Discussion

We found that the risk of pancreatic cancer was increased with alcohol consumption in subjects with the *MTHFR* 677 CC genotype, *MTR* 2756 AA genotype, and *MTRR* 66 G allele. These finding suggest that the association between alcohol drinking and pancreatic cancer risk may be modified by these polymorphism.

Previous two studies in the United States and China showed an increased risk with the *MTHFR* 677 TT genotype (12, 13), whereas no association was found in a second U.S. study (14). The China study also reported an association between *TS* and pancreatic cancer risk (12).

High consumption of dietary folate has been associated with a lower risk of pancreatic cancer (2, 3). Folate status is determined by both folate intake and folate metabolism, which is influenced by folate metabolism enzyme polymorphisms. On the other hand, alcohol consumption may impair folate metabolism (15). These observations suggest that folate intake, the polymorphisms, and alcohol consumption may share some common pathways contributing to pancreatic carcinogenesis.

In this study, stratification of analyses by the respective genotypes revealed a significant effect of alcohol consumption on pancreatic cancer risk among subjects with *MTHFR* 677 CC genotype. Alcohol produces inflammation in pancreatic tissues via various mechanisms, such as the generation of reactive oxygen species and alterations in immune responses (16), which in turn lead to pancreatitis (17). Chronic pancreatitis increases genomic damage and cellular proliferation, leading to the malignant transformation of pancreatic cells (18) and

Table 3. Effect of alcohol consumption on pancreatic cancer risk by one-carbon metabolism-related gene polymorphisms

	Drinking habit			P_{trend}	P_{int}‡
	Never	Moderate*	Heavy†		
	No. cases/controls	No. cases/controls	No. cases/controls		
	OR§ (95% CI)	OR§ (95% CI)	OR§ (95% CI)		
Overall	46/306	73/347	25/88		
	1.00 (reference)	1.47 (0.93-2.33)	1.90 (1.00-3.62)	0.036	
MTHFR (C677T)					
CC	13/113	27/132	10/31		
	1.00 (reference)	2.28 (0.96-5.41)	4.50 (1.44-14.05)	0.008	
CT	27/143	36/161	13/43		
	1.00 (reference)	1.23 (0.65-2.31)	1.50 (0.60-3.73)	0.365	
TT	6/50	10/54	2/14		
	1.00 (reference)	0.75 (0.16-3.54)	0.35 (0.03-3.83)	0.408	0.093
CT + TT	33/193	46/215	15/57		
	1.00 (reference)	1.22 (0.70-2.16)	1.25 (0.55-2.85)	0.511	0.075
MTR (A2756G)					
AA	28/206	48/229	18/55		
	1.00 (reference)	1.64 (0.92-2.94)	2.65 (1.17-6.00)	0.017	
AG	17/88	22/111	5/28		
	1.00 (reference)	1.46 (0.62-3.45)	1.45 (0.37-5.66)	0.449	
GG	1/11	3/6	2/5		
	NA			NA	NA
AG + GG	18/99	25/117	7/33		
	1.00 (reference)	1.59 (0.71-3.54)	1.61 (0.50-5.21)	0.311	0.291
MTRR (A66G)					
AA	26/152	39/154	8/43		
	1.00 (reference)	1.66 (0.87-3.15)	1.22 (0.43-3.45)	0.351	
AG	17/125	29/150	15/39		
	1.00 (reference)	1.46 (0.68-3.13)	2.99 (1.10-8.15)	0.039	
GG	3/29	5/43	2/6		
	1.00 (reference)	2.19 (0.29-16.47)	10.80 (0.51-229.67)	0.154	0.294
AG + GG	20/154	34/193	17/45		
	1.00 (reference)	1.52 (0.76-3.04)	3.35 (1.34-8.36)	0.013	0.316
TS					
Non-2R/non-2R	34/214	45/246	14/53		
	1.00 (reference)	1.11 (0.64-1.94)	1.33 (0.58-3.06)	0.506	
2R/non-2R	12/86	26/93	8/31		
	1.00 (reference)	2.29 (0.89-5.87)	2.42 (0.72-8.16)	0.117	
2R/2R	0/6	2/8	3/4		
	NA			NA	NA
2R/non-2R + 2R/2R	12/92	28/101	11/35		
	1.00 (reference)	2.13 (0.85-5.39)	2.85 (0.92-8.82)	0.065	0.133

Abbreviation: NA, not available.

*Moderate drinker means <46 g ethanol/d or <5 d/wk.

†Heavy drinker means ≥46 g ethanol/d on ≥5 d/wk.

‡P_{int} indicates interaction P value between drinking habit and gene polymorphisms for pancreatic cancer risk.

