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Early- and Late-Onset Breast Cancer Types Among Women in the United States and Japan

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Abstract

Background: **Although differences in breast cancer incidence among Occidental and Asian populations are often attributed to variations in environmental exposures and/or lifestyle, fewer studies have systematically examined the effect of age-related variations.**

Methods: **To further explore age-related geographic breast cancer variations, we compared age-specific incidence patterns among cases of female invasive breast cancer from the Surveillance, Epidemiology, and End Results (SEER) program and the Osaka Cancer Registry (1978-1997).**

Results: **In SEER, there were 236,130 Whites, 21,137 Blacks, and 3,304 Japanese-Americans in Hawaii with invasive breast cancer. In Osaka, there were 25,350 cases. Incidence rates per 100,000 woman-years ranged from 87.6 among Whites to 21.8 in Osaka. Age-specific incidence rates increased rapidly until age 50 years for all race/ethnicity groups, and then continued to increase more slowly for Whites, Blacks, and Japanese-Americans in Hawaii but plateaud for Osaka. Age-specific incidence rates in SEER reflected bimodal (early-onset and late-onset) breast cancer populations, whereas Osaka had only an early-onset age distribution. These age-specific differences in incidence among SEER and Osaka persisted after adjustment for calendar-period and birth-cohort effects using age-period-cohort models.**

Conclusions: **Results confirm striking age-specific differences among Occidental and native Japanese breast cancer populations, probably due to complex age-related biological and/or environmental variations among Occidental and Asian breast cancer populations.** (Cancer Epidemiol Biomarkers Prev 2007;16(7):1437–42)

Introduction

Breast cancer incidence rates are generally higher in Occidental than in Asian populations (1-4), possibly due to a combination of environmental, lifestyle, and/or biological factors. For example, presumptive environmental and/or lifestyle factors shift breast cancer incidence among migrant Asian women from the baseline rate in their native country to the rate in their adopted country (5-8). Biological effects seem to alter the shape of the age-specific incidence rate curve among Occidental and native Asian women (1, 3, 4, 9-15). Among Occidental women, age-specific incidence rates increase rapidly until menopause, and then continue to increase more slowly. Among native Asian women, rates increase rapidly until menopause, and then plateau or decrease. These age-related biological effects have generated interest and debate for decades.

In 1980, Moolgavkar et al. fit a two-stage breast cancer model to six high-risk and low-risk populations, including Connecticut and Osaka (14). The model viewed breast cancer as the end result of two discrete and irreversible events, without distinction for premenopausal (early-onset) and postmenopausal (late-onset) breast cancer types. In this model, among native Asian women, the late-onset drop in incidence was due to a birth-cohort artifact (1, 9) in which the progressive increase in risk from one generation to the next gives the appearance of a decreasing age-specific incidence rate curve. In 1981, Pike and colleagues developed the concept of breast tissue "aging," modified by the timing of certain reproductive risk factors such as the age at menarche, first full-term pregnancy, and menopause (15). Still others have suggested that the different age-specific incidence rate patterns among different breast cancer populations result from the mixing of distinct breast cancer types according to age at onset (16-19). Rates that increase rapidly until age 50 years, and then flatten, reflect mostly early-onset breast cancer populations, whereas rates that increase continuously with aging result from mixed early-onset and late-onset breast cancer types.

To further explore geographic age-related variations among Occidental, migrant Asian, and native Asian breast cancer populations, we examined age-specific incidence patterns (rates and age distributions) using data from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program and the Osaka Cancer Registry (OCR). To account for calendar-period and/or birth-cohort effects, we used age-period-cohort models to simultaneously adjust for age, calendar-period, and birth-cohort effects.

Materials and Methods

Subjects. Female breast cancer case data for Whites, Blacks, and Japanese-Americans in Hawaii (JAHI) were obtained from the SEER 9-Registry database (November 2004 submission; ref. 20). The SEER 9-Registry database includes data from San Francisco-Oakland, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta, covering ~10% of the U.S. population. Case data for native Japanese women were obtained from the OCR (21). The OCR is a population-based registry in Osaka Prefecture, the second most populous prefecture in Japan, covering ~8 million people or ~7% of

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Japan's population (22). All primary malignant cases recorded in the SEER 9-Registry database and OCR during the period 1978 to 1997 were included in the analysis.

Although case data were available for all race/ethnicity groups, population data for JAHI could not be directly obtained from SEER. The state cancer registry for Hawaii reports only case data to SEER; however, it reports both case and population data to the International Agency for Research on Cancer (IARC; ref. 23). Similarly, OCR reports both case and population data to the IARC. To calculate crude incidence rates for JAHI and Osaka, we obtained corresponding population data from the IARC database, which were either actual census data or population counts estimated from census data. For consistency, we also used population data from the IARC database for Whites and Blacks in SEER.

Demographic and Tumor Characteristics. Female breast cancer cases were stratified by four 5-year calendar-periods of diagnosis (1978-1982, 1983-1987, 1988-1992, and 1993-1997), premenopausal and postmenopausal surrogates (age <50 and 50+ years; refs. 24, 25), stage, grade, and histology. SEER and OCR tumor stage categories were matched to approximate localized, regional, and distant breast cancer (26). Localized disease was confined to the breast tissue and fat, including the nipple and/or areola. Regional disease included breast cancers with regional nodal involvement. Distant disease included systemic metastases.

Tumor grade was dichotomized into low-risk and high-risk groups. Low grade included grade I (well differentiated) and grade II (moderately differentiated) tumors. High grade included grade III (poorly differentiated) and grade IV (undifferentiated or anaplastic) tumors. Histopathologic subtypes were categorized into ductal and lobular groups, using the International Classification of Diseases for Oncology, 3rd edition; and the General Rules for Clinical and Pathological Recording of Breast Cancer by the Japanese Breast Cancer Society (27, 28). All other subtypes were designated as other or unknown. Although there is some variation with respect to histologic typing between the two classification systems, they are comparable with respect to breast cancer overall.

Age-Adjusted Incidence Rates. Breast cancer incidence rates were calculated using case data from SEER and OCR and population data from the IARC. Rates were age-adjusted to the World Standard population (29). Our calculated age-adjusted rates were similar to those recorded in the IARC database. Relative risks were expressed as incidence rate ratios (IRR), in which a given characteristic was compared to a referent characteristic with an assigned IRR of 1.0. Secular trends were plotted on a log-linear scale, as previously described (30).

Age-Specific Incidence Rates. Age-specific incidence rates for the study period 1978 to 1997 were calculated according to 12 5-year age groups (25-29 to 80-84). Slope changes in overall rates at age 50 years for each race/ethnicity group were formally tested using piecewise linear Poisson regression models (PROC GENMOD, SAS, v.8e, SAS Institute Inc.). The statistical model was defined as:

$$\log(\text{incidence rate}) = \beta_0 + \beta_1 \times \text{age} + \beta_2 \times (\text{age} - 50) \times I$$

where I was the indicator variable for age 50 years or older, $\exp(\beta_1)$ was the change in incidence per year of age before 50, and $\exp(\beta_1 + \beta_2)$ was the corresponding change in incidence for age 50 years or older. We allowed for overdispersion in the model by including a deviance variable parameter. A change in slope was considered to be statistically significant when we rejected the null hypothesis β_2 equal to zero ($\alpha = 0.05$).

To determine the age effects after adjustment for calendar-period and birth-cohort effects, we fit age-period-cohort models to incidence data for Whites, Blacks, JAHI, and Osaka using Poisson regression (PROC GENMOD, SAS). We used 12 5-year age groups (25-29 to 80-84), 5 5-year calendar-periods (1973-1977 to 1993-1997), and 16 5-year birth-cohorts, referred to by the mid-year of birth (1893 to 1968) for all populations.

In addition to overall age-specific rates, we calculated age-specific incidence rates for 12 5 year age groups (25-29 to 80-84) according to calendar-period (i.e., cross-sectional rates) and birth-cohort (i.e., longitudinal rates). Cross-sectional age-specific rates were determined according to four 5-year calendar-periods (1978-1982 to 1993-1997). Longitudinal age-specific rates were determined according to 15 5-year birth-cohorts, referred to by the mid-year of birth (1898 to 1968).

Age Distributions. We graphed density plots for age at diagnosis by race/ethnicity group and calendar-period (1978-1982 to 1993-1997) using S-PLUS (version 6.2 for Windows, Insightful Corp.). S-PLUS uses kernel density estimation to produce smoothed histograms of the age distributions, and is described in detail elsewhere (31-33). In brief, a Gaussian kernel was used to estimate the underlying probability density function for breast cancer diagnosis conditioned on age. A more detailed description is given in Appendix 1.

Results

Demographic and Tumor Characteristics. Demographic and tumor characteristics for SEER and Osaka for the study period 1978 to 1997 are shown in Table 1. In the nine SEER areas, there were 236,130 White and 21,137 Black female cases of invasive breast cancer. In Hawaii, there were 3,304 Japanese cases. In OCR, there were 25,350 cases. The overall age-adjusted incidence rates per 100,000 woman-years for the study period 1978 to 1997 were highest in Whites (87.6), followed by Blacks (80.0), JAHI (72.4), and Osaka (21.8). Median age-at-diagnosis was oldest in Whites (64 years) and youngest in Osaka (51 years). Similarly, the IRR for cases diagnosed after age 50 years compared with cases diagnosed before age 50 years was highest in Whites (IRR, 10.84) and lowest in Osaka (IRR, 4.73).

All race/ethnicity groups had lower rates of regional stage disease than local stage disease (i.e., IRR for regional compared with local stage disease < 1.0), although the relative differences were greater for Whites and JAHI. For example, IRRs for regional compared with local stage among Whites (IRR, 0.58) and JAHI (IRR, 0.41) were lower than among Blacks (IRR, 0.77) and Osaka (IRR, 0.77). Whites (IRR, 0.86) and JAHI (IRR, 0.60) also had lower rates of high-grade tumors compared with low-grade tumors. In contrast, Blacks were more likely to be diagnosed with high-grade tumors (IRR, 1.46). Grade data for Osaka could not be interpreted given that 77.7% of cases were coded as missing or unknown. All groups had lower rates of lobular carcinoma than ductal carcinoma not otherwise specified. However, due to potential inconsistencies between the coding systems used in the United States and Japan, results should be interpreted with caution. All IRRs in Table 1 were statistically significantly different from 1.00 at the 95% confidence level.

