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Article

Contrasting Epidemiology and Clinicopathology of Female Breast Cancer in Asians versus the US Population

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Abstract

Background: The incidence of breast cancer among younger East Asian women has been increasing rapidly over recent decades. This international collaborative study systemically compared the differences in age-specific incidences and pathological characteristics of breast cancer in women between East Asian and predominantly European ancestry.

Methods: We excerpted analytic data from six national cancer registries (979,675 cases) and eight hospitals (18,008 cases) in East Asian countries/regions and, for comparisons, from the United States Surveillance, Epidemiology, and End Results (SEER) program database. Linear regression analyses of age-specific incidences of female breast cancer and logistic regression analyses of age-specific pathological characteristics of breast cancer were performed. All statistical tests were two-sided.

Results: Unlike female colorectal cancer, the age-specific incidences of breast cancer among East Asian women aged ≤ 59 years increased disproportionally over recent decades relative to rates in United States contemporaries. For years 2010−2014, the estimated age-specific probability of estrogen receptor (ER) positivity increased with age in American patients, whereas that of triple negative breast cancer (TNBC) declined with age. No similar trends were evident in East Asian patients: their probability of ER positivity at age 40–49 years was statistically significantly higher (odd ratio [OR] = 1.50, 95% confidence interval [CI]: 1.36–1.67, $P < .001$) and of TNBC was statistically significantly lower (OR = 0.79, 95% CI: 0.71–0.88, $P < .001$), whereas the probability of ER positivity at age 50-59 years was statistically significantly lower (OR = 0.88, 95% CI: 0.828–0.95, $P < .001$). Subgroup analyses of SEER data showed similarly distinct patterns between East Asian American and white American patients.

Conclusion: Contrasting age-specific incidences and pathological characteristics of breast cancer between East Asian and American women, as well as between East Asian Americans and white Americans, suggests racial differences in the biology.

Although Asian women have lower incidence rates of invasive breast cancer than Western women, the incidence of female breast cancer in East and South-East Asia has increased rapidly over the past 40 years.[1-3] Previous age-period-cohort analyses showed a strong cohort effect on female breast cancer incidence in Asia,[4,5] which has resulted in notable differences in age-specific incidences of breast cancer between Asian and Western females. Specifically, the incidence of breast cancer peaked at around age 50 years in Hong Kong, Japan, Korea, and Taiwan, compared to approximately 70 years in the United States (US).[2,3,6,7] Incidence rates of breast cancer among younger women in some East Asian populations have even surpassed that of recent generations in the US.[8]

This strong cohort effect suggests that lifestyle and environmental changes might be major influences on the pathogenesis of breast cancer in Asian women. Rapidly increasing breast cancer incidence in East Asia has primarily been attributed to 'westernization' including: (1) dietary factors (eg, high fat intake, low vegetable consumption, and low soybean intake); and (2) reproductive factors (eg, delayed childbearing, low parity, less breast feeding, early menarche, and late menopause).[9,10] If rising breast cancer incidence rates were simply due to westernization, emerging age-specific patterns in modern Asian women would eventually resemble those of Western populations. Therefore, a recent study showed

longitudinal age-specific incidence rates with converging incidence rate ratios, and conclude that the age effects for invasive breast cancer were more similar among Asian and Western populations than might be expected according to the extrapolated estimates.[8] However, some evidence suggests racial effects on breast carcinogenesis and tumor biology in younger women. For example, overweight/obesity was inversely associated with premenopausal breast cancer risk in Europids and African Americans, but positively correlated in Asian women.[11,12] A meta-analysis of breast cancer risk found a protective effect of soybean consumption in Asian and Asian American women, but not in Europids.[13] Additionally, 13 genetic polymorphisms associated with breast cancer in Europeans failed to discriminate breast cancer risk in Singaporean Chinese, Malays, or Indians.[14] Recently, multi-omics profiling of breast cancers in younger Korean patients has revealed distinctive molecular signatures, suggesting a more immune-active tumor microenvironment compared with that of western counterparts.[15]

Given the highly debatable issue about the similarity or dissimilarity in epidemiology and tumor biology of young female breast cancer between East Asia and Western countries, we conducted this multi-region study and explored the underlying pathophysiologic factors. We systematically compared temporal trends in age-specific incidences and pathological characteristics of female breast cancer

between East Asians, Asian Americans, and non-Asian Americans. Female colorectal cancer was used as a control for the effect of westernized lifestyle.[16, 17]

