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Female Breast Cancer Incidence Among Asian and Western Populations: More Similar Than Expected

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Abstract

Background: Previous reports suggested that female breast cancer is associated with earlier ages at onset among Asian than Western populations. However, most studies utilized cross-sectional analyses that may be confounded by calendar-period and/or birth cohort effects. We, therefore, considered a longitudinal (forward-looking) approach adjusted for calendar-period changes and conditioned upon birth cohort.

Methods: Invasive female breast cancer data (1988–2009) were obtained from cancer registries in China, Hong Kong, South Korea, Taiwan, Singapore, and the United States. Age-period-cohort models were used to extrapolate longitudinal age-specific incidence rates for the 1920, 1944, and 1970 birth cohorts.

Results: Cross-sectional age-specific incidence rates rose continuously until age 80 years among US white women, but plateaued or decreased after age 50 years among Asian women. In contrast, longitudinal age-specific rates were proportional (similar) among all Asian countries and the United States with incidence rates rising continuously until age 80 years. The extrapolated estimates for the most recent cohorts in some Asian countries actually showed later ages at onset than in the United States. Additionally, over successive birth cohorts, the incidence rate ratios (IRRs) for the longitudinal curves converged (narrowed) between Asian and US white women.

Conclusions: Similar longitudinal age-specific incidence rates along with converging IRRs indicate that the age effects for invasive breast cancer are more similar among Asian and Western populations than might be expected from a solely cross-sectional analysis. Indeed, the Asian breast cancer rates in recent generations are even surpassing the historically high rates in the United States, highlighting an urgent need for efficient prevention and treatment strategies among Asian populations.

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Based upon GLOBOCAN 2012, the estimated age-standardized incidence rate (ASR) for invasive female breast cancer in Asia is 29.1 per 100 000 women-years, which is 30% of Northern America and Europe (ASR: 91.6 and 71.1 per 100 000 women-years, respectively) (1). However, incidence rates have been increasing rapidly in Asian countries and breast cancer is now the most frequently diagnosed cancer and the second leading cause of cancer death among Asian women (2,3).

Previous studies have also shown that the age-specific incidence rates of breast cancer have a different pattern among Asian from Western populations and is characterized by an earlier ages at onset (2,4–6). That is, in contrast to the continuous rise in the age-specific rates with advancing age among Western women (7), rates plateau or decrease after age 50 years among Asian women (2,3,5,8). Explanations for this early-onset incidence rate pattern range from calendar-period effects (changes in case ascertainment and/or screening for all age groups at a given point in time) and/or birth cohort effects (changes in risk factors over successive generations) (9–12) to distinct age-specific etiology (6,13) or biology (4,8,14,15).

However, nearly all previous descriptive studies relied on the cross-sectional assessment of the age-specific biology (2,4,5,16), which can be misleading at best or incorrect at worst because of biases related to calendar-period and/or birth cohort effects (9,17). For example, calendar-period or screening effects might not be applied to all birth cohorts equally, and a progressive increase in risk from one cohort or generation to the next could blunt the age-specific incidence rate curve among older women (12,18). To gain insight into the age-specific effects for breast cancer, a more accurate assessment of age incidence is derived from a longitudinal (forward-looking or prospective) analysis (17).

Therefore, in this study, we examined longitudinal age-specific incidence rates in five Asian countries/regions obtained from age-period-cohort framework (19) and compared the patterns with longitudinal incidence in the United States in order to assess similarities and differences in the age effects while accounting for the influences of secular changes (calendar-period and birth cohort effects) (17). This unique study was possible because we now have two decades of high-quality population-based cancer registry data from five Asian countries/regions that can be compared with data from the United States.