Age-Adjusted Incidence Rates. Breast cancer incidence rates increased among all four groups from the earliest calendar-period 1978-1982 to the latest calendar-period 1993-1997 (Table 1; Fig. 1A). The most rapid increase in rates was observed in JAHI; the age-adjusted rate increased 75%, from 51.1 to 89.2 per 100,000 woman-years (IRR, 1.75). The slowest increase was observed in Whites (IRR, 1.27). Increases were intermediate among Blacks (IRR, 1.37) and Osaka (IRR, 1.51).

Table 1. Breast cancer incidence among Whites, Blacks, and JAHI in the United States (nine SEER areas) and Osaka, Japan during the years 1978 to 1997

	SEER (n = 260,571)						Osaka (n = 25,350)		
	White		Black		JAHI		Osaka		
Number (n)	236,130		21,137		3,304		25,350		
Mean age in years (SE)	63 (0.03)		57.7 (0.10)		61.0 (0.22)		53.5 (0.08)		
Median age in years	64		57		62		51		
Overall rate (SE)	87.6 (0.19)		80.0 (0.56)		72.4 (1.34)		21.8 (0.14)		
	n	Rate SE IRR	n	Rate SE IRR	n	Rate SE IRR	n	Rate SE IRR	
Year of diagnosis									
1978-1982	45,152	74.3 0.37 ref	3,481	64.9 1.12 ref	458	51.1 2.47 ref	4,170	16.9 0.26 ref	
1983-1987	56,999	87.8 0.39 1.18	4,780	78.0 1.16 1.20	717	65.7 2.59 1.29	5,868	21.1 0.28 1.25	
1988-1992	64,519	92.7 0.39 1.25	5,847	84.1 1.14 1.30	961	76.7 2.71 1.50	6,956	22.7 0.28 1.34	
1993-1997	69,460	94.0 0.38 1.27	7,029	88.6 1.10 1.37	1,168	89.2 2.91 1.75	8,356	25.5 0.29 1.51	
Age at diagnosis									
<50	48,651	29.5 0.02 ref	7,010	31.7 0.12 ref	683	29.0 0.99 ref	11,137	12.5 0.01 ref	
50+	187,479	319.9 0.13 0.84	14,127	272.8 1.11 8.61	2,621	245.8 5.03 8.48	14,213	59.1 0.05 4.73	
Summary stage									
Local	137,799	50.6 0.15 ref	10,192	38.6 0.39 ref	2,263	48.8 1.10 ref	12,721	11.0 0.10 ref	
Regional	75,191	29.1 0.11 0.58	7,841	29.9 0.35 0.77	864	20.0 0.72 0.41	9,771	8.5 0.09 0.77	
Distant	13,940	5.1 0.05 0.10	1,996	7.5 0.17 0.19	138	2.9 0.27 0.06	1,453	1.2 0.03 0.11	
Other/unknown	9,200	2.7 0.03 0.05	1,108	3.8 0.12 0.10	39	0.6 0.12 0.01	1,405	1.2 0.03 0.11	
Grade									
Low (I-II)	61,962	22.7 0.10 ref	4,194	16.0 0.25 ref	1,167	24.4 0.77 ref	5,530	4.8 0.07 ref	
High (III-IV)	50,910	19.6 0.09 0.86	6,109	23.3 0.31 1.46	661	14.6 0.61 0.60	119	0.1 0.01 0.02	
Other/unknown	123,258	45.2 0.14 1.99	10,834	40.7 0.40 2.54	1,476	33.4 0.92 1.37	19,701	16.9 0.12 3.52	
Histology									
Duct NOS	183,553	68.1 0.17 ref	16,439	62.2 0.50 ref	2,839	62.2 1.24 ref	7,821	6.7 0.08 ref	
Lobular	17,384	6.3 0.05 0.09	972	3.7 0.12 0.06	102	2.2 0.23 0.04	390	0.3 0.02 0.04	
Other/unknown	35,193	13.2 0.08 0.19	3,726	14.0 0.24 0.23	363	8.0 0.45 0.13	17,139	14.8 0.11 2.21	

NOTE: Rates per 100,000 woman-years, age-adjusted to the World Standard; ref, referent group; all rate ratios were statistically significantly different from the referent group at the 95% confidence level; duct NOS, ductal carcinoma not otherwise specified (histology codes 8000, 8500, 8010, and 8140); lobular carcinoma (histology code 8520).

Age-Specific Incidence Rates. Overall age-specific rates for the calendar-period 1978-1997 increased rapidly until age 50 years then continued to increase more slowly among Whites, Blacks, and JAHI (Fig. 1B). In contrast, rates increased rapidly until age 50 years then flattened or plateaued among women in Osaka. Poisson regression analyses confirmed significant changes in slope at age 50 years for all race/ethnicity groups ($P < 0.001$).

The differences in age-specific incidence rate patterns persisted after adjusting for calendar-period and birth-cohort effects using age-period cohort-models. However, there were statistically significant ($P < 0.05$) birth-cohort effects in all populations. Among Whites and Blacks, there were significant effects for birth-cohorts (referred to by the mid-year of birth) 1918, 1938, and 1943. Among Blacks, the 1908 birth-cohort effect was also significant. Among JAHI, there were significant effects for birth-cohorts 1903, 1923, and 1943. In Osaka, we observed several more significant birth-cohort contrasts, i.e., for 1918, 1928, 1933, 1943, and 1948.

Among Whites and Blacks, cross-sectional age-specific rates for all calendar-periods increased rapidly until age 50 years then continued to increase more slowly after age 50 years (Fig. 2A and B). Rates among JAHI more closely resembled rates among native Japanese in Osaka for the earliest calendar-period (1978-1982), but were more like rates among Whites and Blacks for subsequent calendar-periods (Fig. 2C). Age-specific rates in Osaka increased rapidly until age 50 years then plateaued for all calendar-periods (Fig. 2D).

Longitudinal age-specific rates were presented for 8 of the 15 birth-cohorts (for clearer graphical depiction; the overall interpretation of the results was the same irrespective of which birth-cohort were plotted; Fig. 3). Similar to cross-sectional age-specific rates (Fig. 2), longitudinal age-specific rates among Whites and Blacks increased rapidly until age 50 years then continued to increase at a slower pace with successive birth-cohort (Fig. 3A and B). Age-specific rates in Osaka increased rapidly until age 50 years then tended to plateau, although rates for individual birth-cohorts were not completely flat (Fig. 3D). Rates for JAHI were intermediate to the patterns for Whites, Blacks, and Osaka (Fig. 3C).

Age Distributions. The age density plots varied during the study period 1978 to 1997 according to race/ethnicity group

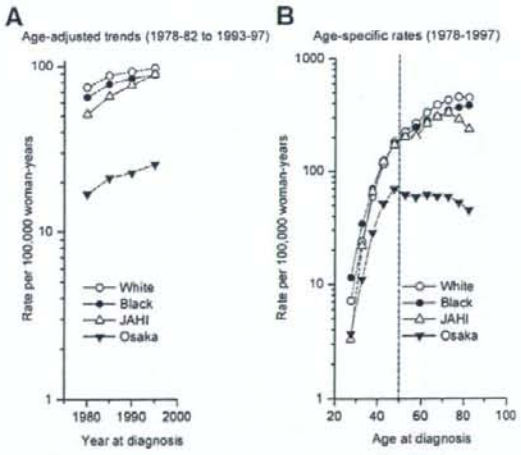

Figure 1. Breast cancer incidence rates among Whites, Blacks, and JAHI in the United States (nine SEER areas) and Osaka, Japan. **A**, trends in age-adjusted rates by calendar-period (1978-1982, 1983-1987, 1988-1992, and 1993-1997). **B**, age-specific rates for the study period 1978 to 1997.

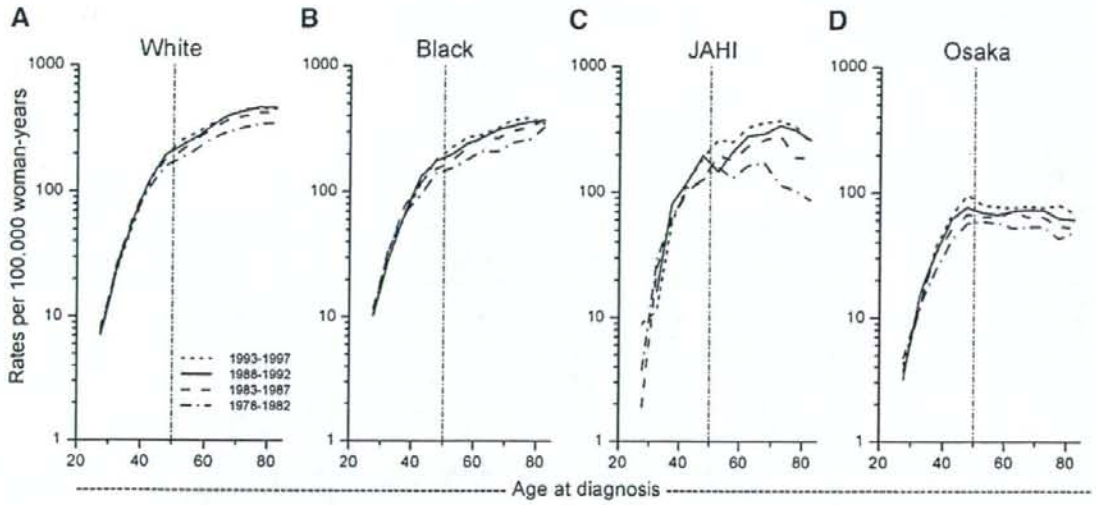

Figure 2. Observed cross-sectional age-specific breast cancer incidence rates by calendar-period (1978-1982, 1983-1987, 1988-1992, and 1993-1997). **A**, Whites in SEER. **B**, Blacks in SEER. **C**, JAHI in SEER. **D**, native Japanese in Osaka, Japan.

(Fig. 4). Although the relative proportions of early-onset and late-onset breast cancer types varied, the peak frequencies (or modes) were generally constant near ages 50 (early-onset) and 70 (late-onset) years. In the earliest calendar-period (1978-1982), the age distributions had single modes among all populations (Fig. 4, *first column*). Osaka had the earliest mode (age 46 years), followed by JAHI (54 years), Blacks (58 years), and Whites (63 years). By the latest calendar-period (1993-1997), a bimodal pattern had emerged among Whites, Blacks, and JAHI (Fig. 4, *fourth column*), although the late-onset peak was not as prominent among Blacks. Among Whites, the modes were at ages 51 and 71 years. Among Blacks, the modes were at ages 48 and 71 years. Among JAHI, the modes were at ages 52 and 68 years. In contrast with the other three groups, Osaka maintained a single early-onset age distribution during the latest calendar-period (Fig. 4, *fourth row*), with a mode at age 48 years.