§Adjusted for age, sex, drinking habit, smoking habit, body mass index, total non-alcohol energy intake, dietary folate intake, history of diabetes mellitus, and referral pattern to our hospital.

ultimately affecting the development of pancreatic cancer. Considering folate metabolism pathway, low activity of MTHFR, *MTHFR* 677 CT or TT genotypes, leads to accumulate of 5,10-methylentetrahydrofolate, which is required for conversion of uridylate to thymidylate, whereas it is thought that individuals harboring the *MTHFR* 677 CC genotype have less DNA synthesis and repair capacity. These finding suggest that the individuals with the CC genotype would be more susceptible to DNA damage by large amounts of alcohol than those with the CT or TT genotypes. Furthermore, alcohol ingestion reduces the intestinal absorption of folate (15), which may accelerate the reduction of DNA repair capacity.

Our results showed that the polymorphism of *MTR* and *MTRR* also may modify pancreatic cancer risk by alcohol drinking. Aberrant DNA methylation by *MTR* and *MTRR* polymorphisms and large amount of alcohol drinking results in altered expression of critical proto-oncogenes and tumor suppressor genes. MTR and MTRR catalyze the remethylation of homocysteine to methionine; thus, their polymorphism may influence the pancreatic cancer risk, although the functional effect of these gene polymorphisms has been well unknown. Frequency of variant allele in *MTR* and *MTRR* was small; thus, the interpretation should be caution.

Frequency of heavy alcohol drinkers in this study is approximately in agreement with that of prospective study in Japan (19). According to WHO report, the percentage of heavy drinkers is relatively high in men compared with other countries (e.g., 6.4% for men in the United States; ref. 20). Therefore, it is important to classify the risky genetic background for heavy drinkers in pancreatic cancer development.

Several studies have shown protective effect of folate on cancers, whereas, in some animal studies and a recent supplement study, adverse effect of folate was observed (21, 22). Future research must clarify the dual effect of folate on pancreatic cancer.

Potential limitations of the present study should be considered. First, our study is hospital-based case-control design; thus, selection bias may be concerned. We used noncancer patients at our hospital for this purpose on the basis that our subjects arose within this population, thereby warranting internal validity. We have confirmed previously the similarity of this population to the general population in terms of a range of exposures of interest, in this case alcohol consumption, thereby warranting external validity (23). Equivalence in the genotype distribution for the *MTHFR* C677T polymorphism between our controls and the general population has also been reported (24). Referral patterns to our hospital were different between cases and controls; thus, relative geographic distributions of residences between cases and controls may be different. However, this finding would not lead to bias, because frequency of *MTHFR* C677T genotype is not different in Japanese (24, 25). Second, this study may suffer from recall bias. Some pancreatic patients might be severe condition at the time of interview. Third, this study focused on four candidate polymorphisms rather than a comprehensive evaluation of the genetic variants. Fourth, we could not obtain the information about the history of pancreatitis, which is risk factor of pancreatic cancer. Lastly, the results in this study may be a false-positive due to small size, particularly in subgroup analysis; thus, large-scale study would assist our results.

In conclusion, our case-control study suggested that effect of alcohol drinking on pancreatic cancer risk may be modified by the folate metabolism enzyme polymorphism in the Japanese population.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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ARTICLE | Annals of Internal Medicine

Declining Incidence of Hepatocellular Carcinoma in Osaka, Japan, from 1990 to 2003

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Background: Japan has the highest incidence rate of primary liver cancer attributed to chronic hepatitis C virus (HCV) infection among developed countries. Molecular clock analysis of HCV sequences revealed that the spread of HCV took place earlier in Japan than in other countries. This might influence recent temporal trends in hepatocellular carcinoma (HCC) incidence.

Objective: To characterize the contribution of HCV-related hepatocellular carcinoma (HCC) to recent changes in HCC incidence in Osaka, Japan.

Design: Population-based survey.

Setting: Osaka Cancer Registry and 10 hospitals in Osaka.

Participants: 63 862 patients with HCC that was diagnosed between 1981 and 2003 in Osaka Prefecture, including 5253 HCV-seropositive patients with HCC that was diagnosed between 1990 and 2003 at 10 hospitals.

Measurements: Incidence of HCC and estimated incidence rate of HCV-related HCC, measured by multiplying the prevalence of anti-HCV by the corresponding HCC incidence rate.

Results: Between 1981 and 2003, peak incidence of HCC among men age 50 to 59 years, 60 to 69 years, and 70 to 79 years occurred in 1986, 1995, and 2000, respectively, with marked downward trends thereafter (average annual change, −7.9, −22.3, and −12.4 per 100 000 persons, respectively). Similar trends were observed in women. Estimated sex- and age-specific incidence of HCV-related HCC (per 100 000 persons) decreased from 255 to 92 cases at the maximum in men age 60 to 69 years and from 61 to 34 cases in women age 60 to 69 years, whereas estimated incidence of non-HCV–related HCC did not change between 1990 and 2003.

