lung cancer. These results are consistent with previous epidemiological study obtained using data at the individual level.[32–34]

Another possible explanation for the change in trends for AD of the lung is changes in exposure to air pollution. Long-term exposure to some components of polluted air, particularly NO*x*, might play a role in the development of AD.[12] Given that air pollution can be considered a general phenomenon, this possibility is not contradicted by the similarity in trends in AD incidence in US males and females but is contradicted by the difference in gender-specific trends in Japanese males and females. In addition, compared with current smokers, the lung cancer rate is very low among never smokers.[35] A prospective cohort study in Norway suggested that although air pollution is one of the causes of lung cancer, it may still much less than cigarette smoking that causes lung cancer.[36,37] A second possible explanation for this AD trend might be related to underlying trends in exposure to environmental tobacco smoke (ETS). Recent regulations have strictly reduced ETS exposure in the United States.[38] The consequent decrease in exposure to ETS might explain the recent decrease in incidence of ADs of the lung in the United States, at least, in part. Although this point should be examined in the future with more detailed exposure and outcome evaluation, it is clear that ETS has much less impact on the risk than active smoking.

Reflecting the wide-scale adoption of filter cigarettes beginning in the 1960s, the United States observed a sharp increase in ADs in the early 1970s, with 9.4% increases annually from 1973 to 1979. Interestingly, although filter cigarettes penetrated the Japanese market more rapidly in the 1970s, the increase in ADs in Japan has not been as sharp as in the United States. There are two explanations for this. First, the greater use of charcoal-containing cigarette filters in Japan (70 *vs.* 1% in the United States) may have had a beneficial effect, perhaps by trapping a greater load of fine particulates

than other filters or by removing a greater load of volatile toxic agents, such as hydrogen cyanide, N-nitrosamines and volatile aldehydes known to act as inhibitors of lung clearance.[19] In this regard, Muscat *et al.* found no association between charcoal filters and an attenuated risk of lung cancer in a Japanese population.[39] Second, it is of course also possible that the differences between the Japanese and US experience may have been affected by the assumptions used in allocating specific morphologies to cases of unknown morphology. Additional analyses focused on this issue may clarify the observed differences.

It is considered paradoxical that a proportion of Japanese who smoke is higher than American males but have a lower incidence of lung cancer.[19] Several factors acting either alone or in combination may explain this lower rate in Japan,[19,40] including age at onset of cigarette smoking, specific personal smoking (*i.e.*, manner of smoking, particularly shallow inhalation), and the contents and construction of cigarettes. Despite the higher smoking prevalence in Japan, total cigarette consumption per capita was lower than in the United States until 1987, suggesting that Japanese smokers smoked fewer cigarettes per day than their American counterparts. Other differences may explain the lower lung cancer rates in Japan: *e.g.*, because consumption of filter cigarettes increased rapidly around the same time that smoking became popular in Japan, Japanese smokers were less exposed to unfiltered cigarettes. Additionally, the Japanese diet may have a protective effect against lung cancer, owing to its relatively high consumption of soybeans,[41,42] which contain the strong tumor inhibitor genistein, and fish[41] and relatively low intake of dietary fat.[43] Frequent consumption of green tea[44] may also have a protective effect. Finally, Americans may have a greater genetic susceptibility to tobacco carcinogens than Japanese. In this regard, the lower relative risks by smoking in epidemiological studies conducted in Japan *versus* the United States is well known.[19,45] In this study, we found a shorter lag time of τ in Americans than in Japanese, which represents the shorter sum of induction and latent period in Americans than in Japanese (*e.g.*, lag times for AD after the advent of filter cigarettes were 25 years in Japan *vs.* 15 years in the United States). This might be a reflection of a difference in patterns of smoking behavior, life styles and susceptibility to lung cancer between Japan and the United States.

Our findings suggest that the trends of incidence of lung cancer by histologic type differ in males and females as well as the associations between changes in the incidences and in filter/nonfilter cigarettes differ among males and females, in both Japan and in the United States. That may be due to the differences in patterns of smoking behavior and the susceptibility to lung cancer in cigarette smokers among males and females. Smoking rate is significantly lower for females than for males in both the countries (11.0 and 39.4% in males and females in Japan, respectively, and 17.4 and 23.4% in the United States).[27,46] Females were more likely than men to smoke filter cigarettes (89.0–90.6% *vs.* 75.0–79.3% in the 1970s,[47,48] and 92.9–94.6% *vs.* 87.0–90% in the 1980s). Females with lung cancer are more likely to be never smokers or less intense smoking history, and have AD subtypes.[49] Therefore, the sex-specific analysis for cigarette types and incidence patterns by histology subtype would sharpen the findings. However, unfortunately, the data on filter/nonfilter cigarette consumption are not available both in Japan and the United States so that we could not analyze the sex specific relationships between the trend in lung cancer incidence by histologic type and consumptions of filter or nonfilter cigarettes. Therefore, the analyses in males and females combined may weaken a true relationship between the increased trend in AD and filter cigarette consumption. Nevertheless, we could obtain the statistically significant relationship between them using the data for males and females combined.

Molecular examinations of lung cancer might give us an insight to interpret different patterns of change in histology-specific incidence by sex and ethnicities discussed above. It has been reported that epidermal growth factor receptor (*EGFR*) mutations commonly present in female, never-smoker and Asian ethnicity.[50] Potential differences in several risk factors including smoking by *EGFR* mutational status have been reported to date.[51,52]

Several limitations of this study warrant mention. First, as an ecological study, it possesses all the limitations inherent to ecological analyses. Aggregate data on exposure and disease—data obtained from population aggregates—cannot be linked to individuals. Although estimated consumption of cigarettes was based on nationally averaged levels for the respective countries, consumption may in fact vary by area (rural *vs.* metropolitan), race/ethnicity, sex, age and education. The increased consumption of filter cigarettes may have played different roles in the increase in AD incidence in males and females, but the present data lacked the sensitivity to detect changes at this level. Second, the data collected from Japanese prefectural population-based cancer registries have major quality issues and fail to meet international data quality standards for the proportion of death-certificate-only cases, incidence-to-mortality ratio and proportion of histologically verified cases.[53] Based on mathematical modeling, true incidence may be underestimated by as much as 20%.[54] Moreover, because one-third of the Japanese cases in this study were of unknown morphology, the data may not adequately reflect the true changes in lung cancer incidence by histologic type. Nevertheless, we do not consider that our allocation methodology biased the results, and reanalysis of the data without the proportional reallocation of cases with unspecified morphology returned virtually identical results. Finally, another limitation may be change over time in the definition of AD[55] or in diagnostic practice,[56] although we consider that these themselves cannot account for the increase in AD incidence. For example, major diagnostic advances such as bronchoscopy, thin-needle aspiration, computed tomography scans

and improved stains for mucin were all introduced in the 1980s,[56] after the increases in the incidence of AD were observed.