Discussion

Although age-adjusted breast cancer incidence rates increased in both SEER and Osaka from 1978-1982 to 1993-1997, age-specific patterns (rates and age distributions) suggest that the nature of this increase differed among the various cancer populations (Fig. 4). In SEER, Whites and Blacks had bimodal (early-onset and late-onset) breast cancer populations. In Osaka, there was a consistent early-onset age distribution of the breast cancer population. JAHI were intermediate to Whites and Blacks, and Osaka. The early-onset age distribution in Osaka was observed despite having an older general population. For example, according to the 2000 census data, the median age for women in Osaka Prefecture was older (41.3 years) than for Whites (39.7 years) and Blacks (31.5 years) in the United States (34-36).

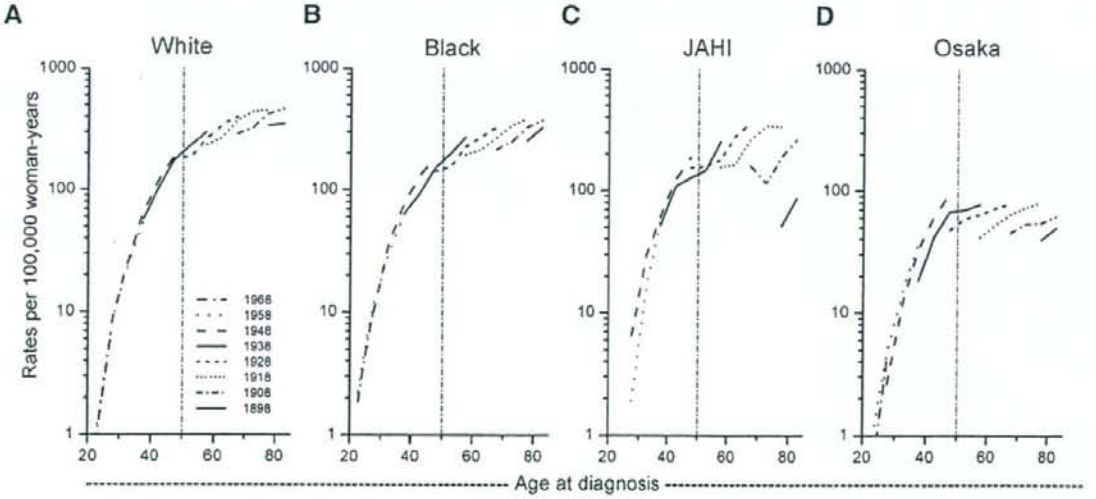

Figure 3. Observed longitudinal age-specific breast cancer incidence rates by the mid-year of birth-cohort (1898, 1908, 1918, 1928, 1938, 1948, 1958, and 1968). **A**, Whites in SEER. **B**, Blacks in SEER. **C**, JAHI in SEER. **D**, native Japanese in Osaka, Japan.

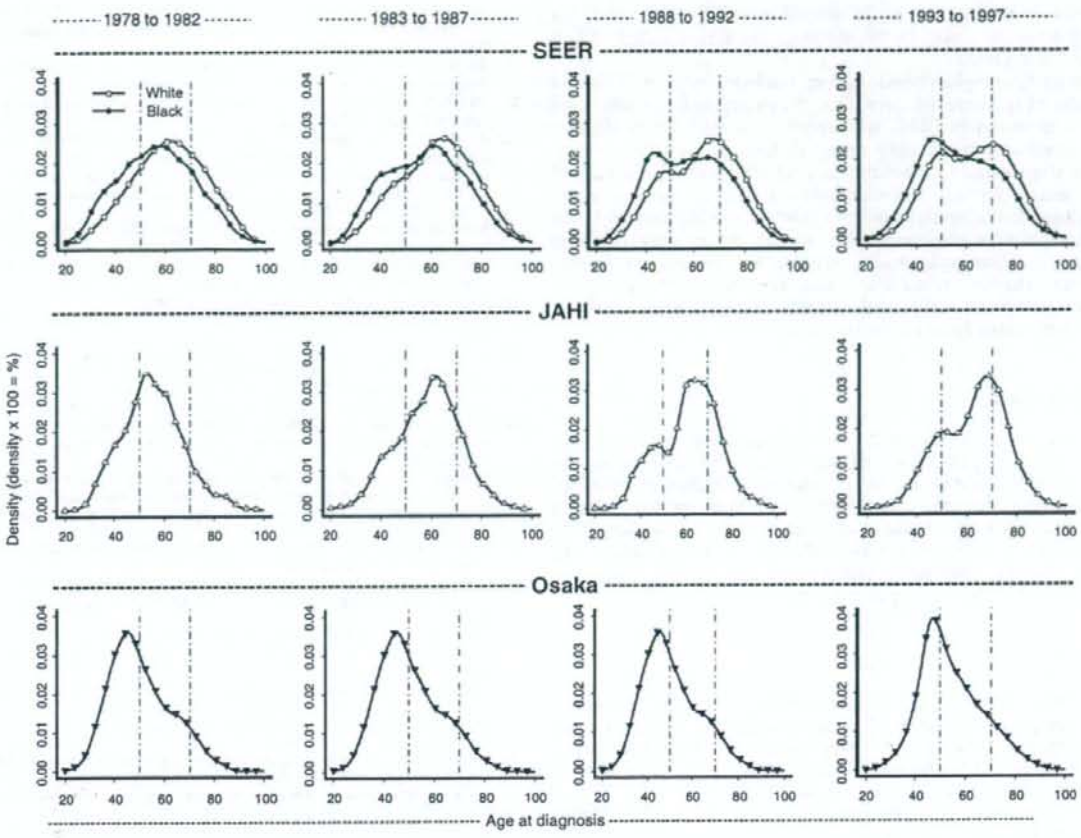

Figure 4. Age distributions among Whites, Blacks, and JAHI in the United States (nine SEER areas) and Osaka, Japan during the calendar-periods 1978 to 1982, 1983 to 1987, 1988 to 1992, and 1993 to 1997. The probability density function is a smoothed estimate of the frequency of women diagnosed at a given age. Reference lines are shown for ages 50 and 70 y.

The changing age distributions among the various breast cancer populations also seemed to affect the shape of the age-specific incidence rate curves. Increasing late-onset breast cancer populations among Whites, Blacks, and JAHI corresponded with successively steeper slopes in the age-specific rates after age 50 years. On the other hand, a constant early-onset age distribution for Osaka corresponded to consistently flattened or plateaued age-specific incidence rates after age 50. Although we observed significant birth-cohort effects for all populations, the age effects were 10-fold higher, and the age-period-cohort–fitted age curves were very similar to the overall (unadjusted) age-specific rate curves (data not shown). This supports that age effects and differences between populations cannot be explained by birth-cohort or calendar-period artifacts.

Although the differences in overall breast cancer incidence rates among Occidental and Asian populations have been often attributed to environmental exposures and/or lifestyle (37), our results suggest important age-specific differences as well. For example, body mass index is inversely associated with premenopausal breast cancer, but is positively associated with postmenopausal breast cancer (38, 39). The much lower prevalence of obesity (defined as body mass index of 30 kg/m^2 or more) in Japan than in the United States (40, 41) may in part explain why the IRRs for postmenopausal relative to premenopausal breast cancer were highest in SEER and lowest in Osaka.

Geographic variations in screening mammography may also explain some of the differences between SEER and Osaka. For example, in the United States, screening mammography became widely implemented during the 1980s, and the coverage rate among women age 40 years and older in 2000 was estimated to be >70% (42). In this study, cross-sectional age-specific incidence rates in SEER increased for all calendar-periods, particularly among women age 50 years and older, i.e., those targeted for screening. The same effect has been shown previously in the United States (43) and in several European countries where screening mammography has been fully established (44, 45). In contrast, screening mammography was not implemented in Japan until the year 2000 (46). In the absence of screening mammography, the age-specific incidence rates in Osaka increased relatively evenly across both younger and older ages for each succeeding calendar-period.

This study is not without limitations. Because we have used registry data, key considerations include the completeness and accuracy of data. Moreover, we obtained data from a number of different sources, so results should be interpreted carefully, as comparability across populations can be hindered by differences in screening practices, disease classification, and data collection. However, both SEER and the OCR meet IARC standards, which ensure a certain degree of data quality and comparability based on a number of factors (47). Indeed, in all groups, >94% of cases were microscopically confirmed in each

5-year calendar-period (1978-1982 to 1993-1997); and the proportion of death certificate only cases was <1% in SEER and 7% in Osaka.

In sum, although breast cancer incidence rates in SEER and Osaka have increased over time, the emergence of a late-onset peak observed in SEER was absent in Osaka. These distinct age-specific patterns may reflect differences in detection, but may also be due to the differential effect of certain age-related exposures. Further hypothesis-driven studies are needed to distinguish the age effects from calendar-period and/or birth-cohort effects on geographic variations in breast cancer patterns. More specifically, studies are needed to further assess whether established risk factors are differentially associated with early- and late-onset breast cancer and the effect this may have on breast cancer patterns worldwide.

Appendix A

The aim of kernel smoothing is to nonparametrically estimate a continuous probability density function f, defined as the derivative of a cumulative probability distribution function. Although a histogram provides such a nonparametric estimate of f, it is not smooth, and is also very dependent on the width and starting points of the intervals or bins. Kernel smoothing avoids both problems. The kernel density estimator for observed data points $x_1, \ldots, x_n$ is of the form

$$\hat{f} = \frac{1}{n}\sum_{i=1}^{N} K(x - x_i; h),$$

where K is a probability density function, known as the kernel function, the variance of which is controlled by h. The variable h is often referred to as the bandwidth or smoothing variable, as it dictates the smoothness of $\hat{f}$, with larger values of h corresponding to smoother curves.

We use a Gaussian kernel, $K(x) = \frac{1}{h\sqrt{2\pi}} exp(-x^2/2h)$ implemented in S-PLUS (31-33).