Methods

Study Population

We obtained invasive female breast cancer case (ICD-10 Code C50) and population data from the Cancer and/or National Statistic Registries in five Asian countries/regions (mainland China, Hong Kong, South Korea, Singapore, and Taiwan). Study subjects included cases diagnosed from 1988 through 2009 (2000 through 2009 for South Korea) and restricted to women age 30 to 79 years. Registry specifics are shown in Table 1 and have been described elsewhere (11,12,20–25). Data from mainland China do not cover Hong Kong or Taiwan, where cancer registries were established and have been maintained independently from China. For comparison, we obtained invasive breast cancer incidence data among US white women from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) 9 Registries Database (SEER 9 Regs Research Data, Nov 2012 Sub [1973–2010]) (20). This study was exempted from the review by the National Institutes of Health (NIH) Office of Human Subject Research because it did not involve interaction with human subjects and/or use personal identifying information (OHSRP No.12079).

Statistical Analysis

We analyzed the observed age-standardized incidence rates (ASRs) per 100 000 women-years and the cross-sectional age-specific incidence rates. Rates were age-standardized to the 2000 US population by the direct method (26). Temporal trends in the ASR were quantified with the estimated annual percentage change (EAPC) of the ASR, using weighted log-linear regression (27).

We used age-period-cohort models to adjust the observed data for the interrelated effects between age at diagnosis, year of diagnosis (period), and year of birth (cohort). To facilitate age-period-cohort analysis, we used equally spaced two-year age groups and two-year time periods among women age 30 to 79 years. We had 25 two-year age groups (30-31,32-34,78–79) and 11 two-year time periods (1988–1989, 1990–1991, …, and 2008–2009), spanning 35 partially overlapping four-year birth cohorts referred to by midyear of birth (1910, 1912, …, and 1978) for all countries except for South Korea. South Korea had the same number of age groups but only five two-year time periods (2000–2001, 2002–2003, …, and 2008–2009) (Supplementary Figure 1 and Supplementary Table 1, available online).

Age-period-cohort parameters and functions included the net drift and longitudinal age-specific incidence rates (17,19). Net drift is the sum of linear trends in the period and cohort effects, and is the age-period-cohort model analog of the EAPC. The longitudinal age-specific incidence rate curve represents an extrapolation of age-specific experience of all of the cohorts in the study. By construction, it is conditioned on a reference cohort and adjusted for period changes. To compare longitudinal age incidence curves over successive cohorts, we used three reference birth-cohorts: 1920 (early cohort), 1944 (midcohort), and 1970 (recent cohort). Given the short time period for data of South Korea, the 1922 birth cohorts was used as reference instead of the 1920 birth cohort for the early cohort (Supplementary Figure 1 and Supplementary Table 1, available online). Age groups at which the reference cohorts were directly observed in the registries were indicated as shaded areas (dark gray area: 68–79 years, 44–65 years, and 30–39 years for 1920, 1944, and 1970 birth cohort, respectively) in the plots, as were the forward and backwards extrapolations (Figure 3).

To quantify the differences in longitudinal age incidence, relative incidence rates for each Asian country compared with the United States were expressed as incidence rate ratios (IRRs) with 95% confidence intervals (CIs) for the central age group (74–75 years, 54–55 years, and 34–35 years for 1920, 1944, and 1970 birth cohort, respectively) for each reference cohort.

Age-adjusted secular trends were plotted by age group on a log-rate by linear time scale. Age-specific incidence rates were plotted on a log-rate by log-age scale. All statistical tests were two-sided and considered significant when *P* values were under .05. Statistical analyses were conducted using MATLAB R2012b (MathWorks Inc., Natick, MA).