While the decreased incidence of SQ among Japanese and Americans is encouraging in terms of cancer prevention and control, it is counterbalanced by the increases in AD, especially among Japanese. As realization of the detrimental health effects of cigarette smoking initially grew, the tobacco industry strove to develop filtered cigarettes as less harmful cigarettes, but subsequent scientific evidence has failed to demonstrate any benefit from changes in cigarette design or manufacturing.[57] Despite the tobacco industry became well aware of the fact that filtered cigarettes were not less harmful, it has been advertised filtered or low-tar cigarettes to intend to reassure smokers and were meant to prevent smokers form quitting since the early 1950s in the United States[58] and later in Japan.[59] The false reassurances provided by marketing strategies of filtered/low-tar cigarettes might be related to the rising incidence of ADs of the lung.

The present results suggest that the shift from nonfilter to filter cigarettes may have had the result of replacing one cancer type with another. These findings emphasize the importance of tobacco control programs, namely programs that prevent the initiation of smoking, hasten the rate of smoking cessation or limit exposure to ETS, have been associated with a decrease in both cigarette consumption and smoking rates, and subsequently with a decrease in lung cancer incidence.[4,60]

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Trend in Incidence of Adenocarcinoma of the Esophagus in Japan, 1993–2001

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Background: Several studies with population-based cancer registry data have suggested that incidence of adenocarcinoma of the esophagus has been increasing since 1970 in some European and North American countries and Australia. However, data from Asian countries with regard to the incidence of esophageal cancer by histological type based on the population-based cancer registry are lacking. The aim of this study was to describe the incidence of esophageal cancer by histological type in a Japanese population.
Methods: Cancer incidence data for 1993–2001 from 15 population-based cancer registries were collected by the Japan Cancer Surveillance Research Group in 2005. We used data from eight registries corresponding to inclusion criteria for data quality.
Results: Squamous cell carcinoma remains the predominant type in all esophageal cancers in Japan. The ratio of squamous cell carcinoma to adenocarcinoma is 26:1. For adenocarcinoma, estimated average annual percentage change was 4.7% (95% confidence interval: 0.7, 8.9) in men and 6.0% (2.4, 9.8) in women. Age-adjusted incidence rate (the world standard population) per 100 000 for 2001 was 0.3 in men and 0.05 in women. Incidence of squamous cell carcinoma was increasing slightly in men and nearly constant in women. Age-adjusted incidence rate for 2001 was 8.2 in men and 1.0 in women.
Conclusion: No dramatic increase in adenocarcinoma has occurred, and absolute incidence remains low in Japan.

Key words: esophagus adenocarcinoma incidence

A rising trend of incidence of adenocarcinomas of the esophagus was first reported from the USA in 1991 (1). Several subsequent reports on the incidence of esophageal cancer by histological type based on population-based cancer registries have revealed dramatic increases in the incidence of adenocarcinomas of the esophagus in the USA, Canada, Australia and some European countries over the last three decades (2–7). Some studies have investigated the associations between this increasing trend and factors, such as misclassification of tumor sites (lower esophagus versus gastric cardia) or overdiagnosis resulting from increased use of upper endoscopy (8,9), and concluded that the rising trend was unlikely to be explained by such information bias.

Recent studies suggest that being a white male, high body-mass index (BMI), Barrett's esophagus, gastro-esophageal reflux disease (GERD) and absence of *Helicobacter pylori* (*H. pylori*) infection represent substantial risk factors for adenocarcinomas of the esophagus (10). In Japan, risk factors such as obesity and absence of *H. pylori* infection seem to be increasing (11,12), and we thus need to start monitoring trends in the incidence of adenocarcinoma of the esophagus. A previous study based on the data collected from a lot of hospitals throughout Japan has reported that no increase in the relative proportion of adenocarcinomas among all reported esophageal cancers was identified over the period 1980–94 (13). International Agency for Research on Cancer provides incidence rates of esophageal cancer by histological type from Osaka, Miyagi and Nagasaki cancer registries up to 1997, respectively (14). However, incidence rates of esophageal cancer by histological type throughout Japan have not been available.

In 2005, a research group supported by the Ministry of Health, Labor and Welfare started collecting cumulative

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incidence data from several population-based cancer registries in Japan that met various criteria for data quality, and included the data into a database. The purpose of this study was to describe the trends in the incidence of esophageal cancer by histological type in Japan during 1993–2001.

MATERIALS AND METHODS

We used cancer incidence data for 1993–2001 from 15 population-based cancer registries collected by the Japan Cancer Surveillance Research Group in 2005. Since 1975, national estimates of cancer incidence in Japan have been provided and published by this research group (15,16).

All primary malignant neoplasms of the esophagus (International Classification of Diseases for Oncology, Third Edition: ICD-O-3) topography codes C15.0–C15.9, morphology codes 8000–9581 and behavior code 3, excluding lymphomas, were included in this study. Seven registries were excluded from the analysis because the percentage of histologically verified diagnosis (%HV) of esophageal cancers comprised <70% registered cases. Finally, this analysis was performed using the data from the following eight registries: Miyagi, Yamagata, Niigata, Fukui, Shiga, Osaka, Saga and Nagasaki. Mean proportion of death certificate only (DCO) cases was 15.6% and %HV was 79.1% in these registries between 1993 and 2001. The population covered by the eight registries totaled 19 400 747, corresponding to 15% of the total population of Japan in 1997. Mortality data were obtained from the Japanese Ministry of Health, Labor and Welfare using the National Vital Statistics.