Methods

Registries and databases used for data collection

The incidence rates of female breast cancer and female colorectal cancer in 5-year intervals for the years of 1973−2014 were obtained from the National Cancer Center of Japan,[18] the Korea Central Cancer Registry,[19] the National Registry of Disease Office of Singapore,[20] and the Taiwan Cancer Registry[21] (**Table 1**). The age-specific incidence data for China and Hong Kong were excerpted from the International Agency for Research on Cancer database,[22] but only data from Shanghai were retrieved for China because the other Chinese registries covered shorter time periods. For comparisons with the US, age-specific incidence data were retrieved from the US Surveillance, Epidemiology, and End Results (SEER) database.[23] Age-specific incidence rates of female breast cancer were estimated from 979,675 cases in East Asians and 645,633 in Americans. The timeframes of age-specific incidence data varied according to the years available in national registries; for example, the female breast cancer incidence rates of Japan were not available until 2003. This study was

approved by the Institutional Review Boards of National Taiwan University Hospital (201510027RINB).

To investigate the age-specific pathological characteristics of female breast cancer, hospitals in Beijing, Hong Kong, Japan, South Korea, Singapore, and Taiwan provided records of breast cancers diagnosed during years 2010−2014 (**Table 1**). For comparisons with the US, age-specific pathological features of breast cancer among women diagnosed during 2010−2013 were ascertained from the SEER database.[24] Age-specific clinicopathological characteristics of female breast cancer were determined based on 18,008 cases in East Asians and 244,819 in Americans. Positivity for estrogen receptor (ER+), progesterone receptor (PR+), and human epidermal growth factor receptor 2 (HER2+) were defined according to the criteria of the individual hospitals. For data specifying proportions of ER and PR expression, we defined 1% as the threshold for ER+, based on the American Society of Clinical Oncology/College of American Pathologists guideline,[25] and 10% as the cut-off for PR+, because past studies showed that a higher PR+ threshold has better prognostic value.[26,27] Either ER+ or PR+ was defined as hormone receptor positive (HR+). Tumors with negative ER, PR, and HER2 staining were defined as triple-negative breast cancer (TNBC).

Using the SEER 18 database,[24] we compared the age-specific pathological characteristics of female breast cancer from years 2010–2013 between Chinese, Japanese, and Korean Americans ('C-J-K' Asian Americans) and white Americans. The corresponding age-specific incidences of female breast and colorectal cancer from years 1990–2010 were estimated from the SEER 11 database.[28]

Statistical analysis

We plotted age-specific incidence rates of female breast and colorectal cancers in 5-year intervals for years 1973–2014 for China (Shanghai), Hong Kong, Japan, South Korea, Singapore, Taiwan, and the US (SEER data). We performed multivariate linear regression analyses of age-specific incidence rates of female breast and colorectal cancers, averaged for years 2011−2014, using data from all national registries, except China (Shanghai) and Hong Kong, due to insufficient data (**Table 1**). We then plotted predicted age-specific incidence rates against age-groups to examine their congruence with corresponding observed values for each country/region. The timeframe of 2011−2014 was chosen to reflect the contemporary impact of westernized lifestyle.

Next, we used data from participating hospitals in East Asia and US SEER data to plot observed age-specific pathological characteristics of female breast cancer,

including the proportions of ER+, PR+, HER2+, HR+/HER2−, HR−/HER2−, HR+/HER2+, HR−/HER2+, and histological grade III subtypes. We then fitted multiple logistic regression models for grouped binomial data including the proportions of ER+, PR+, HER2+, HR+/HER2−, HR−/HER2−, HR+/HER2+, HR−/HER2+, and histological grade III subtypes of female breast cancer with data pooled for years 2010−2014. We also charted conditional-effect plots of predicted age-specific probabilities of ER+, PR+, HER2+, HR+/HER2−, HR−/HER2−, HR+/HER2+, HR−/HER2+, and histological grade III breast cancer subtypes in 10-year intervals for East Asia and the US, to examine their congruence with corresponding observed age-specific positive proportions.

Finally, we plotted the age-specific proportions of ER+, PR+, HER2+, HR+/HER2−, HR−/HER2−, HR+/HER2+, HR−/HER2+, and histological grade III subtypes in 10-year intervals for years 2010-2013 against age groups for C-J-K Asian Americans and white Americans, with pointwise two-sample *z* tests to verify racial differences in the age-specific pathological characteristics of female breast cancer.