Results

Our study included 388 242 Asian cases and 266 482 US white cases age 30 to 79 years diagnosed from 1988 through 2009 (Table 1). Figure 1 shows the standard cross-sectional age incidence curves for breast cancer in Asian countries and among US whites from 1988 to 2009. Among US white women, the incidence rates for the

Table 1. Descriptive statistics for invasive female breast cancer (1998–2009) in five Asian countries/regions and the United States

Cancer registries and screening practices	China (23)	Hong Kong (21)	South Korea (21,23)	Singapore (22,24)	Taiwan (12,25)	US (SEER 9) (20)
Study participants						
Study period	1988–2009	1988–2009	2000–2009	1988–2009	1988–2009	1988–2009
Number of case patients (age 30–79 y)	138 279	35 733	99 984	20 728	93 518	266 482
ASR per 100 000 women-years (95% CI)	59.3 (59.0 to 59.6)	91.3 (90.4 to 92.3)	66.0 (65.6 to 66.4)	116.2 (114.6 to 117.8)	80.6 (80.0 to 81.0)	206.3 (205.5 to 207.1)
EAPC, %/y (95% CI)	2.18 (2.02 to 2.29)	2.02 (1.82 to 2.23)	6.38 (5.98 to 6.79)	2.65 (2.37 to 2.93)	5.64 (5.50 to 5.77)	-0.24 (-0.31 to -0.17)
Net drift, %/y (95% CI)	2.04 (1.92 to 2.16)	1.99 (1.81 to 2.18)	6.99 (6.71 to 7.28)	2.87 (2.61 to 3.13)	5.97 (5.82 to 6.11)	-0.11 (-0.17 to -0.04)
Cancer registries						
Year registration began	1960s for regional; 1998 for 30 regions; 2008 for 56 regions from 10 provinces*	1963	1980 for regional; 1999 for entire population	1968	1979	1943 for Connecticut; 1973 for SEER
Registry coverage of whole population, % (y)	6.21 (2008)	100 (2003)	100 (1999)	97.8 (1968–1977)	80 (2002); 97 (2008)	9.4 (SEER 9)
Death certificate only, % (y)	0.44 (2008)	1.4 (1998–2002)	1.5 (1999–2001)	0 (1998–2002)	0†	0.68 (2009)†
Screening practices						
Year screening program began	N/A	1991 (37)	1999 (38)	2002 (39,40)	2002 (36,41,42)	1980s (43,44)
Screening program type	No population-based screening	Government-subsidized screening program‡	National screening policy with national program implementation	Government-subsidized screening program	Fully government-subsidized screening program	Other
Age groups covered, y	N/A	N/A	40–75+	40–75+	40–69§	40–75+
Participation rate, %	N/A	Not reported	33.2 (2004); 55.2 (2009)	Not reported	3 (2003); 32.5 (2012)	66.5

* National Central Center started collecting data from 56 regional registries since 2006, which did not include the Hong Kong registry.
† All types of cancer.
‡ Either self-financed private breast screening programs or partially subsidized by the government.
§ Women age 40 to 44 years are covered only when having family history of breast cancer within second degree.

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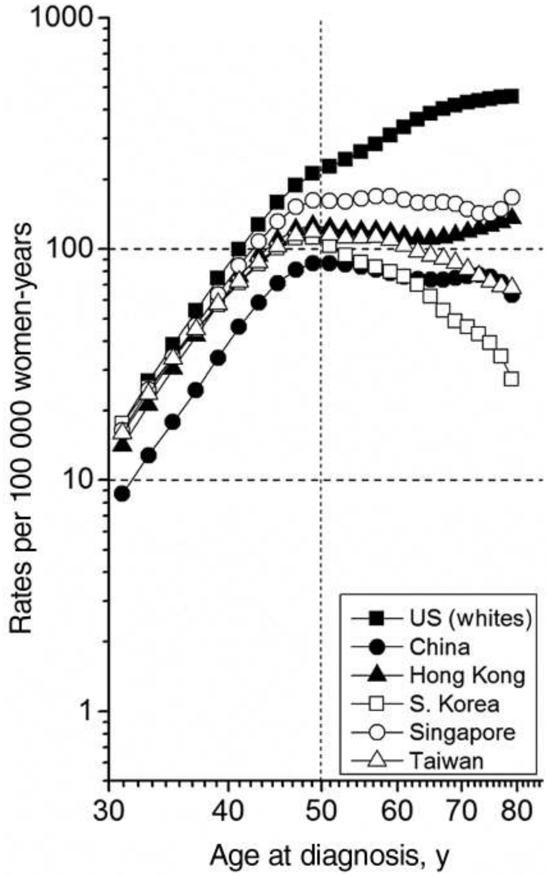

