研究成果の刊行に関する一覧表

書籍

| 著者名 | 論文タイトル | 編集者<br>(書籍全体) | 書籍名 | 出版社 | 出版地 | 出版年 | 頁 |
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# V. 研究成果の刊行物・別刷

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**
Editors' Notes . . . . . 821

**Web-Only**
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***

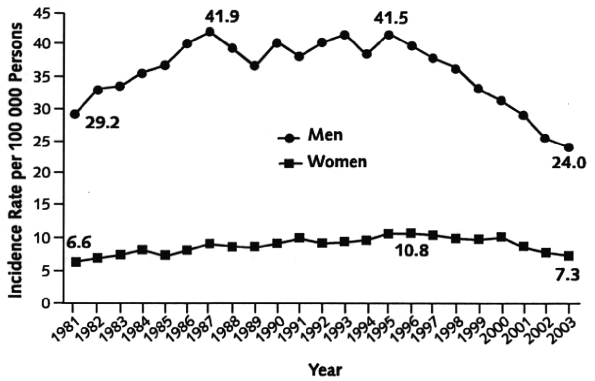
Data from the Osaka Cancer Registry and 10 Osaka hospitals suggest that hepatocellular carcinoma rates began to decrease in 2000, mainly because of a decrease in HCV-associated cancer.

***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.

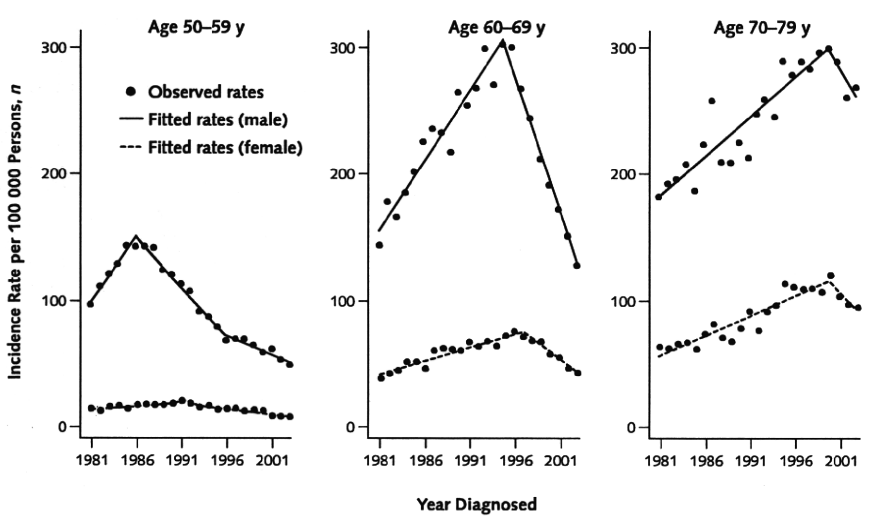


*Table 1.* Joinpoint Analysis of the Hepatocellular Carcinoma Incidence Rate per 100 000 Persons in Osaka, Japan, 1981–2003

| 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**).