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Distinctive Change in Male Liver Cancer Incidence Rate between the 1970s and 1990s in Japan: Comparison with Japanese-Americans and US Whites

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Objective: To characterize the time trend of the male liver cancer incidence rate in Japan.
Methods: We obtained data on male liver cancer incidence rates from the 'Cancer Incidence in Five Continents (CI5) Series'. Data from the population-based cancer registries of Miyagi, Osaka, Nagasaki, Hiroshima, Saga and Yamagata between 1962 and 1997 were combined and used as the data for the Japanese. To characterize the time trend in rate, we chose and combined the data on Japanese-Americans from the cancer registries of Hawaii and Los Angeles County, California between 1968 and 1997. Data on US whites who participated in the Surveillance, Epidemiology, and End Results program in 1973–1997 were obtained from the Data Series. The age-standardized incidence rate (ASR) and birth-cohort-specific rate were calculated in the three groups using a computer program in 'CI5 Vols I–VIII'.
Results: Among Japanese males in Japan, the ASR increased sharply starting in the mid 1970s and leveled off in the mid 1990s. In contrast, among both the Japanese-Americans and US whites, the ASR continued to increase throughout the observation period. Among the US whites, an increasing trend was more apparent during 1983–97 than during 1973–87. The trend by birth cohort among Japanese males in Japan clearly showed that there was a peak incidence among men aged 45–59 years. They had been born between 1931 and 1935.
Conclusions: The present calculations clarified the distinctive time trend of liver cancer between the 1970s and 1990s in Japanese males. A possible explanation for the observed trend is discussed.

Key words: liver cancer – Japanese – incidence – population-based cancer registry – emigrant

INTRODUCTION

Over the last 30 years, liver cancer has been the third leading cause of cancer death among Japanese males (23 421 deaths in 2004) (1). Ninety-five per cent of liver cancer cases consist of hepatocellular carcinoma (2), which is mainly caused by chronic hepatitis C virus (HCV) infection rather than chronic hepatitis B virus (HBV) infection in Japan (3). Liver cancer is more common in males than in females (4) although the prevalence of HCV infection between males and females is similar in Japan (5). The geographic difference in liver cancer incidence is positively correlated with the geographic pattern of the prevalence of HCV infection among the general population of Japan (6). By molecular clock analysis of the sequences of HCV isolates, it has been hypothesized that a major spread of HCV infection in Japan occurred in the 1940s and 1960s, while in the USA it occurred in the late 1960s and 1970s (7). This might yield different trends of liver cancer incidence rates between the two countries.

Comparison of liver cancer incidence trends among Japanese in Japan, Japanese-Americans, and another population in the USA may provide interesting results from an epidemiological and public health perspective. Thus, we studied the trends in male liver cancer incidence rates in the three groups using data from population-based cancer registries.

METHODS

We obtained data on the incidence rate of male liver cancer from the CD-ROM of the 'Cancer Incidence in Five

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Continents (CI5) Vols I–VIII' (8), which is supported by the International Agency of Research on Cancer (Lyon, France). This is a computer program that provides access to data in the CI5 Series. The data in CI5 including the incidence data of cancer together with the corresponding population data, had been submitted from population-based cancer registries worldwide, which had standard data quality (9). We used the data of the cancer registries of Miyagi, Osaka, Nagasaki, Hiroshima, Saga and Yamagata between 1962 and 1997 when these data were available as the data of Japanese in Japan. The data on Japanese-Americans were obtained from the cancer registries of Hawaii and Los Angeles County, California between 1968 and 1997, because these were the only two registries with Japanese immigrants in which consecutive data were available in the CI5 Series. The third group was white Americans who participated in the Surveillance, Epidemiology, and End Results (SEER) program between 1973 and 1997.

The data were selected from the CD-ROM and the subgroups within the three groups were combined to calculate the incidence of liver cancer in each group. Trends in age-standardized incidence rates (ASRs) of male liver cancer for five calendar years (world population as the standard population), and trends in 5-year birth-cohort-specific rates were calculated in the three groups. Classification of liver cancer titled malignant neoplasm of liver and intrahepatic bile ducts in the CI5 in 1963–67 (Vol. II), 1968–77 (Vols III–IV), 1978–92 (Vols V–VII) and 1993–97 (Vol. VIII) was coded to the International Classification of Diseases (ICD) 7th (155.0), 8th (155), 9th (155) and 10th (C22) Revision, respectively. All of the calculations were performed by a computer program in the 'CI5 Vols I–VIII' (8).

RESULTS

Figure 1 shows the time trends of the age-standardized incidence rate of liver cancer among the Japanese males, Japanese-American males and US white males. Among Japanese males in Japan, the ASR increased slowly from 34.2 to 36.7 per 10^5 between 1963 and 1977. From the mid 1970s, the incidence rate rose sharply until the early 1990s to 85.9 per 10^5 and then it leveled off in the mid 1990s. Among Japanese-Americans, the ASR increased slowly throughout the observation period from 10.3 to 14.2 per 10^5. Among US whites, there was an increasing trend in the ASR during the observation period. The trend was more apparent during 1983–97 (5.3–8.6 per 10^5) than during 1973–87 (4.6–5.3).

The time trends of the age-specific incidence rate of liver cancer by birth cohort are shown in Figs 2–4. The horizontal axis shows years of birth. Among the Japanese in Japan, the incidence rate seemed to be constant between the ages of 35 and 44 years in the birth cohort between 1921 and 1960 (Fig. 2). The incidence rates at ages 45–59 were highest in the birth cohort between 1931 and 1935. Among

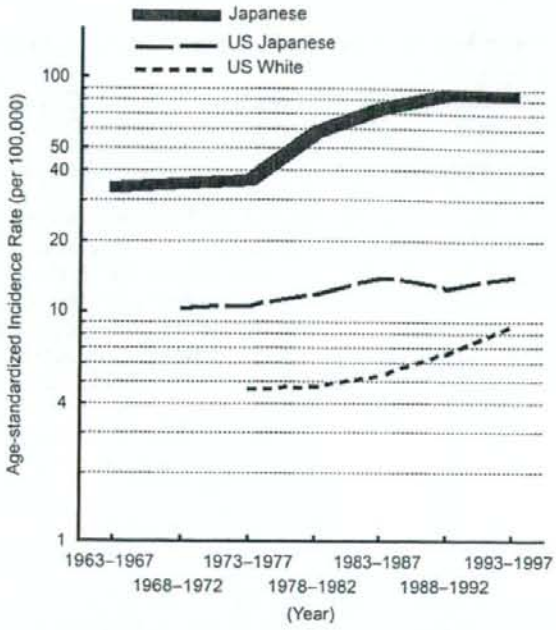

Figure 1. Trends in age-standardized incidence rates of liver cancer in Japanese males, Japanese-American (US Japanese) males and US white males.

Japanese-Americans, the incidence rates seemed to be highest in birth cohorts around 1901–1905 and 1926–1930, although they were fluctuating because of the small number of the incidence in this population (Fig. 3). Among US whites, all of the age-specific incidence rates (35–84 years) among those born from 1891 to 1960 increased as the birth cohort descended (Fig. 4).

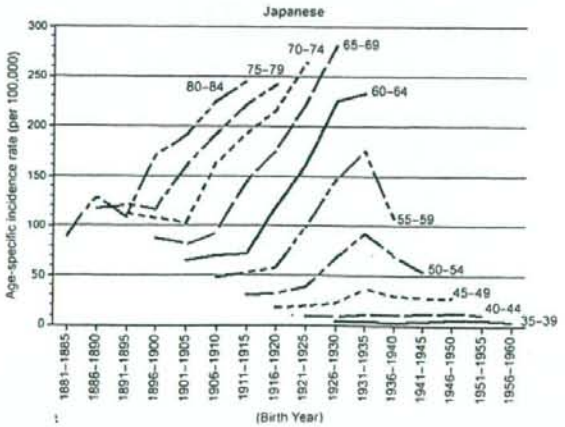

Figure 2. Age-specific incidence rates of liver cancer according to year of birth from 1881 to 1960 in Japanese males in Japan.

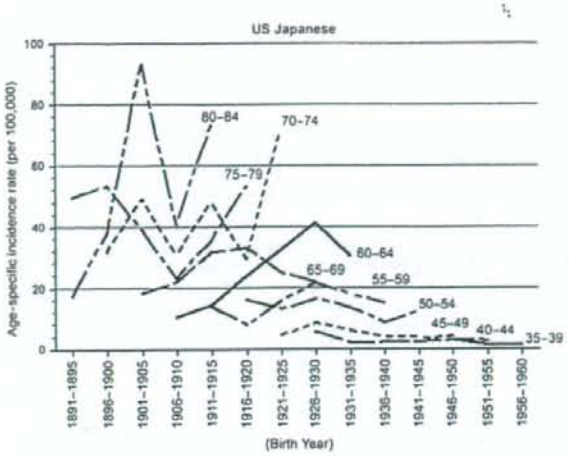

Figure 3. Age-specific incidence rates of liver cancer according to year of birth from 1891 to 1960 in Japanese-American males (US Japanese).

DISCUSSIONS

Our study demonstrated that the ASR of liver cancer among Japanese males in Japan has changed remarkably between the 1970s and 1990s. It increased sharply starting in the mid 1970s and it had more than doubled by the early 1990s, but then it leveled off in the mid 1990s. The time trends by birth cohort clearly showed that the rate was the highest among people born between 1931 and 1935 and with ages of 45 years and over. A similar birth cohort effect on liver cancer mortality in Japanese male has been reported (10). How did this effect appear? The prevalence of HCV infection among Japanese males in Japan was thought to be highest among the generation born around 1931–1935 based on data on first-time blood donor candidates (11), although data on older Japanese individuals are not available (5, 12). This assumption is supported by the recent study on molecular tracing of the HCV epidemic in Japan that reported that exponential spread of HCV-1b infection started in the 1940s (7), which coincided with an outbreak of parenteral amphetamine use in the devastated society after the Second World War (11, 13). The spread was considered to be amplified through blood transfusions and parenteral medical procedures in the 1950s and 1960s (11, 13), but it subsequently ended by the early 1990s at the latest, as evidenced by the very low incidence of HCV infection among repeat blood donors (14, 15). It is realistic to consider that Japanese males born between 1931 and 1935, who were adolescents in the early 1950s, were the most susceptible to HCV transmission from these circumstances.