Figure 1. Cross-sectional age-specific breast cancer incidence rates. The age-specific incidence rates are plotted as log rates by log age over the entire study period.

cross-sectional age incidence curve rose rapidly with advancing age until age 50 years, then continued to rise at a slower pace, peaking around 460 per 100 000 women-years near age 80 years. In contrast, cross-sectional rates in Asian countries either plateaued after age 50 years such as in Singapore and Hong Kong with a slight increase near age 80 years, or declined continuously in Taiwan, China, and South Korea with peak incidence rates of 90 to 170 per 100 000 women-years. APC models were successfully fitted to the observed country-level data, and the goodness of fit was confirmed by examining the consistency of the observed to the fitted age-specific incidence rates, as previously described (28).

From 1988 to 2009, overall ASRs ranged from 59.3 to 206.3 per 100 000 women-years from China to the United States (Table 1). Among US white women, the overall ASR declined slightly with an EAPC of -0.24% per year (95% CI = -0.31 to -0.17) with qualitatively similar annual percentage changes across age groups (Figure 2). In contrast, the overall ASRs rose among all Asian countries with significant EAPCs (Table 1) and also increased across age groups with steeper rates of change among women age 50 years or older than younger than age 50 years (Figure 2). South Korea had the highest EAPC of 6.38% per year (95% CI = 5.98 to 6.79), followed by Taiwan, Singapore, China, and Hong Kong. Corresponding net drifts showed the same ranking and ranges as the EAPCs, with the highest net drift observed in South Korea at 6.99% per year (95% CI = 6.71 to 7.28) and the lowest in Hong Kong at 1.99% per year (95% CI = 1.81 to 2.18) (Table 1). Across all age groups, the ASRs rose rapidly in South Korea and Taiwan, consistent with their high overall net drifts. Notably, the rates among women age 30 to 49 years in all Asian countries attained values similar to rates among US white women in recent years, except for China.

Figure 3 shows longitudinal age incidence curves for successive birth cohorts (Figure 3, A-C) and relative incidence rates in Asian countries/regions compared with the United States expressed as IRRs (Figure 3, D-F). Longitudinal age-specific rates were proportional (similar) among all Asian countries and the United States, with incidence rates rising continuously until age 80 years. Among US white women, the shape of the longitudinal age-specific incidence curve was similar to the cross-sectional curve (Figure 1) across all reference birth cohorts (Figure 3, A-C). However, among Asian women, in constrast to the cross-sectional rates, (Figure 1), the extrapolated longitudinal rates rose continuously with advancing age across all birth cohorts (Figure 3, A-C). Notably, estimates for the youngest birth cohorts in Taiwan, South Korea, and Singapore showed even later ages at onset than in the United States (Figure 3C). Furthermore, IRRs between Asian countries vs the United States approached 1.0 (ie, narrowed and/or converged) over the successive birth cohorts (Figure 3, D-F). For the 1920 cohort (Figure 3D), IRRs ranged from as low as 0.05 in South Korea (95% CI = 0.04 to 0.07) to 0.28 in Singapore (95% CI = 0.23 to 0.34). However, for the 1970 birth cohort (Figure 3F), IRRs ranged from 0.43 in China (95% CI = 0.39 to 0.47) to as high as 1.02 in Taiwan (95% CI = 0.93 to 1.12).