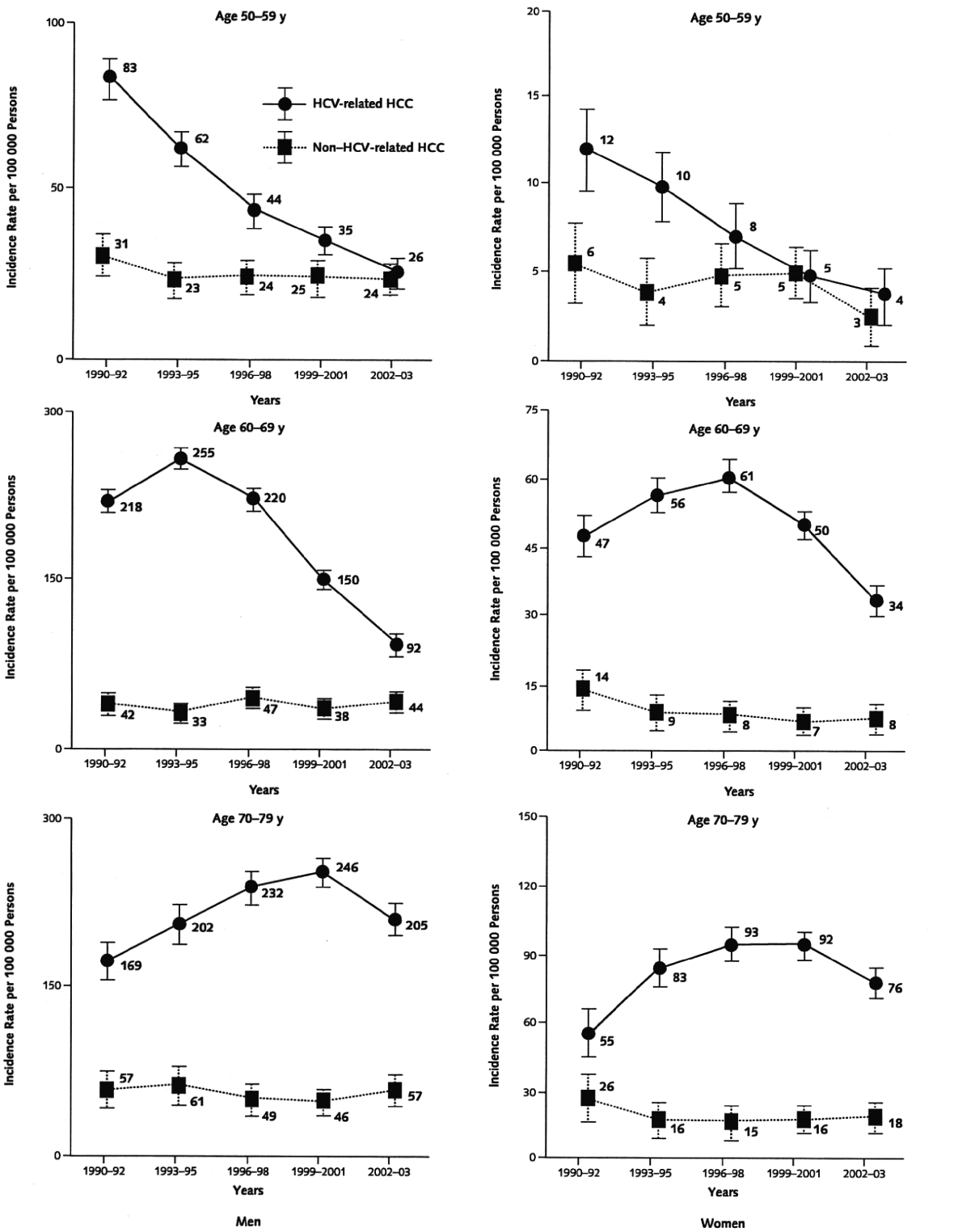
**Figure 3** shows changes in the estimated incidence rate of HCV-related and non–HCV-related HCC from 1990 to 2003. Among men, the estimated incidence rate of HCV-related HCC steadily decreased among Osaka residents age 50 to 59 years from 83 (95% CI, 77 to 89) cases per 100 000 persons in 1990 to 1992 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 $\alpha$-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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# Reduced risk of endometrial cancer from alcohol drinking in Japanese

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**The role of alcohol consumption in the etiology of endometrial cancer has not been clarified. To examine the association between alcohol consumption and endometrial cancer risk, we conducted a case-control study with 148 histologically diagnosed incident endometrial cancer cases and 1468 matched non-cancer controls. Median consumption of alcohol was only 19.3 g/week among cases who drank and 28.2 g/week among controls who drank. These values are lower than in Western countries. Relative risk was analyzed in subjects classified into four groups according to weekly alcohol consumption (non-drinkers, 1–24 g/week, 25–175 g/week, and >175 g/week). Confounder-adjusted odds ratios for those consuming alcohol at <25 g/week, 25–175 g/week, and >175 g/week compared to non-drinkers were 0.79 (95% confidence interval (CI), 0.49–1.28), 0.42 (95% CI, 0.23–0.79), and 0.47 (95% CI, 0.14–1.58), respectively. Further analysis was conducted concerning self-reported physical reaction to alcohol. Among women without flushing after drinking, a significant inverse association between risk and alcohol intake was seen (trend $P = 0.001$). In contrast, no protective effect of alcohol was seen among women who experience flushing after drinking. These results suggest the presence of an inverse association between alcohol drinking and endometrial cancer risk among Japanese women, and that this association is evident among those without flushing. Further investigation of these findings is warranted. (*Cancer Sci* 2008; 99: 1195–1201)**

Endometrial cancer is a common gynecologic cancer in Japan, and its incidence is increasing, possibly due to the recent Westernization of the Japanese lifestyle.[1] The development of endometrial cancer has been related to exposure to unopposed estrogens.[2–4] Several studies have shown a positive association between alcohol intake and estrogen level in postmenopausal women.[5,6] Although alcohol intake could therefore be expected to increase the risk of endometrial cancer by elevating estrogen levels, epidemiologic studies of this association have been inconsistent. Most previous studies have indicated that alcohol consumption is either weakly or not associated with the risk of endometrial cancer.[7–11] However, several others have shown an increased risk in heavy drinkers[12,13] while a case-control study by Swanson *et al.* suggested an inverse association between moderate alcohol consumption and endometrial cancer risk among young women (<55 years).[14] These inconsistent findings, as well as uncertainties regarding the etiology of endometrial cancer, hamper any coherent understanding of this association.