Esophageal cancers were divided into the following histological categories: squamous cell carcinoma (ICD-O-3 codes 8050–8084), adenocarcinoma (ICD-O-3 codes 8140–8384), other specified malignant neoplasm (ICD-O-3 codes 8011–8046, 8090–8131 and 8380–9581) and neoplasm not otherwise specified (NOS) (ICD-O-3 codes 8000–8010). Esophageal cancers were also classified according to one of the following subtypes: upper third or cervical area (ICD-O-3 codes C15.0 and C15.3), middle third or thoracic (ICD-O-3 codes C15.1 and C15.4), lower third or abdominal (ICD-O-3 codes C15.2 and C15.5) and origin intermediate or NOS (ICD-O-3 codes C15.8 and C15.9). Cancer cases were classified according to age (5-year age groups up to +85 years) and sex.

Statistical Methods

Incidence and mortality rates were estimated and age-adjusted to the 1985 Japanese model population or the world model population using direct adjustment. Point estimates and 95% confidence intervals (CIs) of estimated average annual percentage change (EAPC) in incidence and mortality rates during the study period were estimated by fitting a log-linear regression model to the standardized incidence using the least squares method. The model was of the form $\log Y = a + bx$, where Y is the estimated standardized incidence rate and x is the year of incidence. The expression $100\ (10^b - 1)$ is an estimate of the annual percentage change in this rate. All statistical analyses were performed using Intercooled Stata 8.0 for Windows software (StataCorp LP, College Station, TX, USA).

RESULTS

During the period from 1993 to 2001, a total of 20 093 patients were diagnosed with esophageal cancer in the eight regional cancer registries in Japan. Proportions of esophageal cancer by histological type, sub-site, calendar year of diagnosis and sex are shown in Table 1. Squamous cell carcinoma was the predominant histological type during the study period (mean percentage: 73.3% for men; 66.0% for women). Mean percentage of adenocarcinomas was <3% and the ratio of squamous cell carcinomas to adenocarcinomas was 26:1. The distribution of cases with histology of 'other types and unspecified' was almost constant throughout 9 years and mean percentage was 25.3%. Since sub-sites belonging to 'origin intermediate or NOS' accounted for 60.1%, we could not perform further analysis of sub-sites.

Age-standardized (the 1985 Japanese model population) incidence rates (ASIRs) and mortality rates (ASMRs) per 100 000 person-years of esophageal carcinoma between 1993 and 2001 are shown in Fig. 1. For men, incidence rates were slowly increasing, with an EAPC of 1.68% (95% CI: +0.73, +2.63) and a point-estimated ASIR (the world model population) for 2001 of 11.5. For women, incidence rates were nearly constant, and point-estimated ASIR (the world model population) for 2001 was 1.5. Mortality rates increased slightly for men (EAPC: 1.22; 95% CI: 0.13, 2.33) and declined gradually for women (EAPC: −1.09; 95% CI: −2.55, 0.08).

Figure 2 shows the trends in ASIR by the histological types of esophageal cancer. Incidence rates were 7- to 8-fold higher in men than in women irrespective of histological type. Risk of squamous cell carcinoma was over 20-fold greater than that of adenocarcinoma, regardless of sex. Incidence of squamous cell carcinoma increased slightly during the period for men, but was nearly constant in women. Table 2 shows the incidence trends of esophageal cancer by histological types expressed as EAPC over the interval. For men, we observed annual increases in the incidence of all esophageal cancers and all histological subtypes. Point-estimated ASIRs (world population) in 2001 for adenocarcinoma and squamous cell carcinoma were 0.3 and 8.2, respectively. For women, annual changes were not significant in the incidence of all esophageal cancers, squamous cell carcinomas and other types and NOS carcinomas, with only adenocarcinomas showing an annual increasing trend. Point-estimated ASIRs (world population) in 2001 for adenocarcinoma and squamous cell carcinoma were 0.05 and 1.0, respectively.

Table 1. Cases of esophageal cancer by sex, year of diagnosis, histology and anatomic site

	Males						Females					
	1993–95		1996–98		1999–2001		1993–95		1996–98		1999–2001	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%
Total number	4819	100.0	5734	100.0	6360	100.0	990	100.0	1033	100.0	1157	100.0
Carcinoma subtype												
Squamous cell carcinoma	3496	72.5	4277	74.6	4629	72.8	661	66.8	686	66.4	750	64.8
Adenocarcinoma	125	2.6	146	2.5	192	3.0	19	1.9	28	2.7	41	3.5
Other types of carcinoma	87	1.8	120	2.1	140	2.2	21	2.1	23	2.2	33	2.9
Unspecified carcinoma	1111	23.1	1191	20.8	1399	22.0	289	29.2	296	28.7	333	28.8
Subsite of origin												
C 15.0, C 15.3	154	3.2	162	2.8	220	3.5	53	5.4	58	5.6	77	6.7
C 15.1, C 15.4	1348	28.0	1668	29.1	1749	27.5	220	22.2	237	22.9	251	21.7
C 15.2, C 15.5	470	9.8	498	8.7	605	9.5	78	7.9	84	8.1	84	7.3
C 15.8, C 15.9	2847	59.1	3406	59.4	3786	59.5	639	64.5	654	63.3	745	64.4

C15.0–C15.9, topography codes.

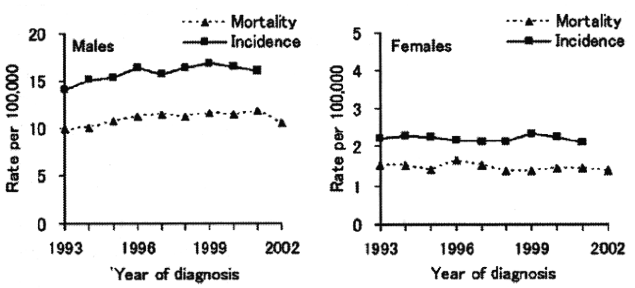

Figure 1. Trends in age-adjusted incidence and mortality rate (the 1985 Japanese model population) of esophageal cancers by sex.