Discussion

The age-specific incidence of invasive female breast cancers among Asian countries/regions and the United States appears more proportional (or similar) when analyzed with longitudinal (forward-looking or prospective) than cross-sectional methods. These results suggest that the age effects of breast cancer may be more similar between Asian and Western women than previously recognized. In fact, the cross-sectional age incidence curves can be heavily biased by substantial EAPCs and therefore do not represent what is observed in the longitudinal follow-up. Importantly, our analysis also indicates that the difference between age incidence curves is narrowing with IRRs approaching 1.0 between all five Asian countries/regions and the United States over successive birth cohorts. Specifically, the most recent birth cohorts in Taiwan, South Korea, and Singapore showed even later ages at onset than in the United States.

Net drift is conceptually similar to the EAPC of the ASR, quantifying the sum of the linear trend in calendar-period and birth cohort effects. All Asian populations/regions examined here had substantially high net drifts, ranging from 2.0% to 7.0% per year from Hong Kong to South Korea. Steep rates of increase have also been reported in Japan with EAPC values of 4.2% and 2.2% per year during the time periods 1968–1985 and 1985–2003 (29). Furthermore, in Japan, cross-sectional age-incidence curves were also similar to other Asian countries (2,6).

Unfortunately, because of the so-called nonidentifiability issue of the age-period-cohort model (19), the net drift cannot separate the linear component of birth cohort effects (ie, changing exposures) from the linear component of calendar-period effects (screening, case ascertainment, etc.). Previous studies in Japan (24), Hong Kong (11,25), Singapore (10,30), and Taiwan (12) suggested that rising breast cancer incidence was largely attributable to substantial birth cohort changes because of the adoption of a westernized lifestyle. Indeed, changes in reproductive risk factors such as earlier age at menarche (31), delayed age at first birth, low parity, reduced breastfeeding, and declining fertility rates (10,30,31) could contribute to generational (or birth cohort) effects. Notably, family planning campaigns in Singapore and South Korea (1960s through 1980s) and the

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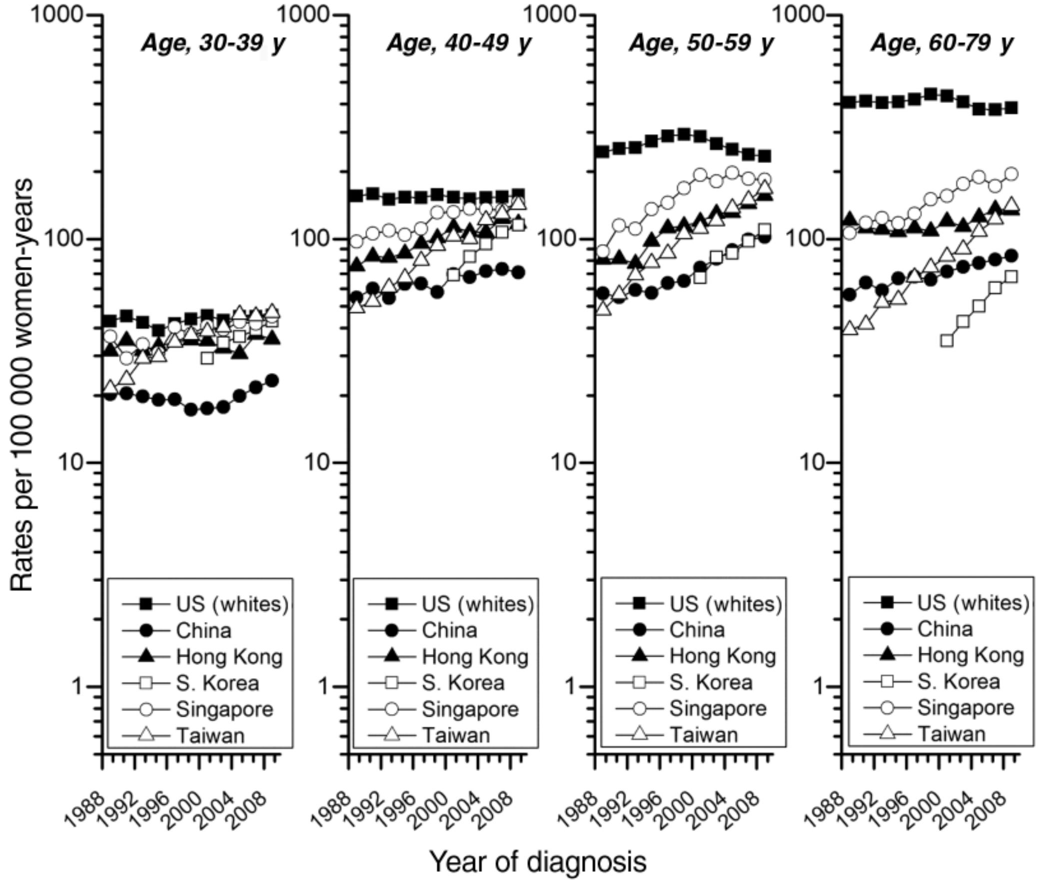