Here, we conducted a hospital-based case-control study to examine the association between alcohol consumption and endometrial cancer risk among Japanese women, considering other predisposing characteristics, such as body mass index and a history of hormone replacement therapy. In addition, given recent findings that a genetic polymorphism in *aldehyde dehydrogenase2 (ALDH2)*, which has a strong impact on alcohol metabolism, was associated with several cancer risks,[15–17] we also analyzed this risk using self-reported reactions after drinking as a surrogate for *ALDH2* genotyping.

## Materials and Methods

**Subjects.** The subjects were 148 patients newly and histologically diagnosed with endometrial carcinoma between January 2001 and June 2005 at Aichi Cancer Center Hospital (ACCH) in Japan. The distribution of histological subtypes among 148 cases was 93 type I tumor (low-grade endometrioid adenocarcinoma) (62.8%), and 55 type II tumor (high-grade endometrioid adenocarcinoma and other adenocarcinomas) (37.2%). Mixed epithelial and mesenchymal tumors were excluded due to the paucity of knowledge on their etiology. Controls ($n = 1476$) were randomly selected and matched by age (± 3 years) and menopausal status (premenopause or postmenopause) to cases with a 1:10 case-control ratio from 11 814 women who were diagnosed as cancer-free (four cases were matched with nine controls). All subjects were recruited in the framework of the Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC), as described elsewhere.[18,19] In brief, information on lifestyle factors was collected using a self-administered questionnaire for all first-visit outpatients at Aichi Cancer Center Hospital aged 20–79 who were enrolled in HERPACC between January 2001 and November 2005. Patients were also asked about lifestyle when healthy or before the current symptoms developed. Responses were checked by a trained interviewer. Approximately 90% of eligible subjects completed the questionnaire. Outpatients were also asked to provide blood samples. Our previous study showed that the lifestyle patterns of first-visit outpatients accorded with those in a randomly selected sample of the general population of Nagoya City.[20] The data were loaded into the HERPACC database and routinely linked with the hospital-based cancer registry system to update the data on cancer incidence. All participants gave written informed consent and the study was approved by Institutional Ethical Committee of Aichi Cancer Center.

**Assessment of alcohol intake and alcohol reaction.** All subjects were asked about their average frequency, beverage type, and amount of drinking per day during the 1-year period before onset of the present disease or before being interviewed. Usual alcohol intake was first reported as frequency of consumption in the five categories of non-drinker, <1 day/week, 1–2 days/week, 3–4 days/week, and 5 or more days per week. Consumption of each type of beverage (Japanese sake, beer, shochu, whiskey,

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**Table 1. Characteristics of subjects**