A two-sided *P* value ≤ .05 was considered statistically significant. Statistical analysis was performed using R 3.3.1 software (R Foundation for Statistical Computing, Vienna, Austria).

Results

Trends in age-specific incidence of breast cancer between the US and East Asia, and between non-Hispanic white Americans and Asian Americans

Supplementary Figure 1 shows the age-specific incidence rates of female breast cancer and female colorectal cancer over years 1973−2014 in the US and East Asian countries/regions. In the US, breast cancer incidence among women aged 50–84 years rose over time, and predominantly affected women aged ≥60 years since 1986 (**Supplementary Figure 1A**, left panel). By contrast, in East Asian countries/regions, the incidence of breast cancer increased over time among women aged ≥ 40 years, becoming disproportionally higher in women aged 40−75 years with concave downward or flat curves (**Supplementary Figures 1B–1G**, left panel). Patterns of age-specific female breast cancer incidence over time were quite different in the US and East Asia. Conversely, patterns of age-specific female colorectal cancer incidence over time in the US and East Asia were rather similar (**Supplementary Figures 1A–1G**, right panel).

The incidence of colorectal cancer among women aged ≥55 years increased monotonically with age in the US and East Asia, but the index year from which this rise began varied between countries/regions; for example, the incidence in Taiwan

has risen sharply since 1995 (**Supplementary Figure 1B**, right panel). **Figures 1A and 1B** show the observed age-specific incidence rates of female breast and colorectal cancers for each country/region for years 2011–2014, and **Figures 1C and 1D**, their estimated age-specific incidence rates based on multiple linear regression models. Two multiple linear regression models contained only those covariates with non-zero regression coefficients (statistical significance reached in 31 of 90 comparisons and 26 of 90 comparisons for breast and colorectal cancers, respectively; the *P* values were .01 or less, shown in **Supplementary Table 1**) and fitted the observed data well (R^2 = 0.9919 and 0.9975 respectively). **Figures 1C and 1D** illustrate quite different patterns of age-specific female breast cancer incidence between the US and East Asia, but similar patterns of age-specific female colorectal cancer incidence.

To verify racial differences, we plotted age-specific incidence rates of female breast and colorectal cancers for years 1990−2010 with US SEER data for Chinese, Japanese, and Korean Americans, and non-Hispanic white Americans (**Supplementary Figures 1H–J**). Unlike those of female colorectal cancer, concave downward curves of age-specific female breast cancer incidence were apparent in C-J-K Asian Americans, and fell below those of non-Hispanic white Americans (**Figures 1E and 1F**).

Trends in the age-specific distributions of the immuno-phenotypes and histological grades of breast cancer between the US and East Asia

The observed proportion of ER+ increased gradually with age in US women (**Figure 2A**), but the proportions of HER2+, TNBC, and histological grade III decreased with age (**Figures 2B–2D**). However, age-associations of these immuno-phenotypes in hospital data from different East Asian countries/regions were not uniform (**Figures 2A–2D**). To elucidate the effects of age and country/region, we performed logistic regression analyses for probabilities of ER+, HER2+, TNBC, and histological grade III female breast cancer with US SEER data and pooled data from the eight East Asian hospitals over years 2010−2014 (**Supplementary Tables 2**); age-groups were <30, 30–39, 40–49, 50–59, 60–69, and ≥70 years, and, a dummy variable “Hospitals in East Asia” was specified (1 = hospital in East Asia, 0 = US). After adjusting for the unique effects of individual hospitals, the estimated probability of ER+ increased with age in the US, but no similar trends were evident in East Asian patients: their probability of ER positivity at age 40–49 years was statistically significantly higher (odds ratio [OR] = 1.50, 95% confidence interval [CI]: 1.36–1.67, $P < .001$) whereas the probability of ER positivity at age 50-59 years was statistically significantly lower (OR = 0.88, 95% CI: 0.82–0.95, $P < .001$). The estimated

probability of TNBC decreased with age in the US, but not in East Asia patients; their probability of TNBC positivity at age 40–49 years was 0.79 (95% CI: 0.71−0.88, *P* < .001) (**Supplementary Table 2**).