Figure 2. Trends in age-standardized incidence rates of breast cancer by age group from 1988 through 2009.

one-child policy in China (from the 1980s to the present) to curb increasing population growth might have substantial impact on the decline in fertility rates (10,16). Indeed, the total fertility rate decreased from five to six children per woman in the 1960s to 1.2 children per woman in Hong Kong, South Korea, and Singapore and 1.6 in China by the early 2010s (32). Dietary shifts towards fats and animal-source foods (33) as well as the trend toward increasing body mass index also could raise breast cancer risk among Asian women.

Moreover, we cannot exclude a calendar-period or screening effect, particularly in South Korea (34), Singapore (35), and Taiwan (36) where population-based screening programs were implemented between the late 1990s and early 2000s and have been effectively executed in more recent years (Table 1). In particular, women born between the 1960s and 1970s, who were in their 40s between 2000 and 2010, would be the first generation influenced by population-based screening programs. Accordingly, this would be reflected in the 1970 birth cohort–specific rates which were comparable or even higher in South Korea, Singapore, and Taiwan than in the United States (Figure 3, C and F). Considering that initial screening may detect an undiagnosed reservoir of preclinical breast cancers, high net drifts could be at least partly because of the screening effect, even though many of the younger women and populations included in this study were not eligible for organized screening programs. Moreover, rapid case ascertainment in a new and expanding cancer registry might also partially account for some of the high drift in Asian countries, especially in China where the nationwide cancer registry began relatively later than other countries and coverage varied over the study period. Changes towards early stages over time might reveal the relative impacts of screening, case ascertainment, and/or catchment artifacts, but unfortunately was beyond the scope of this manuscript and not feasible because stage data were not available.

Besides the usual concerns that are associated with registry-based retrospective and descriptive studies, the major limitation of our study is that the longitudinal age-specific rates were extrapolated from the age-period-cohort model. However, all of the data were fitted successfully (28). Additionally, low coverages of cancer registries in large territories such as China and the United States may limit the representativeness of the results. Nonetheless, all countries included in our analysis have high-quality nationwide cancer registries and the analyzed data met IARC standards for quality and comparability (Table 1). Hence, the results reported here are unlikely to be simply caused by artifacts of an increasing catchment over time.

In summary, the shape of the longitudinal age incidence curves studied for breast cancer in Asian countries appears proportional or similar to that of the United States. Furthermore, our analysis suggests that breast cancer incidence rates in recent cohorts (generations) in Asian countries are converging and even surpassing the historically high rates in the United States, highlighting an urgent need for efficient prevention and treatment strategies among Asian populations. Finally, our results highlight the importance of using longitudinal rather than cross-sectional curves when comparing age incidence patterns in different populations in