| Characteristic | Cases | | Controls | | *P*-values |
|---|---|---|---|---|---|
| **Number** | 148 | | 1476 | | |
| **Age** (median, [min–max]) | 56.0 (26–79) | | 56.0 (23–80) | | 0.846 |
| ≤39 (%) | 22 | (14.9) | 223 | (15.1) | 0.986 |
| 40–49 (%) | 13 | (8.8) | 136 | (9.2) | |
| 50–59 (%) | 64 | (43.2) | 610 | (41.3) | |
| 60–69 (%) | 36 | (24.3) | 385 | (26.1) | |
| ≥70 (%) | 13 | (8.8) | 122 | (8.3) | |
| **Smoking status** | | | | | |
| Ever (%) | 24 | (16.2) | 244 | (16.5) | 0.942 |
| Never (%) | 123 | (83.1) | 1225 | (83.0) | |
| Unknown (%) | 1 | (0.7) | 7 | (0.5) | |
| **Body mass index** (median, [min–max]) | 23.2 (13.4–40.9) | | 21.9 (13.2–42.7) | | <0.001 |
| <25 kg/m² (%) | 104 | (70.3) | 1211 | (82.1) | <0.001 |
| ≥25 kg/m² (%) | 40 | (27.0) | 257 | (17.4) | |
| Unknown (%) | 4 | (2.7) | 8 | (0.5) | |
| **Regular exercise** | | | | | |
| No (%) | 46 | (31.1) | 388 | (26.3) | 0.252 |
| Yes (%) | 101 | (68.2) | 1057 | (71.6) | |
| Unknown (%) | 1 | (0.7) | 31 | (2.1) | |
| **Menstrual status** | | | | | |
| Premenopausal (%) | 51 | (34.5) | 506 | (34.3) | 0.965 |
| Postmenopausal (%) | 97 | (65.5) | 970 | (65.7) | |
| **Age at menarche** (median, [min–max]) | 14.0 (10–20) | | 14.0 (10–21) | | 0.963 |
| ≤12 (%) | 38 | (25.7) | 379 | (25.7) | 0.729 |
| 13–14 (%) | 75 | (50.7) | 701 | (47.5) | |
| ≥15 (%) | 31 | (21.0) | 365 | (24.7) | |
| Unknown (%) | 4 | (2.7) | 31 | (2.1) | |
| **Duration of menstration** (median, [min–max]) | 37.0 (0–49) | | 36.0 (11–43) | | 0.390 |
| ≤32 (%) | 38 | (25.7) | 395 | (26.8) | 0.822 |
| 33–36 (%) | 33 | (22.3) | 367 | (24.9) | |
| 37–39 (%) | 38 | (25.7) | 388 | (26.3) | |
| ≥40 (%) | 34 | (23.0) | 284 | (19.2) | |
| Unknown (%) | 5 | (3.4) | 42 | (2.9) | |
| **Parity** (median, [min–max]) | 2 (0–4) | | 2 (0–6) | | <0.001 |
| 0 (%) | 41 | (27.7) | 207 | (14.0) | <0.001 |
| 1–2 (%) | 82 | (55.4) | 911 | (61.7) | |
| ≥3 (%) | 24 | (16.2) | 348 | (23.6) | |
| Unknown (%) | 1 | (0.7) | 10 | (0.7) | |
| **Diabetes history** | | | | | |
| No (%) | 137 | (92.6) | 1416 | (95.9) | 0.056 |
| Yes (%) | 11 | (7.4) | 60 | (4.1) | |
| **Hypertension history** | | | | | |
| No (%) | 121 | (81.8) | 1273 | (86.3) | 0.135 |
| Yes (%) | 27 | (18.2) | 203 | (13.8) | |
| **Contraceptive usage history** | | | | | |
| No (%) | 138 | (93.2) | 1377 | (93.3) | 0.934 |
| Yes (%) | 8 | (5.4) | 74 | (5.0) | |
| Unknown (%) | 2 | (1.4) | 25 | (1.7) | |
| **Hormone replacement therapy history** | | | | | |
| No (%) | 132 | (89.2) | 1355 | (91.8) | 0.247 |
| Yes (%) | 15 | (10.1) | 100 | (6.8) | |
| Unknown (%) | 1 | (0.7) | 21 | (1.4) | |

and wine) was determined by the average number of drinks per day, which was then converted into a Japanese sake (rice wine) equivalent. One Japanese drink equates to one 'go' (180 mL) of Japanese sake, which contains 23g of ethanol, equivalent to one large bottle (633 mL) of beer, two shots (57 mL) of whiskey, or 2.5 glasses of wine (200 mL). One drink of shochu (distilled spirit), which contains 25% ethanol, was rated as 108 mL. Total alcohol consumption was estimated as the summed amount of pure alcohol consumption (g/drink) of Japanese sake, beer, shochu, whiskey, and wine among current regular drinkers. Weekly ethanol consumption was calculated by combining the amount of ethanol per day and frequency per week. In this study, we used self-reported flushing (yes/no) after a small amount of drinking (a glass of beer) as a stratification factor in the examination of alcohol impact.

**Statistical analysis.** To assess the strength of associations between alcohol consumption and risk of endometrial cancer, odd ratios (OR) with 95% confidence intervals (CI) were estimated using unconditional logistic models adjusted for potential confounders. For subgroup analysis, subjects were classified by



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Table 2. Odds ratios (OR) and 95% confidence intervals (CI) for endometrial cancer according to frequency and quantitiy of alcohol intake

| Category | Cases ($n$ = 148) | Controls ($n$ = 1476) | Age-adjusted OR (95% CI) | Multivariate OR (95% CI)† |
|---|---|---|---|---|
| **Frequency of alcohol intake** | | | | |
| None | 108 | 929 | 1.00 (Reference) | 1.00 (Reference) |
| <1/week | 14 | 166 | 0.72 (0.40–1.29) | 0.71 (0.39–1.29) |
| 1–2/week | 11 | 119 | 0.79 (0.41–1.52) | 0.77 (0.40–1.50) |
| 3–4/week | 8 | 99 | 0.69 (0.33–1.46) | 0.67 (0.31–1.43) |
| 5-/week | 7 | 154 | 0.39 (0.18–0.85) | 0.37 (0.17–0.82) |
| unknown | 0 | 9 | | |
| ***P*-trends** | | | 0.011 | 0.009 |
| **Amount of alcohol consumption** | | | | |
| None | 109 | 933 | 1.00 (Reference) | 1.00 (Reference) |
| <25 g/week | 23 | 246 | 0.79 (0.49–1.27) | 0.79 (0.49–1.28) |
| (median, range) (eta g/week) | (8.6, 2.9–24.2) | (8.6, 1.7–24.2) | | |
| 25–175 g/week | 12 | 232 | 0.44 (0.24–0.81) | 0.42 (0.23–0.79) |
| (median, range) (eta g/week) | (54.3, 25.9–96.6) | (69, 25.3–172.5) | | |
| >175 g/week | 3 | 47 | 0.54 (0.16–1.76) | 0.47 (0.14–1.58) |
| (median, range) (eta g/week) | (201.3, 179.4–552) | (276, 177.1–805) | | |
| unknown | 1 | 18 | | |
| ***P*-trends** | | | 0.006 | 0.005 |