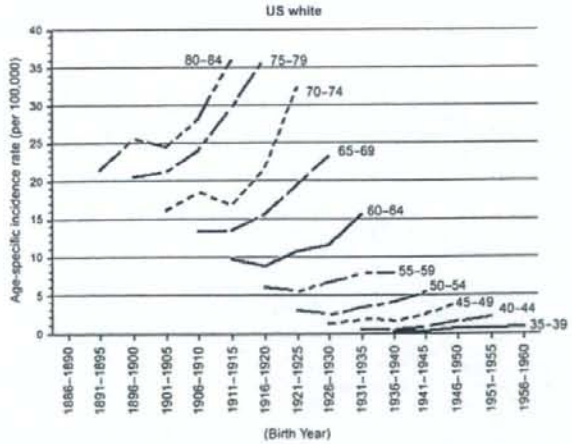

Figure 4. Age-specific incidence rates of liver cancer according to year of birth from 1891 to 1960 in US white males.

As for Japanese-Americans, the first group of Japanese emigrated to the USA before 1924, when immigration of Japanese into the USA was prohibited by the 'Quota Immigration Amendment Act'. Therefore, the next generations of Japanese-Americans were free from HCV epidemics within Japan that yielded different trends of rates between Japanese in Japan and Japanese-Americans. The ASR of liver cancer among US whites has increased since the mid 1980s, although the rates are the lowest among the three groups. This finding may also be attributed to the previous finding that the spread of HCV-1a, a dominant genotype in the USA (16), began in 1965 based on molecular tracing of the HCV epidemic in the USA (7). This is approximately 25 years after the HCV outbreak started in Japan (7).

In conclusion, the present calculation of liver cancer incidence rates shows a distinctive time trend between the 1970s and 1990s in Japanese males. The trend was affected by the birth cohort effect which was possibly attributed to HCV outbreaks in Japan. If this trend is maintained, the male Japanese liver cancer incidence rate is likely to further decline in the current decade.

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Conflict of interest statement

None declared.

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Epidemiology Note

Survival of Cancer Patients Diagnosed between 1993 and 1996: a Collaborative Study of Population-Based Cancer Registries in Japan

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Background: Survival of cancer patients has been measured only in some limited areas in Japan until recently. The purpose of the present study was to collect data of fairly high quality on the population-based cancer registries and to estimate relative 5-year survival of cancer patients in Japan.

Methods: We requested 11 population-based cancer registries within the research group to submit individual data of the patients diagnosed from 1993 to 1996, together with the prognosis after 5 years, to the collaborative study secretariat. Ten population-based cancer registries (Miyagi, Yamagata, Niigata, Chiba, Kanagawa, Fukui, Aichi, Osaka, Tottori and Nagasaki) then accepted data submission (373 000 data). Among 10 registries, only 7 registries met the required standards for the quality of registration data and prognosis investigation. The relative 5-year survival calculated by pooling 279 000 data from seven registries was taken as the national estimate of that of cancer patients in Japan.

Results: The relative 5-year survival was 53.6% for all cancers (males: 49.2%, females: 59.4%); the survivals of stomach, large bowel, prostate and kidney cancer patients were from 62 to 68%; those of breast, uterus, larynx, skin, testis, bladder and thyroid cancer patients were from 74 to 92%; those of liver, gall bladder and bile duct, pancreas and lung cancer patients ranged from 6 to 23%.

Conclusion: On the basis of the data from seven population-based cancer registries in Japan, we calculated the relative 5-year survival of cancer patients diagnosed from 1993 to 1996 for the first time.

Key words: survival – cancer – registry

INTRODUCTION

The survival based on population-based cancer registries, being different from the survivals of the cancer patients diagnosed and treated at specific facilities and departments, is a prerequisite for the designing of projects and the evaluation of measures and treatments for cancers, because only the former is capable of providing patients' data without bias. However, in Japan, the survival has been calculated only in limited areas until now. In addition, regarding the survival calculation, study subjects and methods have not yet been standardized enough. Referring to the EUROCARE study (1), the authors tried to develop the standard methods of calculating survival in Japanese registries through the collaborative study of population-based cancer registries since 1996. In 1998, we proposed the standard methods that required that the vital status of patients be confirmed by inquiring to the resident registration at the time of 5 years after diagnosis, and reported the results of relative 5-year survival based on the data (stomach, lung and

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breast cancer diagnosed from 1985 to 1989) from cancer registries of Yamagata, Fukui and Osaka prefectures (2), which had already started to collect data satisfying the above criteria (3). In 2001, we collected, from 12 registries belonging to the study group, individual data of all cancer patients (for all sites) diagnosed in 1993 with prognosis after 5 years, and tried a nationwide estimate of relative 5-year survival according to the standard methods (4). A nationwide estimate, however, has not been completed because there were differences in the quality of registration and prognosis investigation among 12 registries.

In this study, we requested population-based cancer registries to submit the data of the patients (for all sites) diagnosed from 1993 to 1996 with those on prognosis after 5 years, and pooled the data of the cancer registries that achieved a standard of quality of data in terms of both registration and prognosis investigation in order to estimate relative 5-year survival of cancer patients in Japan.

SUBJECTS AND METHODS

Ten of 11 registries belonging to the research group traced the prognosis after 5 years of patients diagnosed from 1993 to 1996 and submitted their individual data (a total of 373 000 cases) to the research group secretariat. Among 10 registries, 7 registries (Miyagi, Yamagata, Niigata, Fukui, Osaka, Tottori and Nagasaki) met the required standards for the quality of registration and prognosis investigation. According to a total of 279 000 data provided by these registries, we calculated survivals and considered them as nationwide estimates. Standard for the quality of registration was based on the standard adopted in the nationwide estimates of incidence: DCO (death certificate only cases) was <25%, or DCN (death certificate notification) was <30%, and ID ratio (incidence to death ratio) was not <1.5 (5). As far as the standard for the quality of prognoses investigation was concerned, we set two kinds of criteria according to the follow-up methods. For the registries checking survival of patients by referring to inhabitant's registry, the proportion of prognosis-unknown cases 5 years after diagnosis was <5% (Yamagata, Fukui and Osaka). For the registries having no confirmation of survival 5 years after diagnosis, information on personal identification including names would be magnetized in order to collate their registered patients with death information in high accuracy. Therefore, using these criteria, it was guaranteed that they had rather accurate information about death (Miyagi, Niigata, Tottori and Nagasaki).

The method of calculating survival is based on the EUROCARE study (1) in which 12 countries of the European Union had participated in 1990, and our study group also followed this method. In other words, we excluded DCO cases, *in situ* cancer cases and mucosal cancer cases of large bowel from the analysis. In the case of multiple cancers, only the first-diagnosed tumour was analysed. In calculating survival, cumulative 5-year survivals were calculated starting from the date of diagnosis. Expected survivals were calculated using the cohort survival table based on life tables of the Japanese population and afterwards using the survival probability in the general population similar to the patients in sex, birth-year and age. The former was divided by the latter to obtain relative 5-year survivals. Besides, the cases that were unknown as of 5 years after diagnoses were dealt with as alive as of the last date of living (2). However, regarding four registries that had not yet started to check the survival of patients by referring to the resident registry, we regarded all of the cases whose death was not confirmed as alive until 5 years, and survivals were calculated.

RESULTS

Table 1 shows the number of incidence, validity indices of the registration and the number of study subjects for survival analysis, according to the registry. Total number of incidence was 279 469, and the following cases were excluded from the survival analysis: DCO (49 278 cases, 17.6% of the total incidence), subsequent primary tumours (18 596 cases, 6.7% of the total), not malignant tumours (487 cases, 0.2% of the total), *in situ* cancers (3955 cases, 1.4% of the total). In addition, excluding the cases of unknown age at diagnosis and the cases over 100 years old, we analysed the rest of all (209 373 cases, 74.9% of the total) (Subjects 1). Moreover, for DCN cases, complementary cancer reports were requested in Yamagata, Fukui and Osaka prefecture, and the registry records of cases originating from death information were distinguished in Miyagi prefecture. The number of cases in which we traced the death information to incidence were 17 556 (8.4% of the total). The analysis subjects (Subjects 2) excluding these cases were 191 817 cases (68.6% of the total).

Table 2 shows the vital status as of 5 years from diagnosis. In Yamagata, Fukui and Osaka Cancer Registries, where the vital status of patients was checked after 5 years by referring to inhabitant's registry, the proportion of unknown cases for vital status was <2–3%, which indicates that the prognosis investigation was highly accurate.

Table 3 shows the number of study subjects, relative 5-year survival and its standard error according to the primary site. In addition, when selecting the study subjects, we distinguished between the occasion including the cases regarded as incidence according to death information (Subjects 1) and the occasion excluding the former case. Moreover, regarding the sites covering relatively many subjects, we showed the results of analysis by sex; regarding the sites covering relatively small subjects, we showed only the total results of males and females. Usually, mucosal cancer of large bowel cases should be excluded from the survival analysis (2,6), but some registries (Fukui, Niigata and Tottori) submitted the data including these cases undistinguished. Therefore, regarding all sites, large bowel, colon and rectum, each case was divided between their 1 and 2 on the basis of whether or not mucosal cancer of large bowel was included.

Relative 5-year survival of cancer patients of all sites (all sites 2) was 45.1, 54.8 and 49.2% for males, females and total, respectively, on Subjects 1, and 49.2, 59.4 and 53.6% on

Table 1. Number of incidence, validity indices of the registration and number of study subjects for survival, according to the registry—Diagnosed in 1993–96

Registry	No. of incidence	DCO		Subsequent tumours		Not malignant		In situ		Subjects 1		Follow-back		Subjects 2	
		No.	%*[1]	No.	%*[1]	No.	%*[1]	No.	%*[1]	No.	%*[1]	No.	%*[2]	No.	%*[1]
Miyagi	37372	5865	15.7	4147	11.1	107	0.3	919	2.5	26997	72.2	115	0.4	26882	71.9
Yamagata	24315	2542	10.5	835	3.4# (2.7)	0	0.0	250	1.0	20683	85.1	2481	12.0	18202	74.9
Niigata	44647	10845	24.3	1605	3.6	0	0.0	495	1.1	31715	71.0	—	—	31715	71.0
Fukui	13806	581	4.2	0	0.0# (10.3)	0	0.0	142	1.0	13083	94.8	1631	12.5	11452	82.9
Osaka	118931	23549	19.8	7252	6.1	380	0.3	1546	1.3	87366	73.5	13329	15.3	74037	62.3
Tottori	10528	2735	26.0	151	1.4	0	0.0	23	0.2	7645	72.6	—	—	7645	72.6
Nagasaki	29870	3161	10.6	4606	15.4	0	0.0	580	1.9	21884	73.3	—	—	21884	73.3
Total	279469	49278	17.6	18596	6.7	487	0.2	3955	1.4	209373	74.9	17556	8.4	191817	68.6

*[1]Proportion to the total incidence.
*[2]Proportion to the Subjects 1.
#Registries or incidence data without items to distinguish multiple tumours. Figures in the parentheses were proportion of those to the total incidence.
DCO: Death certificate only cases; Subsequent tumours: Second and later primary tumours;
Subjects 1: Study subjects for survival, including cases who were followed back and confirmed as incidence according to death information; Follow-back; Cases who were followed back and confirmed as incidence according to death information;
Subjects 2: Study subjects for survival, excluding cases who were followed back and confirmed as incidence according to death information.