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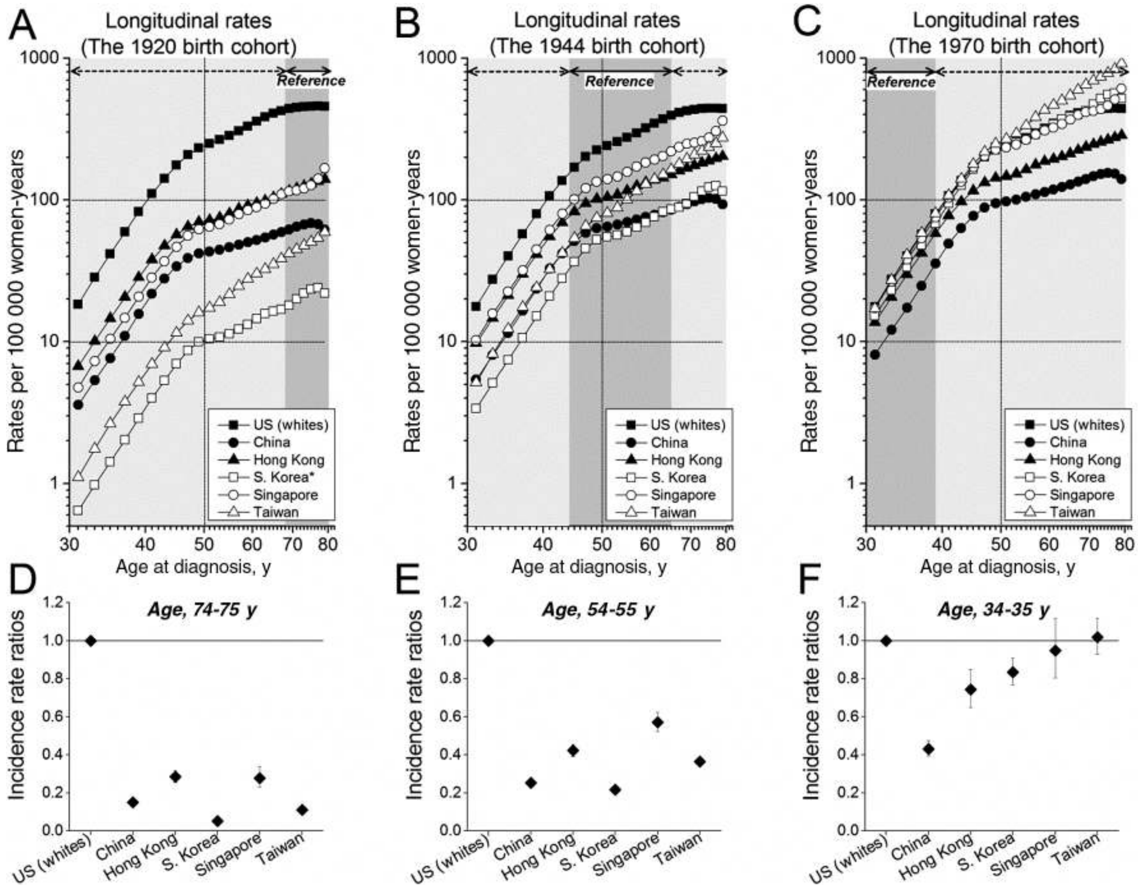

Figure 3. Longitudinal age-specific breast cancer incidence rates and corresponding incidence rate ratios. **A)** 1920 birth cohort. **B)** 1944 birth cohort. **C)** 1970 birth cohort. The longitudinal rates are plotted as log rates by log age, adjusted for calendar-period effects and conditioned upon the reference birth cohort. **Shaded areas** represent the age groups for which each reference cohort was directly observed in the corresponding cancer registries; see text for further details. **D)** 1920 birth cohort. **E)** 1944 birth cohort. **F)** 1970 birth cohort. The IRR calculation was based upon the central age group in each shaded area with the US whites arbitrarily assigned an IRR of 1.0. *1922 birth cohort. IRR = incidence rate ratio.

the presence of high net drift values. Future analytic studies are needed to quantify the proportion of incidence rate increases in Asian countries that are attributable to calendar-period and/or screening vs birth cohort effects, and to investigate the impact of these changes upon the distribution of the breast cancer molecular subtypes.

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Notes

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