†Multivariate models adjusted for age, smoking, body mass index, regular exercise, menstrual status, age at menarche, duration of menstruation, parity, diabetes history, hypertension history, contraceptive usage history, hormone replacement therapy, and flushing after drinking.

alcohol intake into the four groups of non-drinkers, and weekly ethanol intake of 1–24, 25–175, and >175 g. Among controls, median weekly intake in current drinkers was 25 g. Potential confounders considered in the multivariate analyses were age, smoking habit (never smokers or ever smokers), body mass index (BMI; <25 or ≥25 kg/m$^2$ based upon our previous study),[21] regular exercise (yes or no), menstrual status (premenopausal or postmenopausal), age at menarche (≤ 12, 13–14, or ≥ 15), duration of menstruation (years, quartiles), parity (0, 1–2, ≥ 3), diabetes history (yes or no), hypertension history (yes or no), contraceptive usage history (yes or no), hormone replacement therapy history (yes or no), flushing after drinking (yes or no), and histological subtype (type I or type II). Missing values for any covariate were treated as a dummy variable in the logistic model. Differences in categorized demographic variables between the cases and controls were tested by the $\chi^2$-test. Age, age at menarche, duration of menstruation, BMI, and parity between cases and controls were compared by the Mann–Whitney test. Stratification analysis was used to estimate risk for subgroups by drinking habit. $P$-values less than 0.05 were considered statistically significant. All analyses were conducted using STATA version 9 (Stata, College Station, TX, USA).

## Results

Baseline characteristics of the 148 endometrial cancer patients and 1476 controls are shown in Table 1. Median age was 56 years for both patients and controls. Smoking status did not differ between the two groups. Prevalence of ever smokers was 16.2% and 16.5% in case and controls, respectively. BMI was higher among cases than controls ($P < 0.001$). Regarding reproductive factors, only parity showed a significant difference between two groups. Low experience of delivery was more prevalent among cases than controls ($P < 0.001$). A history of diabetes was more common in cases, although with only marginal statistical significance. Although contraceptive usage did not differ, hormone replacement therapy was more prevalent in cases.

Median consumption of alcohol among cases and controls who drank was only 19.3 and 28.2 g/week, respectively. Table 2 shows the impact of drinking habit on endometrial cancer risk. Frequent drinkers showed a reduced risk: compared with non-drinkers, the age-adjusted OR of those who drank 5 or more days per week was 0.39 (95% CI, 0.18–0.85). Although without significance, all groups except non-drinkers showed OR below unity and their point estimates decreased as frequency increased ($P$-trend = 0.011). This trend was consistently observed in the multivariate model. Similarly, with regard to the amount of alcohol consumed, those who consumed less than 25 g per week, those who consumed 25–175 g per week, and those who consumed 175 g or more per week showed a lower risk of endometrial cancer than non-drinkers, with OR of 0.79 (95% CI, 0.49–1.27), 0.44 (95% CI, 0.24–0.81), and 0.54 (95% CI, 0.16–1.76), respectively. The multivariate model again showed consistent results.

Table 3 shows a stratified analysis according to potential confounders designed to examine the consistency of association and to explore the possible interaction with weekly alcohol consumption. The inverse association between endometrial cancer risk and alcohol intake persisted after stratification by BMI, regular exercise, menstrual status, age at menarche, duration of menstruation, parity, diabetes history, hypertension history, and type I tumor. In contrast, no associations were seen for ever smokers, oral contraceptive users, hormone replacement therapy users, and type II tumor. Regarding BMI, obese women (BMI ≥ 25) showed a stronger protective effect by alcohol than leaner women (BMI < 25). Among postmenopausal women, the OR for weekly drinking of less than 25, 25–175, and 175 g or more for EC were 0.83 (95% CI, 0.46–1.52), 0.46 (95% CI, 0.21–1.02), and 0.72 (95% CI, 0.17–3.15), respectively, but the $P$-trend was marginally significant ($P = 0.069$). Generally, endometrial cancer risk was lowest among women with weekly consumption of 25–175 g.