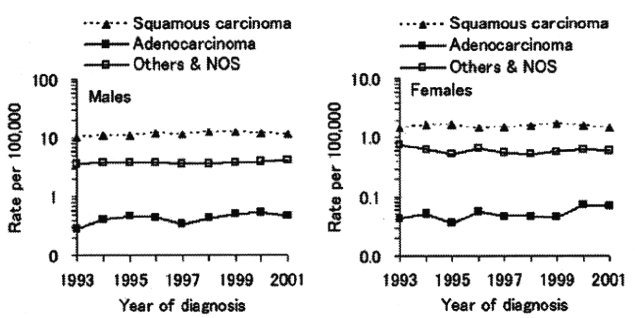

Figure 2. Trends in age-adjusted incidence rate (the 1985 Japanese model population) of esophageal cancers by histological subtypes and sex.

DISCUSSION

Our data demonstrate that no dramatic increase in adenocarcinoma of the esophagus has occurred in Japan. Although incidence rates of adenocarcinoma of the esophagus are gradually increasing in both sexes, absolute incidence rates remain much lower than those of squamous cell carcinoma and those of most Western countries (1,3–6).

Table 2. Estimated annual percentage change (EAPC) in incidence of esophageal cancer by histological subtypes and all esophageal cancers

	EAPC (95% CI)	
	Males	Females
All esophageal cancer	1.68 (0.73, 2.63)	−0.34 (−1.22, 0.54)
Squamous cell carcinoma	1.78 (0.41, 3.17)	0.07 (−1.67, 1.84)
Adenocarcinoma	4.73 (0.74, 8.88)	6.03 (2.37, 9.82)
Other types and NOS	1.02 (0.03, 2.02)	−1.63 (−4.41, 1.23)

CI, confidence interval; NOS, not otherwise specified.

Vizcaino et al. (6) described the time-trend of the incidence of both major histological types of esophageal carcinomas in selected countries worldwide. According to that description, Western countries, with some exceptions, are displaying increasing incidence rates of adenocarcinoma and relatively stable or decreasing rates of squamous cell carcinoma. In most countries in 1970s, the rates of squamous cell carcinoma among men were over one per 100 000 person-years (the world population model) and those of adenocarcinoma were below one per 100 000 person-years. However, in the USA (white), Canada, Australia, Scotland, Denmark and Iceland, the incidence rates of adenocarcinoma among men have caught up with or surpassed those of squamous cell carcinoma up to 1995 and rates of adenocarcinoma reached over one per 100 000 person-years. Reliable incidence data for esophageal cancer

by histological types are limited. Fernandes et al. (7) reported that the incidence rate of squamous cell carcinoma among men had decreased to 3.9 per 100 000 person-years and those of adenocarcinoma was increasing gradually up to 0.5 per 100 000 person-years in 2002 in Singapore. For the current study in Japan, the incidence rate of squamous cell carcinoma among men was still 8.2 per 100 000 person-years (world population), whereas the rate of adenocarcinoma was 0.3 per 100 000 person-years in 2001. With regard to adenocarcinoma, the incidence trends in Japan resemble those in Singapore.

The most potent risk factors for adenocarcinomas of the esophagus appear to be obesity and the absence of *H. pylori* infection (10). The association between high BMI and adenocarcinoma of the esophagus has been investigated in numerous studies, and a meta-analysis eventually supported a positive association in 2006 (17). In Japan, although the proportion of overweight adults (BMI $\geq$ 25) increased from 19.0 to 22.4% ($\times$1.23) between 1980 and 1995, that percentage is still only half the level of many Western and Oceanian countries (WHO: Global Database on Body Mass Index. http://www.who.int/bmi/index.jsp). Another possible risk factor for adenocarcinoma of the esophagus is the absence of *H. pylori* infection. However, previous study results regarding this inverse association have been inconsistent, and many investigators have speculated that *H. pylori* infections causing severe pangastritis could decrease gastric acid secretion and protect against the development of GERD, Barrett's esophagus and adenocarcinoma of the esophagus (10). In Japan, more than 80% of the population born before 1950 is positive for *H. pylori* (12,18), and an active recommendation for eradication of *H. pylori* in patients with gastric ulcer was just started in 2000. The majority of individuals covered in this study were thus still likely to be *H. pylori* positive. The insignificant increase in the incidence of adenocarcinoma is likely to have resulted from a lower prevalence of overweight adults and higher prevalence of *H. pylori* positive individuals in the Japanese population compared with Western countries.

For squamous cell carcinoma of the esophagus, incidences are stable or decreasing slowly in both sexes in most countries (6). As an exception, the incidence of squamous cell carcinoma among females increased rapidly in Switzerland between 1980 and 1995. Conversely, incidence of squamous cell carcinoma decreased progressively in Singapore between 1968 and 2002 (7).

The strongest risk factors for squamous cell carcinoma of the esophagus are smoking and drinking (19). According to the Japanese National Survey, the proportion of daily smokers decreased by 12% among men and increased by 2.6% among women between 1989 and 2004, and 43% of the male population and 12% of the female population remained daily smokers as of 2004 (20). In the same way, the proportion of daily drinkers decreased by 3.1% among men and increased by 2.2% among women between 1989 and 2002, and 49% of the male population and 8.5% of the female population were still daily drinkers as of 2002. Considering the higher prevalence of these risk factors in the Japanese population, the high absolute incidence of squamous cell carcinoma is likely.

The present study displays some limitations. First, despite using combined data from multiple regional cancer registries offering better quality data, DCO was 15.6%. This is considerably inferior to the international standard level (6). However, we consider our data trustworthy enough to evaluate the trends of incidence rate for esophageal cancer by histological subtype, as 5-year relative survival rate for esophageal cancer remains poor in Japan, at 26% in 1993–96, and the trends in the incidence and mortality of all esophageal cancers have been changing in parallel during the study period (21).

Secondly, our data included ~25% of the cases with unspecified histology, 10-fold greater than the cases with adenocarcinoma. However, we consider that our data were sufficient to allow the observation of the incidence trends for esophageal cancer by major histological subtype, since the proportion of histologically unspecified carcinomas was stable throughout the study period. And these data are the only available measures to discuss incidence rate of esophageal cancer by histological type throughout Japan.