Limitation: Infection was determined only by HCV seropositivity.

Conclusion: The incidence of HCC in Osaka started to decrease by 2000, mainly because of decreased HCV-related HCC.

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Primary liver cancer was the fifth most common cancer worldwide by 2000, with approximately 551 000 new cases recorded (1). In most countries, hepatocellular carcinoma (HCC) comprises 85% to 90% of primary liver cancer cases. With some exceptions, developed countries, including the United States, have been experiencing an increase in the incidence of primary liver cancer, considered to be due at least in part to increased prevalence of chronic hepatitis C virus (HCV) infection (2).

Japan has had one of the highest incidence rates of primary liver cancer among developed countries (age-standardized incidence rate in 1995, 25.5 per 100 000 men and 7.7 per 100 000 women) (3). Approximately 90% of liver cancer cases are HCC, which, in Japan, is mainly caused by chronic HCV infection rather than chronic hepatitis B virus infection (4). A recent report on the age-standardized incidence of primary liver cancer among Japanese men, which was calculated from 6 population-based cancer registries, showed a sharp increase that started in the mid-1970s but leveled off in the mid-1990s (5). These distinctive trends were thought to be due to the spread of HCV infection, which began in the 1920s and increased after World War II (6–8). Thus, HCV penetrated Japan earlier than Spain, Egypt, the United States, the former Soviet Union, South Africa, and Hong Kong, as evidenced by molecular clock analysis of the sequences of HCV isolates (8). However, recent temporal trends regarding incidence rates of HCC and the contribution of HCV infection have not been clearly documented in the Japanese population.

We analyzed temporal trends for HCC incidence rates between 1981 and 2003 in Osaka Prefecture (population in 2005, 8.8 million) and interpreted these in the context of HCV infection rates.

See also:

Print
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Conversion of graphics into slides

METHODS

Data Collection on Incident HCC Cases

We obtained data on incident HCC cases from the Osaka Cancer Registry, which was established by the Osaka Prefectural Government in 1962. The registry collects reports on patients with newly diagnosed cancer, including demographic and cancer-related information, from all medical institutions in Osaka Prefecture (9). These have been routinely supplemented by death certificates gathered

by the Osaka Prefectural Government (9). For patients with cancer who were enrolled in the registry on the basis of their death certificate, we contacted the issuing hospital to obtain information on diagnosis and treatment and to establish the date of HCC incidence, which we determined to be the time of diagnosis at that hospital. We site-coded the data according to the International Classification of Diseases for Oncology, Third Edition (10). We included patients with HCC (codes 8170 through 8180). The protocol was approved by the ethics committee of the Osaka Medical Center for Cancer and Cardiovascular Diseases.

From 1981 to 2003, 48 166 men and 15 696 women with HCC were documented in the Osaka Cancer Registry. We calculated the annual age-standardized incidence rates of HCC (world population as a standard population) by sex between 1981 and 2003. To characterize temporal trends for HCC, we assessed 10-year, age-specific incidence rates of HCC between 1981 and 2003 in individuals age 50 to 79 years. We studied these particular age-specific rates because most HCV-related HCC cases in the Japanese population occur between the ages of 50 and 79 years (4). We used the annual population estimates from 1981 to 2003, which were based on the average population in each sex and age category for the Osaka Prefecture during the particular period, as denominators for calculating incidence rates. The annual population estimates were based on data from the 1980, 1985, 1990, 1995, 2000, and 2005 Japanese population censuses, with linear interpolation for the years in between.

Statistical Analysis

To identify years when a statistically significant change in the slope of the temporal trend in the incidence occurred, we applied the joinpoint regression model by using the Joinpoint Regression Program, version 3.0 (U.S. National Cancer Institute, Bethesda, Maryland). We assumed constant variance and uncorrelated errors (11) because we could not detect heteroskedasticity by the White test or autocorrelation by the Durbin-Watson test in men or women in any age group.

We computed the estimated slopes describing the average annual change of incidence rate per 100 000 persons and the corresponding 95% CIs for each trend by fitting a piecewise regression line to the rates, using calendar year as a regression variable. We used the permutation test method to identify years when a statistically significant change had occurred ($P < 0.05$) and set the number of randomly permuted data sets at 4499. We set the number of joinpoints to a minimum of 0 and a maximum of 3 in the Joinpoint Regression Program.