To visualize effect patterns, we made conditional effect plots of estimated age-specific probabilities of ER+, HER2+, TNBC, and histological grade III subtypes of female breast cancer for years 2010−2014 for the US and East Asia, based on our fitted multiple logistic regression models (**Supplementary Table 2**). Associations of these markers with age were quite different between American and East Asian women with breast cancer (**Figure 3**). As shown in **Supplementary Table 2**, the estimated age-specific probability of ER+ increased statistically significantly with age in US women (all *P* values associated with age ≤ .01), whereas those of HER2+, TNBC, and histological grade III breast cancer declined statistically significantly with age (all *P* values associated with age ≤ 0.005). In contrast, the estimated age-specific probability of ER+ in East Asian women with breast cancer peaked at age 40–49 years, HER2+ at 50–59 years, TNBC at all ages except 40–49 years, and histological grade III below age 30 years. We also applied this approach to analyzing the observed age-specific proportions of PR+, HR+/HER2−, HR+/HER2+, and HR−/HER2+ subtypes of female breast cancer in the US and the hospitals in East Asia (**Supplementary Figures 2 and 3**).

Distributions of age-specific pathological characteristics between Asian and white Americans

To verify racial differences, we analyzed the distributions of age-specific pathological characteristics between Asian and white Americans. Intriguingly, the differences between the curves plotted for age-specific probabilities of ER+, HER2+, and TNBC in C-J-K Asian Americans and white Americans (**Figures 4A–C**) resembled those observed between East Asian and US women (**Figures 3A–C**). The histological grade III tumors in C-J-K Asian Americans were more alike those of white Americans (**Figure 4D**) and different from those of East Asians (**Figure 3D**). In addition, the differences between the curves plotted for age-specific probabilities of PR+, HR+/HER2-, and HR-/HER2+ in C-J-K Asian Americans and white Americans (**Supplementary Figures 4A, 4B, and 4D**) resembled those observed between East Asian and US women (**Supplementary Figures 3A, 3B, and 3D**). The HR+/HER2+ tumors in C-J-K Asian Americans were more alike those of white Americans (**Supplementary Figure 4C**) and different from those of East Asians (**Supplementary Figure 3C**).

Discussion

This study identified age-specific pathological differences in breast cancer between Asians and non-Asians that may signify racial differences in its etiology and biology.

During the past four decades, the incidences of breast cancer and colorectal cancer in East Asian women have increased rapidly; the etiologies of both malignancies relate to diet and lifestyle (eg, physical inactivity, smoking, and drinking alcohol).[9,10] Consequently, the profile of increasing age-specific incidence of colorectal cancer in East Asian women closely resembled that in US women in recent years, suggesting that westernization during more than two decades in East Asian has indeed increased women's risk of colorectal cancer. Variation between East Asian countries/regions in when the age-specific incidence of female colorectal cancer began to rise, probably reflect differing speeds of westernization. However, markedly increasing breast cancer incidence in relatively younger East Asian women cannot be attributed solely to the effect of westernization.

Different distributions in age-specific pathological characteristics of female breast cancer between major hospitals in East Asian countries/regions and the US revealed a racial effect on the etiology of female breast cancer. Moreover, comparisons in age-specific incidence and pathological characteristics of female breast cancer between C-J-K Asian Americans and white Americans discriminated the effects of westernized lifestyle and racial ancestry.

It is difficult to disentangle the intertwined genetic and environmental influences without knowing how long the Asian American immigrants had lived in the US. Nevertheless, high probabilities of ER+ breast cancer in younger East Asian women and C-J-K Asian Americans imply that estrogen plays an important etiologic role in younger Asian women. Moreover, the higher probabilities of ER+ and PR+ and lower probability of TNBC in East Asian women who are younger than 50 compared with American women are consistent with previous studies. In Taiwan and Japan, women aged <50 years had higher probabilities of ER+ or PR+ and lower probability of TNBC than older ones.[29-31] Relatively high prevalences of ER+ and PR+ in Asian women aged 40−49 years indicate an estrogen-related causality, as the incidences of endometrioid carcinomas of uterus and ovary have also increased rapidly in younger East Asian women.[7,32,33] The latter cancer subtypes have highly prevalent hormone receptor expressions and are etiologically linked to estrogen exposure.

