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	10.84	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

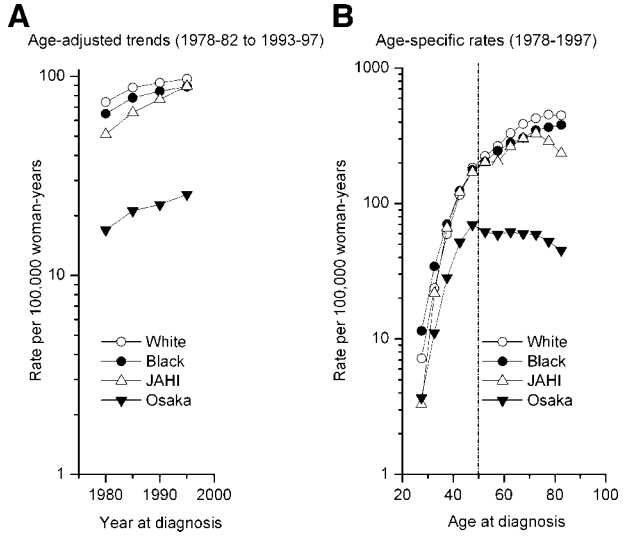

Figure 1. Breast cancer incidence rates among Whites, Blacks, and JAHI in the United States (nine SEER areas) and Osaka, Japan. **A,** trends in age-adjusted rates by calendar-period (1978-1982, 1983-1987, 1988-1992, and 1993-1997). **B,** age-specific rates for the study period 1978 to 1997.

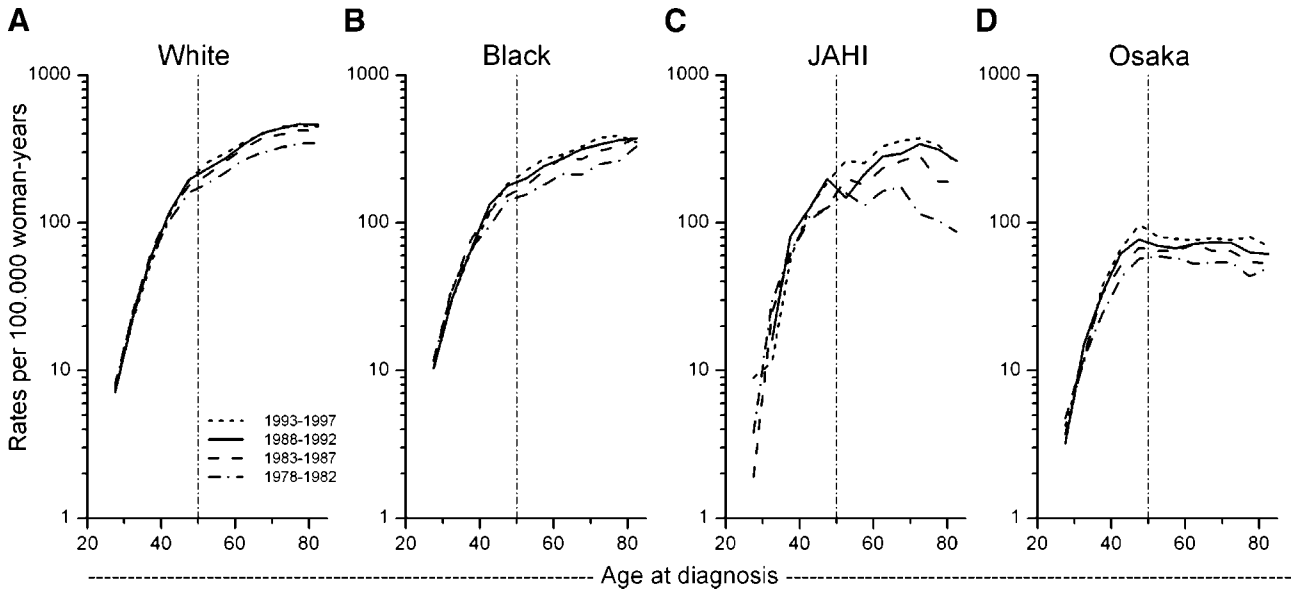

Figure 2. Observed cross-sectional age-specific breast cancer incidence rates by calendar-period (1978-1982, 1983-1987, 1988-1992, and 1993-1997). **A,** Whites in SEER. **B,** Blacks in SEER. **C,** JAHI in SEER. **D,** native Japanese in Osaka, Japan.

(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).