Data Collection on Prevalence of HCV Infection among Patients with HCC

The Osaka Cancer Registry does not collect serologic data on HCV infection in the registered patients. Therefore, we used data on HCV seropositivity from patients with HCC that was diagnosed at 10 hospitals in Osaka Prefecture (1 university hospital, 2 cancer centers, and 7 general hospitals) to estimate the prevalence of HCV infection in patients with HCC. We considered the HCC diagnosis confirmed when the patient had positive histologic or positive radiologic results by enhanced computed tomography or hepatic angiography. We collected data on the patient's sex, date of birth, date of diagnosis between 1990 and 2003, first Chinese letter of the family name, and presence of hepatitis B surface antigen and antibody to hepatitis C (anti-HCV) as assessed by any commercially available kit. We did not collect the full first and family name for reasons of confidentiality. Because anti-HCV testing first became available in Japan in 1990, we collected data on patients whose HCC diagnosis was between 1990 and 2003. One investigator checked for duplication of the data set, because some patients might have been registered multiple times among the participating hospitals as a result of referrals and recurrence of HCC. We defined HCV-related HCC as occurring in patients who were HCV-seropositive at the time of diagnosis.

We calculated the sex-specific, age-specific (50 to 59, 60 to 69, or 70 to 79 years), and period-specific (1990 to 1992, 1993 to 1995, 1996 to 1998, 1999 to 2001, or 2002 to 2003) prevalences of HCV seropositivity for patients with HCC. We then multiplied prevalence rates by the corresponding strata of the HCC incidence rate obtained from the Osaka Cancer Registry data. Thus, we derived the denominators from the general population in Osaka through the denominators of the HCC incidence rate and obtained the numerators by multiplying the prevalence rates by the HCC incidence rate. We calculated the incidence rate of non–HCV-related HCC by subtracting HCV-related HCC from total HCC. Thus, we describe trends for the estimated incidence rates of HCV-related

Context

Hepatitis C virus (HCV) infection in Japan began to spread during the 1920s, increased after World War II with an explosion in parenteral amphetamine use and paid blood donation, and decreased in the 1950s to 1960s with voluntary blood donation and penalties against amphetamine use. Evidence linking the trends in HCV infection to hepatocellular carcinoma rates in Japan is limited.

Contribution

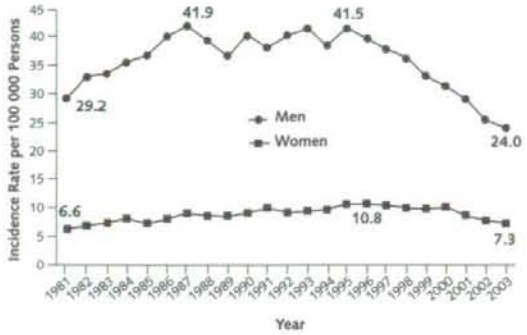
Data from the Osaka Cancer Registry and 10 Osaka hospitals suggest that hepatocellular carcinoma rates began to decrease in 2000, mainly because of a decrease in HCV-associated cancer.

Implication

Control of HCV transmission within a population seems to be followed by a decrease in hepatocellular carcinoma.

—The Editors

Figure 1. **Trends in age-standardized (world population) incidence of hepatocellular carcinoma in Osaka, Japan, 1981–2003.**



and non–HCV-related HCC between 1990 and 2003 in Osaka Prefecture. We calculated the CI of the estimated rates by multiplying the lower and upper limits of the CI of the prevalence based on SE by the corresponding HCC incidence rate.

Role of the Funding Source

This study was supported by the Osaka Prefectural Government between 1990 and 2000 and Grants-in-Aid for Hepatitis Research of the Japanese Ministry of Health, Labor, and Welfare. There is no conflict of interest in the study. The funding sources had no role in the collection, management, or analysis of data.

RESULTS

The age-standardized incidence rate of HCC in men increased between 1981 and 1987 from 29.2 to 41.9 cases per 100 000 persons, then fluctuated until 1995. After that, it steadily decreased to 24.0 cases per 100 000 persons in 2003 (**Figure 1**). Among women, the age-standardized incidence rate of HCC increased between 1981 and 1996 from 6.6 to 10.8 cases per 100 000 persons, then gradually decreased to 7.3 cases per 100 000 persons in 2003 (**Figure 1**).

Figure 2 shows the trends in the incidence of HCC among men and women age 50 to 59 years, 60 to 69 years, and 70 to 79 years in Osaka between 1981 and 2003. The HCC incidence rate increased from 1981 to 1986 among men age 50 to 59 years, from 1981 to 1995 among men age 60 to 69 years, and from 1981 to 2000 among men age 70 to 79 years (average annual change of the incidence rate [per 100 000 persons], 10.0, 10.7, and 6.2, respectively) (**Table 1**). A striking downward trend occurred after the year of peak incidence in the 3 age groups (−7.9 until 1996, −22.3 until 2003, and −12.4 until 2003, respectively). Among men age 50 to 59 years, there was a second joinpoint (a change from rapid to moderate decrease) in 1996, resulting in a slope of −3.1 until 2003. Among women age 50 to 59 years, 60 to 69 years, and 70 to 79 years, the incidence rates of HCC peaked in 1991, 1997, and 2000, respectively (**Table 1**). The rates in women seemed to increase slightly from 1981 until the year of the joinpoint, with slopes of 0.43, 2.07, and 3.10, respectively. Thereafter, HCC incidence rates in women decreased through 2003 at a statistically significant average annual rate of −0.9, −5.7, and −7.9, respectively (**Table 1**).