In conclusion, we identified that no dramatic increase in adenocarcinoma of the esophagus has occurred and the absolute incidence remained low in Japan. The incidence trends for esophageal cancer by histological type in Asia appear to differ from those of many Western countries. This fact could be useful in identifying risk factors for adenocarcinomas of the esophagus.

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Conflict of interest statement

None declared.

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Epidemiology Note

Cancer Incidence and Incidence Rates in Japan in 2002: Based on Data from 11 Population-based Cancer Registries

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The number of cancer incidences, crude incidence rates, age-standardized incidence rates in 2002 in Japan are estimated. The estimated total number of incidences was 570 598.

Key words: cancer incidence – incidence estimates – cancer registry – Japan

The Japan Cancer Surveillance Research Group estimated the number of cancer incidences in Japan in 2002 as a part of Monitoring of Cancer Incidence in Japan (MCIJ) on the basis of data collected from 11 population-based cancer registries: Miyagi, Yamagata, Kanagawa, Niigata, Fukui, Shiga, Osaka, Tottori, Okayama, Saga and Nagasaki. The methods of estimation and their limitations have been explained previously (1–3). The number of incidences, crude rates, age-standardized rates and completeness of registration in 2002 are shown in Table 1, and the number of incidences based on age and the rates according to sex and primary site are shown in Tables 2 and 3. The estimated total number of incidences in Japan for 2002 was 570 598. The time trends of age-standardized incidence rates for five major sites and male- and female-specific sites in 1975–2002 are shown in Figs 1 and 2. The leading site according to the crude and age-standardized incidence rates was stomach for males and breast for females, as shown in Figs 1 and 2. The estimated cancer incidence data in Japan by sex, site, five-year age group and calendar year during the period of 1975–2002 are available on the website: http://www.ganjoho.ncc.go.jp/pro/statistics/en/table_download.html.

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Table 1. Incidence, completeness of reporting and accuracy of diagnosis in Japan according to sex and primary site, 2002

Primary sites	ICD-10th	Number of incidences	Crude rate*	Age-standardized rate*		Completeness of reporting		Accuracy of diagnosis
				World population	Japanese 1985 model population	DCO/I (%)	I/M	MV/I (%)
Male								
All sites (incl. CIS)	C00–C96 D05–D06	339 650	545.6	271.1	385.0	19.3	1.84	68.1
All sites	C00–C96	333 029	535.0	265.6	377.4	19.7	1.81	67.6
Lip, oral cavity and pharynx	C00–C14	8207	13.2	7.1	9.7	15.5	2.16	75.4
Esophagus	C15	13 679	22.0	11.1	15.5	15.8	1.51	74.5
Stomach	C16	71 634	115.1	57.4	81.3	16.1	2.25	78.6
Colon	C18	37 045	59.5	29.6	41.9	12.8	2.95	79.1
Rectum and anus	C19–C21	24 925	40.0	20.9	28.8	10.3	3.11	82.9
Liver	C22	27 876	44.8	22.6	31.6	28.7	1.17	30.0
Gallbladder and bile ducts	C23–C24	8491	13.6	6.2	9.3	29.4	1.17	39.5
Pancreas	C25	11 665	18.7	9.1	13.1	31.5	1.08	28.4
Larynx	C32	3380	5.4	2.7	3.8	9.9	3.53	80.7
Lung, bronchus and trachea	C33–C34	51 988	83.5	38.4	57.4	25.9	1.26	62.8
Skin	C43–C44	3765	6.0	2.9	4.2	6.0	7.53	91.6
Prostate	C61	29 345	47.1	20.7	31.4	14.8	3.62	75.5
Bladder	C67	12 091	19.4	9.3	13.5	12.8	3.45	80.3
Kidney, renal pelvis, ureter and others	C64–C66 C68	8179	13.1	6.8	9.5	15.7	2.33	69.7
Brain and nervous system	C70–C72	2148	3.5	2.5	2.9	30.5	2.40	59.3
Thyroid	C73	1621	2.6	1.6	2.1	11.9	3.85	80.5
Malignant lymphoma	C81–85 C96	8728	14.0	7.7	10.5	15.3	1.84	82.0
Multiple myeloma	C88–C90	2095	3.4	1.6	2.3	32.9	1.12	65.5
All leukemias	C91–C95	5032	8.1	5.1	6.3	26.2	1.22	76.3

Continued

Table 1. *Continued*

Primary sites	ICD-10th	Number of incidences	Crude rate*	Age-standardized rate*		Completeness of reporting		Accuracy of diagnosis
				World population	Japanese 1985 model population	DCO/I (%)	I/M	MV/I (%)
Female								
All sites (incl. CIS)	C00–C96 D05–D06	249 643	383.0	183.9	247.4	18.7	2.07	69.0
All site	C00–C96	237 569	364.5	170.6	230.7	19.3	1.97	67.6
Lip, oral cavity and pharynx	C00–C14	2752	4.2	2.0	2.6	16.6	1.80	74.7
Esophagus	C15	2554	3.9	1.5	2.2	23.3	1.52	62.9
Stomach	C16	35 126	53.9	22.2	31.1	21.3	2.01	73.4
Colon	C18	29 382	45.1	18.1	25.5	17.5	2.37	73.1
Rectum and anus	C19–C21	13 843	21.2	9.5	13.1	11.7	2.95	80.5
Liver	C22	12 728	19.5	7.1	10.3	32.9	1.18	25.1
Gallbladder and bile ducts	C23–C24	9385	14.4	4.5	6.7	33.9	1.11	32.3
Pancreas	C25	9721	14.9	5.2	7.6	34.5	1.04	22.9
Larynx	C32	221	0.3	0.1	0.2	32.4	2.70	62.6
Lung, bronchus and trachea	C33–C34	21 647	33.2	12.8	18.2	26.3	1.42	60.4
Skin	C43–C44	4480	6.9	2.5	3.5	4.5	8.60	92.3
Breast	C50 D05	41 960	64.4	40.4	52.2	5.9	4.36	86.7
Uterus (incl. CIS)	C53–C55 D06	23 306	35.8	24.7	31.3	7.6	4.37	87.2
Uterus (only invasive)	C53–C55	16 572	25.4	15.7	20.3	10.2	3.11	83.3
Cervix uteri	C53	8779	13.5	9.1	11.6	4.1	6.35	91.2
Corpus uteri	C54	6625	10.2	5.9	7.7	5.4	5.10	89.5
Ovary	C56	7418	11.4	6.8	8.7	18.4	1.80	69.5
Bladder	C67	3823	5.9	2.0	2.9	19.6	2.34	72.0
Kidney, renal pelvis, ureter and others	C64–C66 C68	4062	6.2	2.7	3.6	20.5	2.17	63.7
Brain and nervous system	C70–C72	1754	2.7	1.7	2.0	26.3	2.52	60.0
Thyroid	C73	5645	8.7	5.4	6.8	8.0	6.03	84.4
Malignant lymphoma	C81–85 C96	6823	10.5	4.9	6.5	17.3	1.93	80.7
Multiple myeloma	C88–C90	2016	3.1	1.1	1.6	28.3	1.18	68.4
All leukemias	C91–C95	3638	5.6	3.4	4.0	26.8	1.27	75.3