Table 4 shows a stratified analysis according to self-reported reaction to alcohol. Flushing after drinking depends mainly on the activity of aldehyde dehydrogenase, particularly ALDH2, and might therefore reflect lower ALDH2 activity. Among women who did not experience flushing after drinking, an inverse association was seen between endometrial cancer risk and alcohol intake. The age-adjusted OR for weekly drinking of less than 25, 25–175, and 175 g or more for endometrial cancer were 0.51 (95% CI, 0.26–0.98), 0.24 (95% CI, 0.11–0.56), and 0.49 (95% CI, 0.14–1.69), respectively, and the $P$-trend was statistically significant ($P = 0.001$). By contrast, the protective

**Table 3. Odds ratios (OR) and 95% confidence intervals (CI) for endometrial cancer stratified according to weekly alcohol consumption and lifestyle factors**

| Category | Alcohol consumption | | | | |
|---|---|---|---|---|---|
| | None | <25 g/week | 25–175 g/week | >175 g/week | *P*-trends |
| **Total** (case/control)† | 109/933 | 23/246 | 12/232 | 3/47 | |
| OR (95% CI) | 1.00 (Reference) | 0.79 (0.49–1.27) | 0.44 (0.24–0.81) | 0.54 (0.16–1.76) | 0.006 |
| **Smoking** | | | | | |
| Never (case/control) | 98/829 | 18/213 | 5/157 | 1/16 | |
| OR (95% CI) | 1.00 (Reference) | 0.70 (0.41–1.18) | 0.26 (0.11–0.66) | 0.51 (0.07–3.87) | 0.002 |
| Ever (case/cotrol) | 11/98 | 4/33 | 7/75 | 2/31 | |
| OR (95% CI) | 1.00 (Reference) | 1.25 (0.36–4.40) | 0.89 (0.33–2.46) | 0.63 (0.13–3.04) | 0.586 |
| Unknown (case/cotrol) | 0/6 | 1/0 | 0/0 | 0/0 | |
| **Body mass index** | | | | | |
| <25 kg/m² (case/control) | 73/757 | 17/197 | 11/202 | 2/40 | |
| OR (95% CI) | 1.00 (Reference) | 0.92 (0.53–1.61) | 0.58 (0.30–1.12) | 0.54 (0.13–2.31) | 0.090 |
| ≥25 kg/m² (case/control) | 32/168 | 6/49 | 1/30 | 1/7 | |
| OR (95% CI) | 1.00 (Reference) | 0.55 (0.21–1.43) | 0.15 (0.02–1.13) | 0.48 (0.05–4.34) | 0.035 |
| Unknown (case/control) | 4/8 | 0/0 | 0/0 | 0/0 | |
| **Regular exercise** | | | | | |
| No (case/control) | 36/257 | 7/40 | 2/63 | 1/22 | |
| OR (95% CI) | 1.00 (Reference) | 1.27 (0.53–3.05) | 0.23 (0.05–0.97) | 0.34 (0.04–2.57) | 0.047 |
| Yes (case/control) | 72/654 | 16/201 | 10/167 | 2/25 | |
| OR (95% CI) | 1.00 (Reference) | 0.70 (0.40–1.24) | 0.53 (0.27–1.05) | 0.69 (0.16–3.00) | 0.053 |
| Unknown (case/control) | 1/22 | 0/5 | 0/2 | 0/0 | |
| **Menstrual status** | | | | | |
| Premenopausal (case/control) | 35/280 | 9/99 | 5/98 | 1/23 | |
| OR (95% CI) | 1.00 (Reference) | 0.72 (0.34–1.57) | 0.41 (0.15–1.07) | 0.35 (0.05–2.65) | 0.038 |
| Postmenopausal (case/control) | 74/653 | 14/147 | 7/134 | 2/24 | |
| OR (95% CI) | 1.00 (Reference) | 0.83 (0.46–1.52) | 0.46 (0.21–1.02) | 0.72 (0.17–3.15) | 0.069 |
| **Age at menarche** | | | | | |
| ≤12 (case/control) | 28/236 | 8/61 | 1/64 | 1/13 | |
| OR (95% CI) | 1.00 (Reference) | 1.04 (0.45–2.40) | 0.12 (0.02–0.92) | 0.56 (0.07–4.49) | 0.053 |
| 13–14 (case/control) | 53/428 | 11/127 | 9/114 | 1/22 | |
| OR (95% CI) | 1.00 (Reference) | 0.72 (0.36–1.42) | 0.65 (0.31–1.37) | 0.38 (0.05–2.90) | 0.120 |
| ≥15 (case/control) | 26/249 | 2/54 | 2/48 | 1/11 | |
| OR (95% CI) | 1.00 (Reference) | 0.39 (0.09–1.73) | 0.44 (0.10–1.91) | 1.07 (0.13–8.88) | 0.260 |
| Unknown (case/control) | 2/20 | 2/4 | 0/6 | 1/0 | |
| **Duration of menstruation** | | | | | |
| ≤32 years (case/control) | 27/219 | 7/77 | 4/71 | 0/22 | |
| OR (95% CI) | 1.00 (Reference) | 0.69 (0.28–1.67) | 0.43 (0.15–1.29) | NE | 0.029 |
| 33–36 years (case/control) | 27/246 | 5/51 | 1/54 | 0/9 | |
| OR (95% CI) | 1.00 (Reference) | 0.93 (0.34–2.55) | 0.18 (0.02–1.35) | NE | 0.063 |
| 37–39 years (case/control) | 29/249 | 3/71 | 4/57 | 1/8 | |
| OR (95% CI) | 1.00 (Reference) | 0.36 (0.11–1.23) | 0.60 (0.20–1.78) | 1.07 (0.13–8.88) | 0.249 |
| ≥40 years (case/control) | 23/189 | 6/43 | 3/43 | 2/7 | |
| OR (95% CI) | 1.00 (Reference) | 1.13 (0.43–2.95) | 0.56 (0.16–1.95) | 2.23 (0.43–11.49) | 0.932 |
| Unknown (case/control) | 3/30 | 2/4 | 0/7 | 0/1 | |
| **Parity** | | | | | |
| 0 (case/control) | 30/115 | 6/36 | 4/42 | 1/10 | |
| OR (95% CI) | 1.00 (Reference) | 0.63 (0.24–1.65) | 0.36 (0.12–1.09) | 0.38 (0.05–3.10) | 0.046 |
| 1–2 (case/control) | 58/599 | 15/147 | 6/129 | 2/25 | |
| OR (95% CI) | 1.00 (Reference) | 1.12 (0.61–2.05) | 0.50 (0.21–1.20) | 0.90 (0.21–3.93) | 0.271 |
| ≥3 (case/control) | 21/213 | 2/61 | 1/59 | 0/12 | |
| OR (95% CI) | 1.00 (Reference) | 0.37 (0.08–1.64) | 0.19 (0.02–1.43) | NE | 0.035 |
| Unknown (case/control) | 0/6 | 0/2 | 1/2 | 0/0 | |
| **Diabetes history** | | | | | |
| No (case/control) | 99/894 | 22/237 | 12/224 | 3/45 | |
| OR (95% CI) | 1.00 (Reference) | 0.81 (0.50–132) | 0.47 (0.25–0.87) | 0.57 (0.17–1.89) | 0.015 |
| Yes (case/control) | 10/39 | 1/9 | 0/8 | 0/2 | |
| OR (95% CI) | 1.00 (Reference) | 0.48 (0.05–4.33) | NE | NE | 0.212 |
| **Hypertension history** | | | | | |
| No (case/control) | 87/797 | 21/225 | 10/200 | 2/38 | |
| OR (95% CI) | 1.00 (Reference) | 0.85 (0.51–1.40) | 0.45 (0.23–0.89) | 0.47 (0.11–2.00) | 0.016 |
| Yes (case/control) | 22/136 | 2/21 | 2/32 | 1/9 | |
| OR (95% CI) | 1.00 (Reference) | 0.54 (0.12–2.47) | 0.36 (0.08–1.62) | 0.64 (0.08–5.32) | 0.178 |