Figure 2. **Joinpoint analysis of the incidence rate of hepatocellular carcinoma among individuals age 50 to 79 years in Osaka, Japan, 1981–2003.**

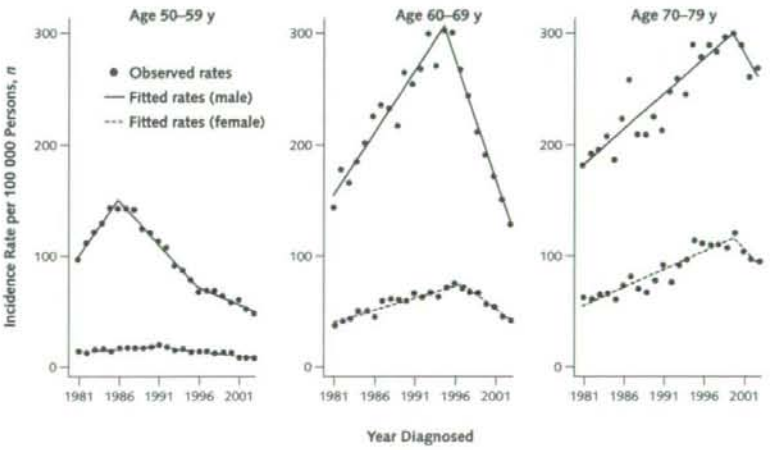


Table 1. **Joinpoint Analysis of the Hepatocellular Carcinoma Incidence Rate per 100 000 Persons in Osaka, Japan, 1981–2003**

Age Range	Peak Year	Incidence Rate per 100 000 Persons	Trend 1		Trend 2		Trend 3	
			Years	Slope (95% CI)	Years	Slope (95% CI)	Years	Slope (95% CI)
Men								
50–59 y	1986	142.0	1981–1986	10.0 (8.2 to 11.8)*	1986–1996	−7.9 (−8.6 to −7.1)*	1996–2003	−3.1 (−4.2 to −2.1)*
60–69 y	1995	299.6	1981–1995	10.7 (9.1 to 12.3)*	1995–2003	−22.3 (−26.0 to −18.6)*	–	–
70–79 y	2000	296.4	1981–2000	6.2 (4.8 to 7.5)*	2000–2003	−12.4 (−35.7 to 10.9)	–	–
Women								
50–59 y	1991	19.7	1981–1991	0.4 (0.2 to 0.7)*	1991–2003	−0.9 (−1.1 to −0.7)*	–	–
60–69 y	1997	68.5	1981–1997	2.1 (1.7 to 2.4)*	1997–2003	−5.7 (−7.3 to −4.1)*	–	–
70–79 y	2000	118.1	1981–2000	3.1 (2.5 to 3.7)*	2000–2003	−7.9 (−18.1 to 2.4)	–	–

* $P < 0.001$.

Table 2 shows the prevalence of anti-HCV antibodies among 5253 patients age 50 to 79 years with HCC that was diagnosed at 10 hospitals in Osaka between 1990 and 2003. The prevalence was highest in men with HCC that was diagnosed in 1993 to 1995 (82.4%). The proportion of HCV-seronegative patients ranged from 18% to 29% through the observation period. The prevalence of anti-HCV was almost constant (81% to 83%) among women with HCC that was diagnosed between 1993 and 2003 (**Table 2**).