Table 2. Vital status as of 5 years from diagnosis

Registry	No. of Subjects 1	Dead		Alive		Unknown	
		N	%*[1]	*N*	%*[1]	*N*	%*[1]
Yamagata	20683	11206	54.2	9307	45.0	170	0.8
Fukui	13083	7467	57.1	5197	39.7	419	3.2
Osaka	87366	54199	62.0	31633	36.2	1534	1.8
Niigata	31715	15144	47.8	16570	52.2	1	0.0
Miyagi	26997	12767	47.3	14230	52.7	—	—
Tottori	7645	3595	47.0	4050	53.0	—	—
Nagasaki	21884	11830	54.1	10054	45.9	—	—
Total	209373	116208	55.5	91041	43.5	—	—

*[1]Proportion to the total number of Subjects 1.

Subjects 2; the former is higher than the latter. This is because Subjects 1 includes the cases regarded as incidence according to death information. Same as many registries in Japan, under the situation of high proportion of the cases not reported and the cases registered on the basis of death certificates, it will be possible for the survival calculated on the basis of Subjects 1 to be estimated lower than it is. In contrast, it is also possible for survival to be estimated higher than it is on Subjects 2. In Japan, each population-based registry decides whether or not to request medical institutions to submit information on cancer diagnosis and treatment for DCN. Consequently, if we need domestic comparison of survival, the survival of Subjects 2 would be better than that of Subjects 1 in terms of comparability. Therefore, in this study, we will regard the survival calculated on the basis of Subjects 2 as that of cancer patients in Japan.

The relative 5-year survivals by site on Subjects 2 were calculated as follows: the survivals of cancers of stomach, large bowel, prostate, and kidney were 62–68%; those of cancers of breast, uterus, larynx, skin, testis, bladder and thyroid were 74–92%; those of cancers of liver, gallbladder and bile duct, pancreas and lung were 6–23%.

Table 4 shows observed and relative 1- to 5-year survival by sites. Observed 1- to 5-year survival in all sites 2 were 72.5, 61.1, 54.9, 50.6 and 47.5% in order; relative survival were 74.4, 64.2, 59.0, 55.7 and 53.6% in order.

Table 5 shows relative 5-year survivals for major sites of cancer (all sites 2, stomach, large bowel 2, liver, lung, breast and uteri) by sex and age at diagnosis. The relative 5-year survivals for cancers of stomach, liver, lung and uterus decreased markedly in old age; however, the difference was not pronounced in age regarding those for cancers of large bowel 2 and breast. Regarding lung cancer, females had a higher survival than males in all age groups. Besides, the same difference was also observed for the survival of liver cancer, where there was a marked difference in sex. In contrast,

Table 3. Relative 5-year survival for selected sites of cancer diagnosed in 1993–96

Study subjects	Sex	Items	All sites 1	All sites 2	Stomach	Large bowel 1	Large bowel 2	Colon 1	Colon 2	Rectum 1	Rectum 2	Liver	Lung	Breast	Uterus
Major sites by sex															
1	Male	N*1	121 454	119 555	32 195	21 218	19 319	12 987	11 555	8231	7764	12 111	17 671	—	—
		RSR*2	46.0	45.1	59.0	69.5	66.2	72.3	68.5	65.1	62.9	17.0	18.3	—	—
		SE*3	0.2	0.2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.4	0.3	—	—
	Female	N	87 919	87 037	16 542	15 279	14 397	10 245	9606	5034	4791	4558	6645	14 673	5732
		RSR	55.2	54.8	57.0	64.6	62.4	65.1	62.7	63.7	61.8	17.4	24.1	83.1	70.5
		SE	0.2	0.2	0.4	0.4	0.5	0.5	0.6	0.8	0.8	0.6	0.6	0.4	0.7
	Both	N	209 373	206 592	48 737	36 497	33 716	23 232	21 161	13 265	12 555	16 669	24 316	14 673	5732
	sexes	RSR	49.9	49.2	58.3	67.5	64.6	69.1	65.8	64.6	62.5	17.1	19.9	83.1	70.5
		SE	0.1	0.1	0.3	0.3	0.3	0.4	0.4	0.5	0.5	0.3	0.3	0.4	0.7
2	Male	N	111 012	109 113	30 253	20 250	18 351	12 362	10 930	7888	7421	10 081	15 467	—	—
		RSR	50.1	49.2	62.6	72.7	69.5	75.8	72.2	67.8	65.6	20.1	20.7	—	—
		SE	0.2	0.2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.4	0.4	—	—
	Female	N	80 805	79 925	15 419	14 437	13 557	9615	8978	4822	4579	3685	5756	14 391	5419
		RSR	59.8	59.4	60.9	68.2	66.0	69.1	66.8	66.4	64.6	21.0	27.6	84.6	74.3
		SE	0.2	0.2	0.4	0.5	0.5	0.6	0.6	0.8	0.8	0.7	0.6	0.3	0.7
	Both sexes	N	191 817	189 038	45 672	34 687	31 908	21 977	19 908	12 710	12 000	13 766	21 223	14 391	5419
		RSR	54.3	53.6	62.0	70.8	68.0	72.9	69.8	67.3	65.2	20.3	22.6	84.6	74.3
		SE	0.1	0.1	0.3	0.3	0.3	0.4	0.4	0.5	0.5	0.4	0.3	0.3	0.7

Minor sites, both sexes combined

Study subjects	Sex	Items	Mouth, oral cavity and pharynx	Oesophagus	Gall bladder and bileduct	Pancreas	Larynx	Skin	Ovary	Prostate	Testis	Kidney, etc.	Bladder	Brain and nervous system	Thyroid	Lymphoma	Myeloma	Leukaemia	Childhood cancer
1	Both sexes	N	3699	5820	6501	6393	1693	2182	2492	4681	503	3958	4908	1438	3247	4720	1070	3351	1284
		RSR	50.9	25.0	17.5	5.5	76.7	87.5	43.8	63.4	90.0	59.2	74.2	31.4	90.3	43.7	25.0	28.1	71.8
		SE	0.9	0.6	0.5	0.3	1.3	1.3	1.0	1.0	1.4	0.9	0.8	1.3	0.7	0.8	1.5	0.8	1.3
2	Both sexes	N	3527	5396	5622	5301	1657	2130	2169	4348	502	3637	4644	1217	3179	4302	847	2935	1257
		RSR	53.3	26.8	20.1	6.5	78.2	89.6	50.0	67.6	90.1	64.0	78.1	36.6	92.0	47.8	29.9	31.5	73.4
		SE	0.9	0.7	0.6	0.4	1.3	1.2	1.1	1.0	1.4	0.9	0.8	1.4	0.6	0.8	1.7	0.9	1.3

Subjects 1: Including cases who were followed back and confirmed as incidence according to death information.
Subjects 2: Excluding cases who were followed back and confirmed as incidence according to death information.
*1Number of study subjects.
*2Relative 5-year survival.
*3Standard error.

Table 4. Cumulative and relative 1- to 5-year survival for selected sites of cancer diagnosed in 1993–96

Primary sites	Observed survival					Relative survival				
	1	2	3	4	5	1	2	3	4	5
All sites 2	72.5	61.1	54.9	50.6	47.5	74.4	64.2	59.0	55.7	53.6
Mouth, oral cavity and pharynx	79.1	62.7	55.8	51.5	47.9	80.8	65.4	59.5	56.1	53.3
Oesophagus	55.7	37.3	29.9	25.7	23.5	57.3	39.3	32.4	28.6	26.8
Stomach	75.0	65.5	60.5	57.0	54.4	77.0	69.0	65.4	63.3	62.1
Large bowel 2	83.8	73.9	67.5	62.9	59.6	86.0	77.8	73.0	69.9	68.1
Liver	59.9	44.1	33.0	24.2	18.3	61.2	46.1	35.2	26.3	20.4
Gall bladder and bile duct	41.2	27.3	21.5	18.9	17.2	42.8	29.3	23.7	21.5	20.2
Pancreas	23.4	11.4	8.0	6.4	5.7	24.2	12.1	8.7	7.1	6.6
Larynx	91.3	83.8	77.5	72.3	67.2	93.9	88.8	84.5	81.4	78.2
Lung	52.1	33.5	25.9	22.1	19.5	53.8	35.6	28.3	24.9	22.6
Skin	92.4	85.0	79.0	74.7	71.0	96.6	93.2	90.7	89.9	89.6
Breast	96.7	92.3	87.6	84.1	80.9	97.5	93.8	89.9	87.0	84.6
Uterus	89.0	80.6	76.0	72.8	70.9	90.0	82.2	78.2	75.7	74.3
Ovary	78.2	64.6	56.2	51.1	48.2	79.0	65.7	57.6	52.6	50.0
Prostate	88.6	76.2	65.6	57.3	50.2	93.7	85.4	78.0	72.4	67.6
Testis	94.0	91.0	89.6	89.2	89.0	94.2	91.4	90.2	90.1	90.1
Bladder	87.1	78.7	73.4	68.5	64.8	90.4	84.7	82.0	79.5	78.1
Kidney, etc.	80.1	70.4	65.1	60.9	57.0	82.0	73.8	69.8	66.8	64.1
Brain and nervous sysytem	70.3	50.4	43.2	38.8	35.3	71.1	51.4	44.4	40.1	36.7
Thyroid	93.8	92.0	90.6	89.2	87.4	94.8	93.9	93.4	92.9	92.0
Lymphoma	68.5	56.6	50.5	46.5	43.5	70.1	59.0	53.6	50.2	47.8
Myeloma	70.8	56.2	42.9	33.4	26.1	72.9	59.4	46.6	37.3	29.9
Leukaemia	59.8	44.0	37.0	32.6	29.9	60.8	45.2	38.4	34.1	31.5
Childhood cancer	89.9	81.7	77.1	74.7	73.3	89.9	81.7	77.2	74.8	73.4

Table 5. Relative 5-year survival for major sites of cancer by sex and age at diagnosis

Age at diagnosis	All sites 2			Stomach			Large bowel 2			Liver			Lung			Breast	Uterus
	Male	Female	Both sexes	Male	Female	Both sexes	Male	Female	Both sexes	Male	Female	Both sexes	Male	Female	Both sexes	Female	Female
15–44	61.9	75.7	70.4	70.3	63.9	67.3	67.8	65.9	67.0	23.4	—	21.9	27.9	29.5	28.4	84.0	85.9
45–54	53.6	70.6	62.2	67.7	65.6	67.0	68.3	68.2	68.3	20.9	29.4	22 2	25.2	32.6	27.6	84.4	77.5
55–64	50.8	61.9	54.9	65.8	65.7	65.8	71.1	67.6	69.8	20.8	26.4	21.9	23.9	33.8	26.5	82.8	75.3
65–74	48.5	56.5	51.5	63.2	64.7	63.7	71.3	69.5	70.5	20.8	21.9	21.2	21.7	31.6	24.2	87.6	69.4
75–	41.4	43.2	42.3	50.8	49.9	50.4	65.9	59.9	62.7	12.3	10.5	11.5	13.6	16.4	14.5	86.3	48.3

females had a lower survival than males in the following sites and ages: the young patients of stomach cancer aged from 15 to 44 years old, and the old patients of large bowel cancer aged over 75 years old.