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Table 3 (*Continued.*)

| Category | Alcohol consumption | | | | |
|---|---|---|---|---|---|
| | None | <25 g/week | 25–175 g/week | >175 g/week | *P*-trends |
| **Contraceptive usage history** | | | | | |
| No (case/control) | 101/871 | 23/231 | 12/216 | 1/43 | |
| OR (95% CI) | 1.00 (Reference) | 0.85 (0.53–1.38) | 0.47 (0.26–0.88) | 0.20 (0.03–1.45) | 0.005 |
| Yes (case/control) | 6/44 | 0/11 | 0/15 | 2/4 | |
| OR (95% CI) | 1.00 (Reference) | NE | NE | 3.63 (0.53–24.92) | 0.892 |
| Unknown (case/control) | 2/18 | 0/4 | 0/1 | 0/0 | |
| **Hormone replacement therapy history** | | | | | |
| No (case/control) | 101/860 | 18/227 | 10/212 | 2/40 | |
| OR (95% CI) | 1.00 (Reference) | 0.66 (0.39–1.12) | 0.39 (0.20–0.77) | 0.41 (0.10–1.72) | 0.002 |
| Yes (case/control) | 7/59 | 5/15 | 2/19 | 1/7 | |
| OR (95% CI) | 1.00 (Reference) | 2.79 (0.78–10.05) | 0.89 (0.17–4.64) | 1.21 (0.13–11.31) | 0.826 |
| Unknown (case/control) | 1/14 | 0/4 | 0/1 | 0/0 | |
| **Histological subtype** | | | | | |
| Type I (case/control) | 68/933 | 17/246 | 6/232 | 1/47 | |
| OR (95% CI) | 1.00 (Reference) | 0.71 (0.51–1.57) | 0.34 (0.14–0.79) | 0.27 (0.04–1.97) | 0.007 |
| Type II (case/control) | 41/933 | 6/246 | 6/246 | 2/47 | |
| OR (95% CI) | 1.00 (Reference) | 0.60 (0.25–1.43) | 0.63 (0.26–1.50) | 1.09 (0.25–4.69) | 0.323 |