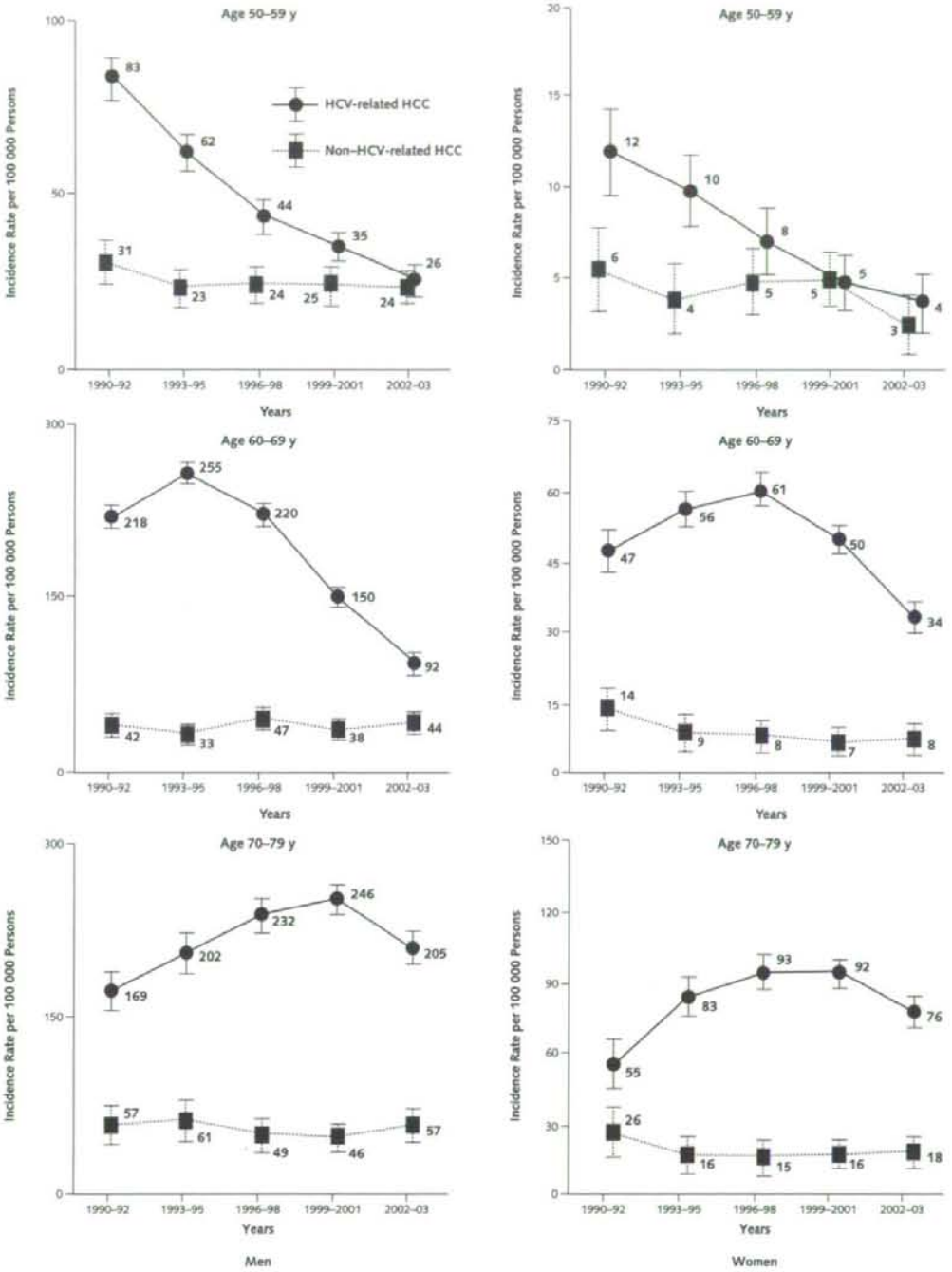
Figure 3 shows changes in the estimated incidence rate of HCV-related and non–HCV-related HCC from 1990 to 2003. Among men, the estimated incidence rate of HCV-related HCC steadily decreased among Osaka residents age 50 to 59 years from 83 (95% CI, 77 to 89) cases per 100 000 persons in 1990 to 1992 to 26 (CI, 21 to 30) cases per 100 000 persons in 2002 to 2003. Among men age 60 to 69 years, incidence seemed to peak (255 [CI, 247 to 264] cases per 100 000 persons) from 1993 to 1995. Among men age 70 to 79 years, the incidence rate increased from 1990 to 1992 (169 [CI, 153 to 186] cases per 100 000 persons) to 1999 to 2001 (246 [CI, 234 to 258] cases per 100 000 persons) and leveled off afterward. The estimated incidence rate of HCV-related HCC among women age 50 to 59 years decreased from 12.4 (CI, 10.1 to 14.7) cases per 100 000 persons during 1990 to 1992 to 4.2 (CI, 2.5 to 5.8) cases per 100 000 persons during 2002 to 2003, whereas among women age 60 to 69 years, the incidence peaked (61 [CI, 57 to 64] cases per 100 000 persons) during 1996 to 1998. The trend in women age 70 to 79 years seemed to be similar to that in men of the same age: increasing during the 1990s and leveling off in the early 2000s (**Figure 3**). The estimated incidence rate of non–HCV-related HCC was lower than that of HCV-

Table 2. **Prevalence of Anti-HCV among 5253 Patients Age 50 to 79 Years with Hepatocellular Carcinoma at 10 Hospitals in Osaka, Japan, 1990–2003***