DISCUSSION

On the basis of the data from seven population-based cancer registries in Japan that achieved a standard of quality of data in terms of both registration and prognosis investigation, we calculated relative 5-year survival of cancer patients for the first time. On the basis of the standard methods of calculating survival employed in EUROCARE study (1), we estimated the Japanese representative survival for major sites of cancer as well as childhood cancers diagnosed before the age of 15 years. This study estimated the survival not only for the cancers including the followed-back cases from DCN (Subjects 1) but also the cancers excluding them (Subjects 2). The former used the same method as EUROCARE study employed, and it is the estimate that should be utilized for international

comparison of survival based on population-based cancer registries. In contrast, the latter is the estimate that should be utilized for domestic comparison of survival in Japan where some registries do not conduct follow-back inquiries according to death information.

Now we would like to discuss the issues for the study in the future. First of all, it is important to improve the quality of registration, because the high proportion of patients not registered will degrade the accuracy of survival estimate. In this study, we required each registry to meet the necessary standards for participating in the nationwide estimates of incidence (5). Therefore, it would be reasonable to assume that the survival in Japan has been calculated on the basis of the fairly accurate data of population-based cancer registries for the first time. However, from the viewpoint of international standards, where the registry data showing DCO >10% for all sites are regarded as poor completeness of registration, the cases not registered are still not negligible in Japan (7). Thus, we have to admit that the validity of survival has not improved to the desired extent. Moreover, it should be taken into consideration that the survival calculated in this study was based on the data submitted by the very limited areas of seven prefectures. If we assume the difference among prefectures, it will be desirable to utilize wider range of data from more prefectural regions.

In the three prefectures where the vital status of patients was checked after 5 years from diagnosis, the proportion of unknown cases for vital status was 3% or less, which implies that the prognosis investigation was highly accurate. However, the other four prefectures did not check the vital status of patients. The fact that they do not check the survival of patients would have a relatively small effect on the overestimation of the survival, because it is estimated that collating with death information can be done with high accuracy in these four prefectures, and that frequency of moving out to different prefectures is relatively low. However, for collecting more accurate data of survival, it is necessary from now on to investigate prognosis of patients by referring to resident registry.

Regarding mucosal cancers of large bowel, we should have excluded them from the survival analysis, since they were regarded as *in situ* cancers according to the agreement of UICC (6). However, some population-based cancer registries did not distinguish them in this study. Therefore, we calculated the following two cases: the case including mucosal cancer of large bowel (all sites 1, large bowel 1, colon 1, rectum 1) and the case excluding distinguished mucosal cancer (all sites 2, large bowel 2, colon 2, rectum 2). Moreover, it was not easy for some population-cancer registries to distinguish multiple cancers. For more reliable results of survival, it is necessary to distinguish them from other cancers. In this study, however, it seems that the proportion of mucosal cancer of the large bowel and that of multiple cancers except the first-diagnosed tumour were not very large; therefore, it is reasonable to think that they did not affect the result of survival that much.

The EUROCARE study started as a collaborative study of the European Union (1), and it currently involves 67 population-based cancer registries operating in 22 European countries (8). Furthermore, the CONCORD study (9) extends the EUROCARE study to include North America (the USA and Canada), Australia and Japan. In Japan, the cancer registries of Yamagata, Fukui and Osaka prefecture currently participate in this study, all of which have already started to check the vital status of patients after 5 years from diagnosis. It is desirable that more registries will take part in this study. In the CONCORD study, the following studies are developed: Phase 1 study based on existing data of registries; Phase 2 study to investigate clinical data retrospectively by taking samplings from databases of population-based cancer registries; and Phase 3 study on the central review of pathological specimens. Currently, it is only the Phase 1 study that Japan is participating in; however, it will be necessary to build up a framework for our participation in the high-resolution study of Phase 2 and 3. Through our participation in these types of international collaborative studies, it is expected that the reliability of the study on the survival based on population-based cancer registries in Japan will be improved.

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Cervical and corpus cancer survival disparities by socioeconomic status in a metropolitan area of Japan

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The purpose of this study was to analyze socioeconomic differences in cervical and corpus cancer survival, and to investigate if the differences are due to differences in age, cancer stage, histology and treatment. A total of 14 055 cases with cervical cancer and 3113 cases with corpus cancer were obtained from the Osaka Cancer Registry. Municipality-based SES measurements were obtained from the System of Social and Demographic Statistics. Survival analysis was carried out with Kaplan–Meier survival curves. Three types of Cox proportional hazards regression models were tested to assess survival differences among groups and effects of SES on survival, controlling for clinical factors. SES was related to age and cancer stage for cervical and corpus cancer patients, and histology for cervical cancer patients. Differences were observed in cumulative 5-year survival for cervical cancer patients among low, middle and high unemployment municipalities (68.9%, 64.3% and 50.9%, respectively, $P < 0.0001$). Differences in cumulative 5-year survival for cervical cancer patients were also observed among high, middle and low education municipalities (65.1%, 62.2% and 56.1%, respectively, $P < 0.0001$). Similar patterns in 5-year survival were also found for corpus cancer patients. After adjusting for age, cancer stage, histology and treatment, survival differences between patients from high and low SES areas still remained. In conclusion, our population-based analysis of a metropolitan representative sample in Japan has demonstrated, for the first time in Japan, SES differences in survival following cervical and corpus cancer. (*Cancer Sci* 2006; 97: 283–291)

Social inequalities in cancer survival need to be taken into consideration, especially in terms of equal provision for cancer detection and treatment.[1–5] Differences in cancer survival among patients from different socioeconomic backgrounds may be due to inequalities in access to quality treatment as well as variations in cancer stage at presentation.[6] Survival differences in cervical and corpus cancer by SES have been studied in different countries.[4,5,7–13]

In Japan, cancer has been a leading cause of death since 1981, with one in three persons dying from cancer. Cancer mortality rates for males and females in 2002 were 298.8 and 187.1 per 100 000, respectively (ICD, 10th revision, codes C00 and C97).[14] Age-standardized incidence rates (standard; world population) for cancer in 1999 estimated by the Research Group for Population-based Cancer Registration in Japan were 271.1 for males and 168.6 for females per 100 000.[15] The mortality rate for cervical, corpus cancer and uterine cancer not otherwise specified (NOS) (ICD, 10th revision, codes C53-55) mortality rate was 8.3 per 100 000 females.[14] The estimated cervical cancer (ICD, 10th revision, codes C53) incidence rate has decreased by approximately 50% from 13.4 in 1975 to 6.6 in 1999 per 100 000 females, however, the rate among young females has increased. By contrast, corpus cancer (ICD, 10th revision, code C54) incidence rates increased from 1.4 in 1975 to 5.4 in 1999 per 100 000 females.[15,16] Relative 5-year survival following cervical and corpus cancer reached a plateau of around 70% after 1980.[17]

In March 2005, the Japanese Ministry of Health, Labour and Welfare Special Committee on the Equation of Cancer Control released its national cancer control strategy. One of the programs of the national strategy focuses on enhancing the provision of cancer prevention and treatment efforts targeted at women. Despite the launch of the national comprehensive cancer control strategy, however, few studies in Japan have addressed socioeconomic disparities in cancer survival.

We sought to analyze socioeconomic differences in cervical and corpus cancer survival in Osaka, a major metropolitan area of Japan, and to investigate if the disparities were due to differences in age, cancer stage, histology or treatment.

Materials and Methods

Data on newly diagnosed uterine cancer cases (ICD, 10th revision, codes C53 and C54) between January 1975 and December 1997 were extracted from the Osaka Cancer Registry (OCR). Death certificate only registrations were excluded. We analyzed 14 055 cases of cervical cancer and 3113 cases of corpus cancer. The OCR is one of the largest and longest-running population-based cancer registries in Japan. The validity and procedures of the OCR have been described elsewhere.[18]

Variables extracted age, cancer stage, histology, treatment, area-based SES and cumulative 5-year survival. Cancer stage at diagnosis was classified into three groups: localized, regional

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Abbreviations: ICD, International Classification of Diseases; SES, socioeconomic status.

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and distant stage. Localized stage cancer was limited to the original organ. Regional stage cancers were those that had spread to regional lymph nodes and/or adjacent tissues, and distant stage cancers were those that had metastasized to distant organs. Histology was categorized using Berg's classification used by the International Agency for Research on Cancer for identifying groups of malignant neoplasms considered to be histologically distinct for the purpose of classifying tumors in their Recommendations for Coding Multiple Primaries.[19] The histology of cervical cancer was categorized as squamous carcinomas, adenocarcinomas, other specific carcinomas and 'other'. The histology of corpus cancer was categorized as squamous carcinomas, adenocarcinomas, other specific carcinomas, sarcomas and soft tissue tumors, and 'other'. Treatment was categorized into nine groups: surgery alone, radiation alone, chemotherapy alone, surgery and radiation, surgery and chemotherapy, radiation and chemotherapy, combined surgery/radiation/chemotherapy, other treatments, and unknown.