*Per 100 000 population. ICD-10th, International Classification of Disease, 10th Revision; DCO/I, proportion of cases with the death certificate only to incident cases; I/M, number of incidence/number of deaths; MV/I, proportion of microscopically verified cases to incident cases; CIS, carcinoma *in situ*.

Table 2. Age-specific incidence in Japan according to sex and primary site, 2002

Primary sites	ICD-10	All ages	Age group (years)																	
			0–4	5–9	10–14	15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–59	80–84	85+
Male																				
All sites (incl. CIS)	C00–C96 D05–D06	339 650	398	196	185	320	488	832	1416	2095	3944	8113	19 742	27 870	40 748	54 509	65 234	54 579	31 920	27 061
All sites	C00–C96	333 029	398	196	185	313	486	824	1404	2069	3823	7950	19 260	27 169	39 718	53 286	64 087	53 559	31 494	26 808
Lip, oral cavity and pharynx	C00–C14	8207	0	0	4	10	26	38	75	96	131	344	794	916	1294	1441	1349	848	467	374
Esophagus	C15	13 679	0	0	0	0	0	0	8	19	66	311	866	1619	2314	2362	2651	1890	944	629
Stomach	C16	71 634	0	0	0	13	26	54	210	409	901	1989	4784	6530	9086	11 993	13 420	10 925	6148	5146
Colon	C18	37 045	0	0	2	6	27	39	102	213	448	928	2202	3251	4915	6352	7069	5698	3107	2686
Rectum and anus	C19–C21	24 925	0	0	0	6	6	26	109	181	407	804	1973	2784	3883	4563	4255	3147	1562	1219
Liver	C22	27 876	20	5	0	0	10	4	46	96	295	639	1977	2770	3889	5259	5715	3765	1911	1475
Gallbladder and bile ducts	C23–C24	8491	0	0	0	0	0	0	5	9	35	125	349	450	821	1068	1528	1514	1294	1293
Pancreas	C25	11 665	0	0	0	2	5	2	4	39	99	241	692	1044	1498	1718	2145	1863	1243	1070
Larynx	C32	3380	0	0	0	0	8	0	0	4	19	54	251	392	500	572	642	538	245	155
Lung, bronchus and trachea	C33–C34	51 988	0	2	0	1	4	22	72	146	350	862	2199	3241	4728	7341	11170	10 422	6470	4958
Skin	C43–C44	3765	2	0	3	4	11	33	50	32	48	95	159	212	369	444	623	647	428	605
Prostate	C61	29 345	2	2	0	0	0	2	0	0	6	35	312	894	2704	4868	7157	6384	3688	3291
Bladder	C67	12 091	6	0	0	4	2	17	21	65	117	272	682	886	1223	1724	2294	2153	1321	1304
Kidney, renal pelvis, ureter and others	C64–C66 C68	8179	23	4	0	2	15	29	45	85	173	283	667	806	887	1341	1413	1243	673	490
Brain and Nervous system	C70–C72	2148	42	65	46	44	48	67	67	57	89	140	197	194	208	230	266	188	96	104
Thyroid	C73	1621	0	0	4	8	16	30	47	78	72	102	210	173	211	206	199	130	68	67
Malignant lymphoma	C81–85 C96	8728	18	25	35	65	69	77	117	144	294	378	535	787	976	1257	1268	1278	749	656
Multiple myeloma	C88–C90	2095	0	0	0	0	0	0	2	6	12	39	77	147	221	293	396	343	303	256
All leukemias	C91–C95	5032	103	73	39	57	74	100	107	100	153	186	343	377	457	729	759	670	368	337