Variable	1990–1992		1993–1995		1996–1998		1999–2001		2002–2003	
	Patients, *n*	Prevalence (±SE), %	Patients, *n*	Prevalence (±SE), %	Patients, *n*	Prevalence (±SE), %	Patients, *n*	Prevalence (±SE), %	Patients, *n*	Prevalence (±SE), %
Men										
Anti-HCV(+)	602	78.3 ± 1.5	677	82.4 ± 1.3	651	78.7 ± 1.4	709	76.6 ± 1.4	385	70.9 ± 1.9
Anti-HCV(+) and HBsAg(+)	18	2.3 ± 0.5	17	2.1 ± 0.5	11	1.3 ± 0.4	16	1.7 ± 0.4	8	1.5 ± 0.5
Anti-HCV(+) and HBsAg(−)	584	75.9 ± 1.5	660	80.3 ± 1.4	640	77.4 ± 1.5	693	74.8 ± 1.4	377	69.4 ± 2.0
Anti-HCV(−)	167	21.7 ± 1.5	145	17.6 ± 1.3	176	21.3 ± 1.4	217	23.4 ± 1.4	158	29.1 ± 1.9
Anti-HCV(−) and HBsAg(+)	60	7.8 ± 1.0	57	6.9 ± 0.9	71	8.6 ± 1.0	106	11.4 ± 1.0	68	12.5 ± 1.4
Anti-HCV(−) and HBsAg(−)	107	13.9 ± 1.2	88	10.7 ± 1.1	105	12.7 ± 1.2	111	12.0 ± 1.1	90	16.6 ± 1.6
Total	769	100.0	822	100.0	827	100.0	926	100.0	543	100.0
Women										
Anti-HCV(+)	165	73.0 ± 3.0	211	82.7 ± 2.4	248	82.9 ± 2.2	274	80.8 ± 2.1	200	81.0 ± 2.5
Anti-HCV(+) and HBsAg(+)	8	3.5 ± 1.2	2	0.8 ± 0.6	5	1.7 ± 0.7	2	0.6 ± 0.4	2	0.8 ± 0.6
Anti-HCV(+) and HBsAg(−)	157	69.5 ± 3.1	209	82.0 ± 2.4	243	81.3 ± 2.3	272	80.2 ± 2.2	198	80.2 ± 2.5
Anti-HCV(−)	61	27.0 ± 3.0	44	17.3 ± 2.4	51	17.1 ± 2.2	65	19.2 ± 2.1	47	19.0 ± 2.5
Anti-HCV(−) and HBsAg(+)	21	9.3 ± 1.9	17	6.7 ± 1.6	29	9.7 ± 1.7	29	8.6 ± 1.5	18	7.3 ± 1.7
Anti-HCV(−) and HBsAg(−)	40	17.7 ± 2.5	27	10.6 ± 1.9	22	7.4 ± 1.5	36	10.6 ± 1.7	29	11.7 ± 2.0
Total	226	100.0	255	100.0	299	100.0	339	100.0	247	100.0

* HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus.

Figure 3. **Trends in estimated incidence rates of hepatitis C virus (*HCV*)–related and non–HCV-related hepatocellular carcinoma (*HCC*) in Osaka, Japan, 1990–2003.**



Information on anti-HCV status only became available after 1989. Error bars indicate 95% CIs.

related HCC in most strata. We observed no distinctive changes in the temporal trends for non–HCV-related HCC during the study period.

Discussion

Our analysis of HCC incidence in the Japanese population between 1981 and 2003 identified calendar years in which significant changes in temporal trends occurred. The HCC incidence rates in men and women age 50 to 59 years peaked during 1986 and 1991, respectively; in men and women age 60 to 69 years during 1995 and 1997, respectively; and in men and women age 70 to 79 years in 2000. We also found that temporal trends for HCC incidence between 1990 and 2003 by age group were mainly determined by trends in the incidence rates of HCV-related HCC.

The most likely explanation for these observations is the particular mode of HCV transmission in Japanese society. According to a study on molecular tracing of endemic HCV (8), the exponential spread of HCV-1b infection, a dominant genotype of HCV in Japan, started in the 1920s. This was associated with treatment of *Schistosoma japonicum* beginning in 1921 (12). Later, HCV infection coincided with an increase in parenteral amphetamine use in the devastated country during and after World War II (6, 7). Subsequently, viral spread was considered to be amplified through blood transfusions and parenteral medical procedures in the 1950s and 1960s (6, 7). Data on first-time blood donor candidates in Osaka indicate that the prevalence of anti-HCV antibodies among those born in 1925 to 1935 was much higher (7% to 10%) than that in the younger generation born in 1936 to 1955 (13). It is plausible that Japanese people born between 1925 and 1935, who were adolescents in the early 1950s, were most susceptible to HCV transmission under these circumstances. Age groups with peak incidence of HCC in men and women in the current study (1986 and 1991, respectively, for 50 to 59 years; 1995 and 1997, respectively, for 60 to 69 years; and 2000 for 70 to 79 years) included the generation for which prevalence of anti-HCV was high in Osaka (born in 1925 and 1935) (13). Stiffening of legal penalties against amphetamine use starting in 1954 and conversion from paid to voluntary blood donation in the late 1960s may have reduced HCV transmission, thereby resulting in the lower prevalence of HCV infection in generations born after 1935. Indeed, the spread of HCV in Japan essentially ended by the early 1990s at the latest, as evidenced by the current very low incidence of HCV infection among repeat blood donors (14, 15). Better detection methods introduced in the early 1980s for HCC in patients with cirrhosis through ultrasonography and measurement of α-fetoprotein may have contributed to the apparent increase in the incidence of HCC found in this study. However, the distinctive changes we observed in the age-specific incidence of HCC during the 1990s through the early 2000s cannot be explained by the increased ability to detect HCC, because the different joinpoints in age-specific incidence rates would not be derived from a single period effect of detection of HCC.