Because of lack of individual socioeconomic data in the OCR, we used municipality-based SES as a proxy, drawing on the percentages of male unemployment, and college or graduate school graduates within the 67 municipalities of the Osaka area. The percentage of unemployment in 1995 and college or graduate school graduates in 1990 were obtained from the System of Social and Demographic Statistics (SSDS) provided by the Ministry of Internal Affairs and Communications, drawn from the national census. The 67 municipalities were categorized into three socioeconomic groups: 22 municipalities with low percentages of unemployment (2.54–5.37%), or high proportions of college or graduate school graduates (13.98–25.04%) ('high SES municipalities'); 23 municipalities with middle percentages of unemployment (5.41–6.82%) or college or graduate school graduates (10.54–13.96%) ('middle SES municipalities'); and 22 municipalities with high percentages of unemployment (7.13–17.4%) or low proportions of college or graduate school graduates (6.22–10.34%) ('low SES municipalities').

Survival analysis was carried out with Kaplan–Meier survival curves with follow-up for 5 years. The survival time was defined as the time from the date of first diagnosis to the date of death from any causes. Log–rank tests were used to determine the significance of differences between survival curves by SES and other prognostic factors. Three sets of sequential Cox proportional hazards regression models were carried out to assess survival differences among SES groups, controlling for clinical factors. In the first model, we controlled for age as a confounder. In the second model we controlled for age, plus biological factors (cancer stage and histology of cervical cancer, cancer stage of corpus cancer). In the third model, we controlled for all of the variables in the second model, plus treatment type. The statistical significance of differences in distributions of clinical factors was determined by χ^2 tests for categorical variables and by Kruskal–Wallis tests for continuous variables. STATA (version 7.0) was used for statistical analyses.

Results

The characteristics of cervical and corpus cancer patients by SES area are shown in Tables 1 and 2. Histology for all cases in 'sarcomas and soft tissue tumors' (according to Berg's classification) was sarcoma. Significant SES differences were found in the age of patients as well as cancer stage for cervical and corpus cancer patients. The distribution of histology for corpus cancer patients did not differ by SES. Proportions of localized cervical (59.2%) and corpus (68.7%) cancers were higher among patients from low unemployment areas compared to patients from middle (57.2%, 61.1%) or high (51.6%, 61.0%) unemployment municipalities. Similarly, the proportions of localized cervical (57.6%) and corpus (67.1%) cancers in high education municipalities were higher compared to middle (56.8%, 62.1%) and low (51.7%, 59.4%) education municipalities. The proportion of squamous carcinomas in cervical cancer in low unemployment municipalities (82.2%) was lower compared to middle (84.9%) and high (85.6%) unemployment municipalities. We observed significant differences in the distribution of treatment for both cervical and corpus cancer patients. The proportions of cervical cancer patients who underwent surgery alone were higher among patients from low (32.4%) and middle (30.2%) unemployment municipalities compared to patients from high unemployment municipalities (25.5%). Surgery alone was more common among patients from high (30.6%) and middle (30.0%) education municipalities compared to those from low education municipalities (25.9%).

As shown in Figs 1 and 2, a difference was observed in the cumulative 5-year survival for cervical cancer patients from low, middle and high unemployment municipalities: 68.9%, 64.3% and 50.9%, respectively ($P < 0.0001$). A difference in cumulative 5-year survival for cervical cancer patients was also observed for high, middle *versus* low education municipalities: 65.1%, 62.2% and 56.1%, respectively ($P < 0.0001$). Patients from high unemployment municipalities had a much lower cervical cancer 5-year survival than patients from middle and high socioeconomic municipalities. The cumulative 5-year survival differences for corpus cancer by level of SES showed a similar pattern as that for cervical cancer patients (Figs 3, 4). However, the SES disparities in corpus cancer cumulative 5-year survival were even wider than cervical cancer survival differences.

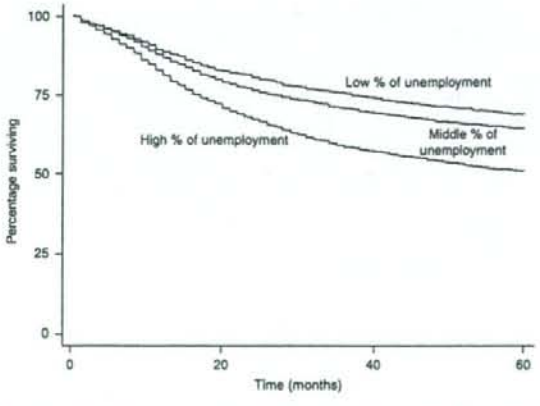

Fig. 1. Kaplan–Meier survival curves by socioeconomic status (SES) (unemployment) for cervical cancer patients.

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Table 1. Characteristics of cervical cancer patients by area-based socioeconomic status (SES)

Factor	Percentage of male unemployment in each municipality				Percentage of college or graduate school graduates in each municipality			
	Low	Middle	High	*P*-value	High	Middle	Low	*P*-value
No. of patients	3308	5838	4909		4265	6100	3690	
Mean age (years)	54	54	56	0.086	54	54	55	0.054
Age (years)				<0.0001				0.026
Under 40	477 (14.4)	875 (15.0)	608 (12.4)		580 (13.6)	914 (15.0)	466 (12.6)	
40–49	908 (27.5)	1453 (24.9)	1129 (23.0)		1107 (26.0)	1485 (24.3)	898 (24.3)	
50–59	786 (23.8)	1411 (24.2)	1231 (25.1)		1039 (24.4)	1464 (24.0)	925 (25.1)	
60–69	653 (19.7)	1162 (19.9)	1113 (22.6)		881 (20.7)	1232 (20.2)	815 (22.1)	
70–79	388 (11.7)	724 (12.4)	657 (13.4)		510 (12.0)	794 (13.0)	465 (12.6)	
80+	96 (2.9)	213 (3.6)	171 (3.5)		148 (3.5)	211 (3.5)	121 (3.3)	
Cancer stage				<0.0001				<0.0001
Localized	1957 (59.2)	3338 (57.2)	2534 (51.6)		2458 (57.6)	3462 (56.8)	1909 (51.7)	
Regional	930 (28.1)	1725 (29.5)	1585 (32.3)		1217 (28.5)	1844 (30.2)	1179 (32.0)	
Distant	107 (3.2)	229 (3.9)	212 (4.3)		158 (3.7)	225 (3.7)	165 (4.5)	
Unknown	314 (9.5)	546 (9.4)	578 (11.8)		432 (10.2)	569 (9.3)	437 (11.8)	
Histology				<0.0001				<0.0001
Squamous carcinomas	2719 (82.2)	4955 (84.9)	4201 (85.6)		3508 (82.2)	5221 (85.6)	3146 (85.3)	
Adenocarcinomas	263 (8.0)	356 (6.1)	277 (5.6)		337 (7.9)	348 (5.7)	211 (5.7)	
Other specific carcinomas	97 (2.9)	117 (2.0)	62 (1.3)		110 (2.6)	113 (1.9)	53 (1.4)	
Other	229 (6.9)	410 (7.0)	369 (7.5)		310 (7.3)	418 (6.8)	280 (7.6)	
Treatment				<0.0001				<0.0001
Surgery alone	1073 (32.4)	1765 (30.2)	1254 (25.5)		1307 (30.6)	1830 (30.0)	955 (25.9)	
Radiation alone	494 (14.9)	96 (16.6)	80 (22.8)		734 (17.2)	1084 (17.8)	764 (20.7)	
Chemotherapy alone	48 (1.5)	96 (1.6)	80 (1.6)		66 (1.6)	84 (1.4)	74 (2.0)	
Surgery + radiation	647 (19.6)	972 (16.7)	861 (17.5)		800 (18.8)	1022 (16.7)	658 (17.8)	
Surgery + chemotherapy	236 (7.1)	397 (6.8)	371 (7.6)		308 (7.2)	431 (7.1)	265 (7.2)	
Radiation + chemotherapy	275 (8.3)	593 (10.2)	439 (8.9)		357 (8.4)	615 (10.1)	335 (9.1)	
Surgery, radiation + chemotherapy	363 (11.0)	704 (12.1)	493 (10.0)		453 (10.6)	710 (11.6)	397 (10.7)	
Other treatments	21 (0.6)	62 (1.1)	21 (0.4)		23 (0.5)	59 (1.0)	22 (0.6)	
Unknown	151 (4.6)	282 (4.8)	269 (5.5)		217 (5.1)	265 (4.3)	220 (6.0)	

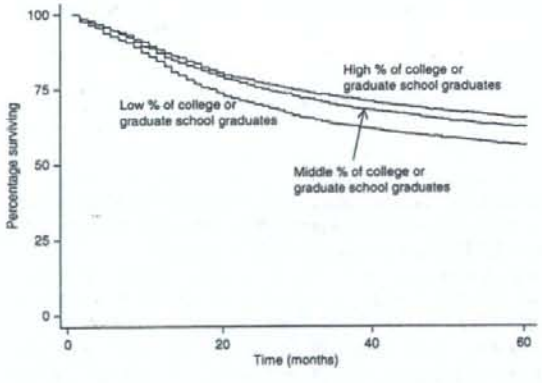

Fig. 2. Kaplan–Meier survival curves by socioeconomic status (SES) (education) for cervical cancer patients.

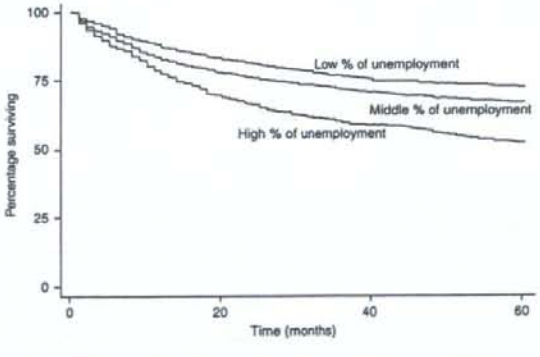

Fig. 3. Kaplan–Meier survival curves by socioeconomic status (SES) (unemployment) for corpus cancer patients.

Prognostic factors such as age, cancer stage, histology and treatment were each significantly related to cumulative 5-year survival for both cervical and corpus cancer patients ($P < 0.0001$) (Table 3). Cumulative 5-year survival for younger and older women was broadly comparable for cervical and corpus cancer. Cumulative 5-year survival for both cervical and corpus cancer patients was worse for distant stage cases compared to more localized stages. The cumulative 5-year survival of squamous carcinomas (65.1%) and adenocarcinomas (54.8%) for cervical cancer patients differed from survival for corpus cancer patients (48.9% and 69.7%, respectively). The worst 5-year survival among corpus cancer patients was 29.5% for sarcomas.