Female

All sites (incl. CIS)	C00–C96 D05–D06	249 643	319	142	207	334	796	1956	4567	6109	8786	12 984	20 548	20 418	23 540	27 927	31 515	31 219	26 212	32 064
All site	C00–C96	237 569	319	142	207	319	633	1339	3121	4699	7532	11 866	19 495	19 599	22 563	27 097	30 626	30 521	25 781	31 710
Lip, oral cavity and pharynx	C00–C14	2752	0	0	0	11	36	18	34	70	70	80	216	203	286	335	352	345	308	388
Esophagus	C15	2554	0	0	0	0	0	0	1	17	10	65	163	207	244	338	369	321	337	482
Stomach	C16	35 126	0	0	0	2	21	95	220	405	778	1108	2100	2458	3151	4179	5157	5366	4409	5677
Colon	C18	29 382	0	2	0	16	21	40	134	218	367	714	1659	2149	2928	3773	4508	4435	3796	4622
Rectum and anus	C19–C21	13 843	0	0	0	4	5	21	73	144	266	467	1132	1410	1737	1869	1941	1822	1394	1558
Liver	C22	12 728	13	0	5	8	6	22	11	7	51	83	254	565	1091	2057	2511	2316	1915	1813
Gallbladder and bile ducts	C23–C24	9385	0	0	0	1	0	5	2	10	47	63	238	354	568	843	1194	1676	1819	2565
Pancreas	C25	9721	0	0	1	0	0	3	13	24	65	147	357	532	806	1047	1455	1655	1577	2039
Larynx	C32	221	0	0	1	0	0	0	2	0	0	10	5	20	25	38	34	35	24	27
Lung, bronchus and trachea	C33–C34	21 647	2	0	0	10	4	17	36	80	249	450	1112	1469	2018	2654	3415	3456	2969	3706
Skin	C43–C44	4480	12	0	7	8	24	20	46	53	54	92	143	183	272	451	496	664	654	1301
Breast	C50 D05	41 960	0	0	0	6	55	233	896	1730	3370	5604	6655	5133	4858	4162	3431	2789	1719	1319
Uterus (incl. CIS)	C53–C55 D06	23 306	0	0	0	12	201	928	2306	2447	2084	2164	2781	2491	1826	1651	1494	1154	874	893
Uterus (only invasive)	C53–C55	16 572	0	0	0	1	50	335	938	1170	1064	1451	2241	2148	1544	1449	1352	1086	857	886
Cervix uteri	C53	8779	0	0	0	1	47	294	803	960	781	925	923	771	663	628	599	535	426	423
Corpus uteri	C54	6625	0	0	0	0	3	32	125	195	261	462	1187	1292	813	720	648	445	276	166
Ovary	C56	7418	0	2	25	37	85	151	176	217	381	654	1228	951	743	703	678	527	392	468
Bladder	C67	3823	0	0	0	0	2	7	5	10	26	38	135	150	269	452	589	628	640	872
Kidney, Renal pelvis, Ureter and others	C64–C66 C68	4062	9	14	3	2	1	9	13	24	75	112	272	279	401	563	599	623	504	559
Brain and nervous system	C70–C72	1754	39	22	36	30	24	16	67	51	72	64	109	141	147	212	221	201	147	155
Thyroid	C73	5645	4	0	10	25	99	136	233	261	344	441	750	658	627	603	589	383	231	251
Malignant lymphoma	C81–85 C96	6823	11	24	24	50	86	65	72	100	174	216	458	455	643	762	990	1031	846	816
Multiple myeloma	C88–C90	2016	0	0	0	0	0	0	6	12	13	13	76	115	182	235	328	354	297	385
All leukemias	C91–C95	3638	100	48	39	42	55	64	86	94	130	137	254	224	346	402	440	424	347	406

Table 3. Age-specific incidence rate per 100 000 population in Japan according to sex and primary site, 2002

Primary sites	ICD-10	All ages	Age group (years)																	
			0–4	5–9	10–14	15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–59	80–84	85+
Male																				
All sites (incl. CIS)	C00–C96 D05–D06	545.6	13.2	6.4	5.8	8.7	11.9	17.4	29.5	50.3	100.6	198.6	373.4	653.8	1036.8	1560.5	2306.7	2829.4	3250.5	3737.7
All sites	C00–C96	535.0	13.2	6.4	5.8	8.5	11.8	17.2	29.3	49.7	97.5	194.6	364.3	637.3	1010.6	1525.5	2266.2	2776.5	3207.1	3702.8
Lip, oral cavity and pharynx	C00–C14	13.2	0.0	0.0	0.1	0.3	0.6	0.8	1.6	2.3	3.3	8.4	15.0	21.5	32.9	41.3	47.7	44.0	47.6	51.7
Esophagus	C15	22.0	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.5	1.7	7.6	16.4	38.0	58.9	67.6	93.7	98.0	96.1	86.9
Stomach	C16	115.1	0.0	0.0	0.0	0.4	0.6	1.1	4.4	9.8	23.0	48.7	90.5	153.2	231.2	343.3	474.5	566.4	626.1	710.8
Colon	C18	59.5	0.0	0.0	0.1	0.2	0.7	0.8	2.1	5.1	11.4	22.7	41.6	76.3	125.1	181.8	250.0	295.4	316.4	371.0
Rectum and anus	C19–C21	40.0	0.0	0.0	0.0	0.2	0.1	0.5	2.3	4.3	10.4	19.7	37.3	65.3	98.8	130.6	150.5	163.1	159.1	168.4
Liver	C22	44.8	0.7	0.2	0.0	0.0	0.2	0.1	1.0	2.3	7.5	15.6	37.4	65.0	99.0	150.6	202.1	195.2	194.6	203.7
Gallbladder and bile ducts	C23–C24	13.6	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.2	0.9	3.1	6.6	10.6	20.9	30.6	54.0	78.5	131.8	178.6
Pancreas	C25	18.7	0.0	0.0	0.0	0.1	0.1	0.0	0.1	0.9	2.5	5.9	13.1	24.5	38.1	49.2	75.8	96.6	126.6	147.8
Larynx	C32	5.4	0.0	0.0	0.0	0.0	0.2	0.0	0.0	0.1	0.5	1.3	4.7	9.2	12.7	16.4	22.7	27.9	24.9	21.4
Lung, bronchus and trachea	C33–C34	83.5	0.0	0.1	0.0	0.0	0.1	0.5	1.5	3.5	8.9	21.1	41.6	76.0	120.3	210.2	395.0	540.3	658.9	684.8
Skin	C43–C44	6.0	0.1	0.0	0.1	0.1	0.3	0.7	1.0	0.8	1.2	2.3	3.0	5.0	9.4	12.7	22.0	33.5	43.6	83.6
Prostate	C61	47.1	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.9	5.9	21.0	68.8	139.4	253.1	330.9	375.6	454.6
Bladder	C67	19.4	0.2	0.0	0.0	0.1	0.0	0.4	0.4	1.6	3.0	6.7	12.9	20.8	31.1	49.4	81.1	111.6	134.5	180.1
Kidney, renal pelvis, ureter and others	C64–C66 C68	13.1	0.8	0.1	0.0	0.1	0.4	0.6	0.9	2.0	4.4	6.9	12.6	18.9	22.6	38.4	50.0	64.4	68.5	67.7
Brain and nervous system	C70–C72	3.5	1.4	2.1	1.4	1.2	1.2	1.4	1.4	1.4	2.3	3.4	3.7	4.6	5.3	6.6	9.4	9.7	9.8	14.4
Thyroid	C73	2.6	0.0	0.0	0.1	0.2	0.4	0.6	1.0	1.9	1.8	2.5	4.0	4.1	5.4	5.9	7.0	6.7	6.9	9.3
Malignant lymphoma	C81–85 C96	14.0	0.6	0.8	1.1	1.8	1.7	1.6	2.4	3.5	7.5	9.3	10.1	18.5	24.8	36.0	44.8	66.3	76.3	90.6
Multiple myeloma	C88–C90	3.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.3	1.0	1.5	3.4	5.6	8.4	14.0	17.8	30.9	35.4
All leukemias	C91–C95	8.1	3.4	2.4	1.2	1.5	1.8	2.1	2.2	2.4	3.9	4.6	6.5	8.8	11.6	20.9	26.8	34.7	37.5	46.5