Increases in the incidence of and deaths from liver cancer in the 1970s to 1990s have been reported in Japan (5, 16), Australia (2), the United Kingdom (17), France (2, 18), Italy (2, 18), and the United States (2, 19). The increases in Japan and the United States are attributable to increased seroprevalence of HCV (6, 13, 20, 21), whereas this relationship has not been clearly established in the other countries.

Certain limitations of this study should be considered. First, because cancer reporting in Osaka is not mandated by law, HCC could have been underreported. However, because it is fatal, most of the unreported cases should have been detected by examination of the death certificate. In addition, because the proportion of persons with HCC included only on the basis of their death certificate was almost constant (22% to 25%) during the observation period (22–24), such underreporting would not be expected to affect the temporal trends for HCC incidence rates shown in our study. Second, the proportion of HCV-seropositive patients among the 5253 cases diagnosed at 10 hospitals might differ somewhat from the entire cohort of patients with HCC in Osaka. However, all Japanese patients, including those with HCC, have easy access to hospitals because of the national medical insurance system, and the 10 participating hospitals did not select patients with HCC on the basis of their etiologic background. Therefore, it is realistic to suppose that selection bias on prevalence of anti-HCV among these 5253 patients would have been limited. Finally, the temporal trends seen in the present study might differ from those among the entire Japanese population. We previously reported age-specific incidence rates of liver cancer by birth year in Japanese men between 1962 and 1997 (5) by using 6 population-based cancer registries from Cancer Incidence in Five Continents (9) (registries for Miyagi, Yamagata, Osaka, Hiroshima, Saga, and Nagasaki). Our previous study found the peak incidence of HCC among those born between 1931 and 1935 (5). In addition, the age-dependent prevalence of anti-HCV among first-time blood donors in Osaka (13) was similar to those in other areas of Japan (25). These findings may indicate that the timing of the outbreak of HCV infection and its reduction were similar in the different geographic areas of the country.

In conclusion, our calculation of HCC incidence rates demonstrated that they are already decreasing in both sexes in Osaka, Japan. That the outbreak of HCV infection in Japan after World War II and its termination occurred earlier in Japan than in the rest of the world is the most likely explanation for these observations. These findings confirm that HCV-related HCC is a preventable disease that can be decreased by controlling parenteral HCV transmission. In the early 1990s, interferon therapy for patients

with chronic HCV infection was started in Japan to reduce the risk for HCC (26, 27). A nationwide, community-based anti-HCV screening system targeting individuals age 40 to 70 years was introduced by municipal governments in Japan in 2002. Further observation of the temporal trends of HCC incidence is needed to assess the efficacy of these interventions in Japan.

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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.

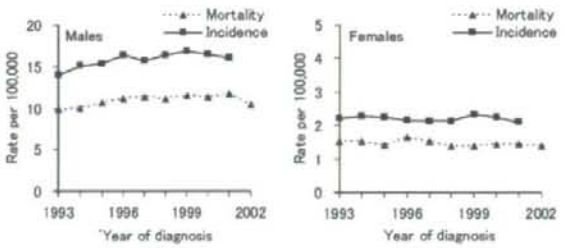

Figure 1. Trends in age-adjusted incidence and mortality rate (the 1985 Japanese model population) of esophageal cancers by sex.

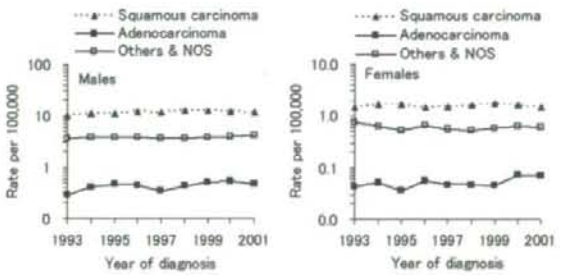

Figure 2. Trends in age-adjusted incidence rate (the 1985 Japanese model population) of esophageal cancers by histological subtypes and sex.

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).

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

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.

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