†One case and 18 controls were excluded from analyses due to lack of information on alcohol drinking.
NE, not estimated because of no case in this category.

**Table 4. Impact of alcohol consumption according to self-reported reaction to alcohol**

| Category | Alcohol consumption | | | | |
|---|---|---|---|---|---|
| | None | <25 g/week | 25–175 g/week | >175 g/week | *P*-trends |
| **Total** (case/control)† | 109/933 | 23/246 | 12/232 | 3/47 | |
| Age-adjusted OR (95% CI) | 1.00 (Reference) | 0.79 (0.49–1.27) | 0.44 (0.24–0.82) | 0.54 (0.16–1.76) | 0.006 |
| Multivariate OR (95% CI) | 1.00 (Reference) | 0.79 (0.49–1.28) | 0.42 (0.23–0.79) | 0.47 (0.14–1.58) | 0.005 |
| **Flushing after drinking** | | | | | |
| No (case/control) | 44/292 | 13/157 | 7/175 | 3/36 | |
| Age-adjusted OR (95% CI) | 1.00 (Reference) | 0.51 (0.26–0.98) | 0.24 (0.11–0.56) | 0.49 (0.14–1.69) | 0.001 |
| Multivariate OR (95% CI) | 1.00 (Reference) | 0.53 (0.27–1.05) | 0.25 (0.11–0.59) | 0.48 (0.14–1.67) | 0.002 |
| Yes (case/control) | 61/574 | 9/86 | 5/55 | 0/10 | |
| Age-adjusted OR (95% CI) | 1.00 (Reference) | 1.03 (0.49–2.15) | 0.89 (0.34–2.30) | NE | 0.560 |
| Multivariate OR (95% CI)‡ | 1.00 (Reference) | 1.07 (0.51–2.27) | 0.97 (0.37–2.57) | NE | 0.677 |
| Unknown (case/control) | 4/67 | 1/3 | 0/2 | 0/1 | |

†One case and 18 controls were excluded from analyzes due to lack of information on alcohol drinking.
‡Multivariate models adjusted for age, smoking, body mass index, regular exercise, menstrual status, age at menarche, duration of menstruation, parity, diabetes history, hypertension history, contraceptive usage history, and hormone replacement therapy.
CI, confidence interval; NE, not estimated because of no case in this category; OR, odds ratio.

effect of alcohol was not observed among women who had flushing after drinking (age-adjusted *P*-trend = 0.560). The multivariate model again showed consistent results.

## Discussion

In this study, we found that a small amount of alcohol consumption was protective against endometrial cancer among Japanese women. This association was consistently observed regardless of potential confounders. OR were lowest among those who consumed 25–175 g per week. In addition, the protective effect of alcohol drinking decreased among women who reported flushing after drinking.

Results to date regarding the relationship between alcohol intake and endometrial cancer risk are inconsistent. Although most previous studies have indicated a null association,[7–9,11,22–25] three have shown a protective effect of alcohol,[10,14,26] while three others have reported that alcohol intake was a risk factor of endometrial cancer.[12,13,27] Newcomb *et al.* suggested a significant inverse association in premenopausal women consuming one drink per day or more (RR = 0.20; 95% CI, 0.06–0.71)[10] while Swanson *et al.* showed an inverse association between moderate consumption and endometrial cancer risk among young women (<55 years), with relative risks for three levels of drinking (<1, 1–4, >4 drinks per week) from lowest to highest of 0.78, 0.64, and 0.41 compared to non-drinkers.[14] Webster *et al.* showed that non-drinkers aged 20–54 years had a higher relative risk (RR = 1.83; 95% CI, 1.11–3.01) than women who consumed an average of 150 g or more of alcohol per week.[26] These results may indicate that light alcohol consumption decreases endometrial cancer risk in younger women. In contrast, Setiawan *et al.* suggested that alcohol consumption equivalent to two or more drinks per day increased the risk of endometrial cancer in postmenopausal women.[12] The other two case-control studies showed similar positive associations between increased alcohol consumption and risk.[13,27]

Here, our study has added to the evidence for a protective effect of alcohol on endometrial cancer. The degree of consumption