Female

All sites (incl. CIS)	C00–C96 D05–D06	383.0	11.1	4.9	6.8	9.5	20.4	42.1	97.2	149.0	226.7	319.5	386.2	464.7	564.4	719.6	931.8	1137.7	1399.5	1791.3
All site	C00–C96	364.5	11.1	4.9	6.8	9.1	16.2	28.8	66.4	114.6	194.3	292.0	366.4	446.0	540.9	698.2	905.6	1112.3	1376.5	1771.5
Lip, oral cavity and pharynx	C00–C14	4.2	0.0	0.0	0.0	0.3	0.9	0.4	0.7	1.7	1.8	2.0	4.1	4.6	6.9	8.6	10.4	12.6	16.4	21.7
Esophagus	C15	3.9	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.4	0.3	1.6	3.1	4.7	5.8	8.7	10.9	11.7	18.0	26.9
Stomach	C16	53.9	0.0	0.0	0.0	0.1	0.5	2.0	4.7	9.9	20.1	27.3	39.5	55.9	75.5	107.7	152.5	195.6	235.4	317.2
Colon	C18	45.1	0.0	0.1	0.0	0.5	0.5	0.9	2.9	5.3	9.5	17.6	31.2	48.9	70.2	97.2	133.3	161.6	202.7	258.2
Rectum and anus	C19–C21	21.2	0.0	0.0	0.0	0.1	0.1	0.5	1.6	3.5	6.9	11.5	21.3	32.1	41.6	48.2	57.4	66.4	74.4	87.0
Liver	C22	19.5	0.5	0.0	0.2	0.2	0.2	0.5	0.2	0.2	1.3	2.0	4.8	12.9	26.2	53.0	74.2	84.4	102.2	101.3
Gallbladder and bile ducts	C23–C24	14.4	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.2	1.2	1.6	4.5	8.1	13.6	21.7	35.3	61.1	97.1	143.3
Pancreas	C25	14.9	0.0	0.0	0.0	0.0	0.0	0.1	0.3	0.6	1.7	3.6	6.7	12.1	19.3	27.0	43.0	60.3	84.2	113.9
Larynx	C32	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.2	0.1	0.5	0.6	1.0	1.0	1.3	1.3	1.5
Lung, bronchus and trachea	C33–C34	33.2	0.1	0.0	0.0	0.3	0.1	0.4	0.8	2.0	6.4	11.1	20.9	33.4	48.4	68.4	101.0	125.9	158.5	207.0
Skin	C43–C44	6.9	0.4	0.0	0.2	0.2	0.6	0.4	1.0	1.3	1.4	2.3	2.7	4.2	6.5	11.6	14.7	24.2	34.9	72.7
Breast	C50 D05	64.4	0.0	0.0	0.0	0.2	1.4	5.0	19.1	42.2	86.9	137.9	125.1	116.8	116.5	107.2	101.4	101.6	91.8	73.7
Uterus (incl. CIS)	C53–C55 D06	35.8	0.0	0.0	0.0	0.3	5.1	20.0	49.1	59.7	53.8	53.2	52.3	56.7	43.8	42.5	44.2	42.1	46.7	49.9
Uterus (only invasive)	C53–C55	25.4	0.0	0.0	0.0	0.0	1.3	7.2	20.0	28.5	27.5	35.7	42.1	48.9	37.0	37.3	40.0	39.6	45.8	49.5
Cervix uteri	C53	13.5	0.0	0.0	0.0	0.0	1.2	6.3	17.1	23.4	20.1	22.8	17.3	17.5	15.9	16.2	17.7	19.5	22.7	23.6
Corpus uteri	C54	10.2	0.0	0.0	0.0	0.0	0.1	0.7	2.7	4.8	6.7	11.4	22.3	29.4	19.5	18.6	19.2	16.2	14.7	9.3
Ovary	C56	11.4	0.0	0.1	0.8	1.1	2.2	3.3	3.7	5.3	9.8	16.1	23.1	21.6	17.8	18.1	20.0	19.2	20.9	26.1
Bladder	C67	5.9	0.0	0.0	0.0	0.0	0.1	0.2	0.1	0.2	0.7	0.9	2.5	3.4	6.4	11.6	17.4	22.9	34.2	48.7
Kidney, renal pelvis, ureter and others	C64–C66 C68	6.2	0.3	0.5	0.1	0.1	0.0	0.2	0.3	0.6	1.9	2.8	5.1	6.3	9.6	14.5	17.7	22.7	26.9	31.2
Brain and nervous system	C70–C72	2.7	1.4	0.8	1.2	0.9	0.6	0.3	1.4	1.2	1.9	1.6	2.0	3.2	3.5	5.5	6.5	7.3	7.8	8.7
Thyroid	C73	8.7	0.1	0.0	0.3	0.7	2.5	2.9	5.0	6.4	8.9	10.9	14.1	15.0	15.0	15.5	17.4	14.0	12.3	14.0
Malignant lymphoma	C81–85 C96	10.5	0.4	0.8	0.8	1.4	2.2	1.4	1.5	2.4	4.5	5.3	8.6	10.4	15.4	19.6	29.3	37.6	45.2	45.6
Multiple myeloma	C88–C90	3.1	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.3	0.3	0.3	1.4	2.6	4.4	6.1	9.7	12.9	15.9	21.5
All leukemias	C91–C95	5.6	3.5	1.6	1.3	1.2	1.4	1.4	1.8	2.3	3.4	3.4	4.8	5.1	8.3	10.4	13.0	15.5	18.5	22.7