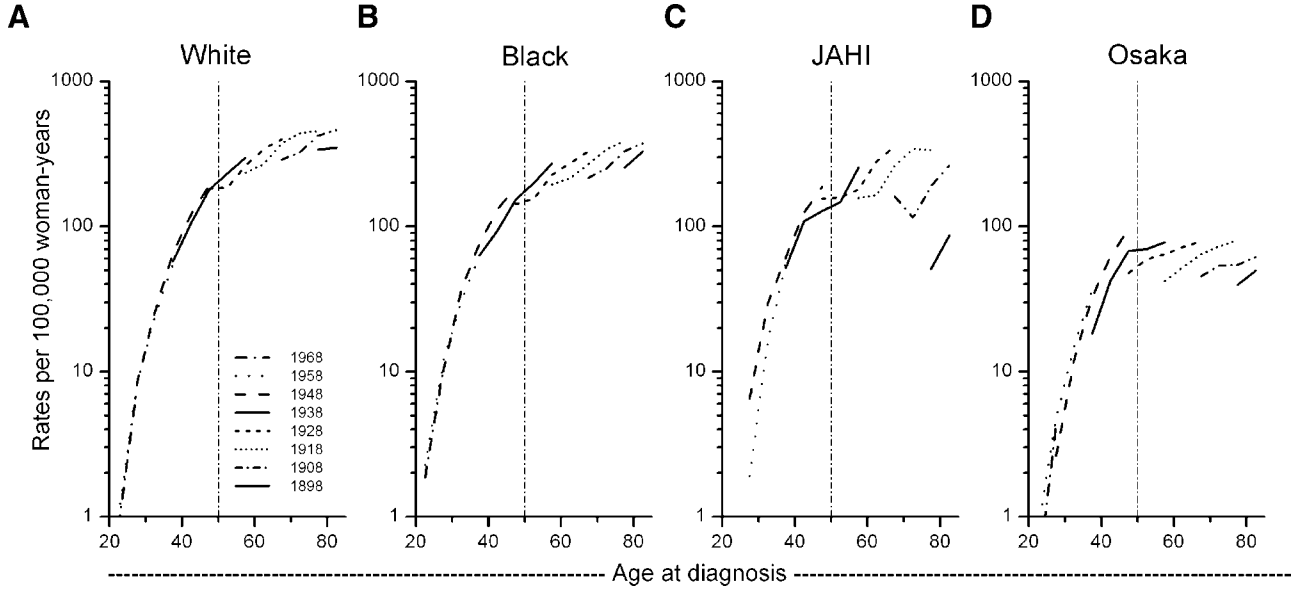

Figure 3. Observed longitudinal age-specific breast cancer incidence rates by the mid-year of birth-cohort (1898, 1908, 1918, 1928, 1938, 1948, 1958, and 1968). **A,** Whites in SEER. **B,** Blacks in SEER. **C,** JAHI in SEER. **D,** native Japanese in Osaka, Japan.

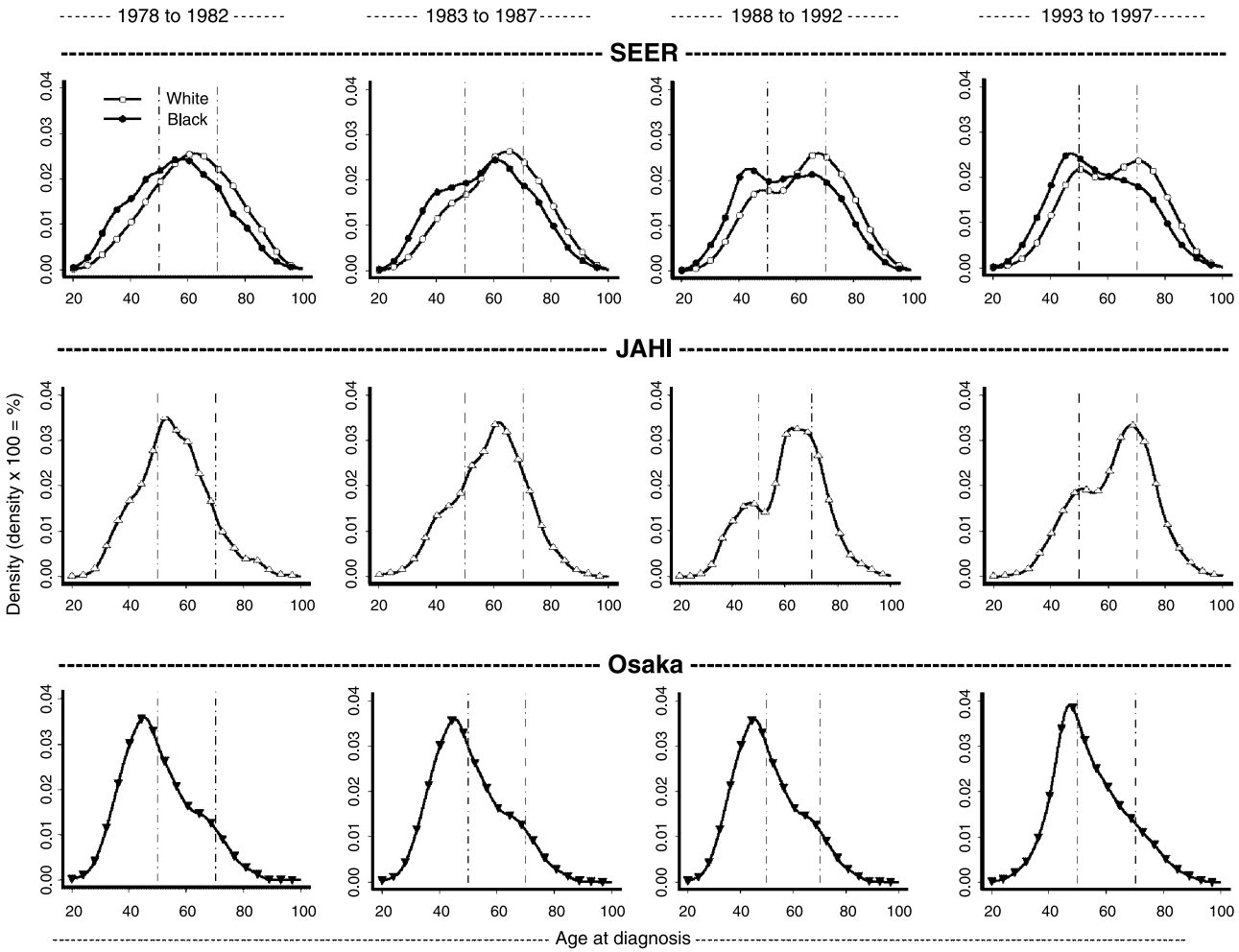

Figure 4. Age distributions among Whites, Blacks, and JAHI in the United States (nine SEER areas) and Osaka, Japan during the calendar-periods 1978 to 1982, 1983 to 1987, 1988 to 1992, and 1993 to 1997. The probability density function is a smoothed estimate of the frequency of women diagnosed at a given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