On the other hand, Asian women born after the 1960s have higher caloric and animal-based protein intake than ancestral generations, which may increase endogenous estrogen production and lead to earlier menarche.[34] Early studies conducted among premenopausal women in Japan,[35] China,[36, 37] and recent southeast Asian immigrants to Hawaii,[38] reported serum estradiol levels 30%−70% lower in Asians than white contemporaries. Yet, an immigration study published

approximately 10 years later found comparable plasma estradiol levels between Asian and Western premenopausal women,[39] and another study even showed a higher estradiol level in Asian Americans than Caucasians.[40] In addition to earlier menarche, drastically reduced fertility rates and delayed childbearing in East Asian countries[41, 42] could increase women's risk of breast cancer. Exogenous estrogen exposure by industrial and environmental estrogenic pollutants is another potential cause of breast cancer. The rapid industrialization during the 1960s in East Asia led to more exposures to cosmetic products, pesticides, and plastics that contained estrogenic ingredients during manufacturing or produced estrogenic pollutants after degradation.[43-46] Such changes of lifestyle, society, and environments in East Asia could interact with genetic predisposition to produce a unique profile of age-specific female breast cancer incidence. Direct comparisons of these potential risk factors and genetic predispositions between East Asian and European ancestry are warranted.

Although expressions of certain immuno-phenotypic markers were similar between C-J-K Asian Americans and East Asians, the age-specific probabilities of HR+/HER2+ and histological grade III tumors in C-J-K Asian Americans were more alike those of white Americans and different from East Asians. Thus, the differences between East Asians and C-J-K Asian Americans in lifestyle and environmental

exposures might also affect the clinicopathological characteristics and risk of breast cancer. For example, the consumption of green tea and soy products differs between East Asians and C-J-K Asian Americans. Some studies found that that green tea and soy isoflavone consumption among Asian women reduced their risks of breast cancer and recurrence.[47-49]

Finally, we acknowledge that this study has some limitations. First, national registry data covering certain time periods in some East Asian countries/regions were not available. Second, data from the participating hospitals in East Asia might not be nationally representative. However, this might not be a serious concern because one of the major findings concerning the unique age-specific probabilities of ER+ in East Asia evident in the hospital databases evaluated in this study was consistent with other studies that assessed the national registries in Taiwan[30] and Japan.[31] Third, as in a previous study using the US SEER data,[50] the criteria for ER and PR positivity could differ somewhat between participating hospitals. Nonetheless, the frequencies of low (1%–10%) ER and PR tumors were 4.3% and 12.8%, respectively, and the distributions of age-specific probabilities of ER and PR positivity were similar whether using 1% or 10% as the cutoff in this study (data not shown). In addition, the distributions were established separately in East Asian and US populations. Last, different cancer screening policies and accessibility of

screening tools in East Asian countries/regions and the US might affect the age-specific incidence rates of female breast cancer and colorectal cancer.

In summary, the proportions of key pathological features of breast cancer across different age groups in East Asian women were statistically significantly different from those of white American women but resembled those of C-J-K Asian Americans. Unlike colorectal cancer, lifestyle westernization cannot fully account for the rapidly increasing incidence of breast cancer in younger East Asian women. Interactions of race-associated genetic and environmental factors might exacerbate carcinogenesis in younger East Asian women with estrogen-related malignancies.

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Notes

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Author Contributions: Yen-Shen Lu had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Ching-Hung Lin, Seock-Ah Im, and Yen-Shen Lu. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Ching-Hung Lin, Fu-Chang Hu, and Yen-Shen Lu. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Fu-Chang Hu.

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Tables

Table 1. National and hospital data sources, sample sizes, and survey periods

	National		Hospital		
Country/Region	**Data Source**	**Years Covered**	**Data Source**	**Sample**	**Years Covered**
China	International Agency for Research on Cancer	Shanghai: 1988-2007	Beijing Cancer Hospital	316	2010-2012
Hong Kong	International Agency for Research on Cancer	1983-2007	Prince of Wales Hospital/ Chinese University of Hong Kong	630	2012
			University of Hong Kong, Hong Kong West Cluster Database	1655	2010-2014
Japan	National Cancer Center	Breast cancer: 2003-2012 Colorectal cancer: 1975-2012	Kyorin University Hospital	487	2010-2012
			National Cancer Center Hospital East	1464	2010-2014
Korea	Korea Central Cancer Registry	2002-2013	Seoul National University Hospital	5216	2010-2014
Singapore	National Registry of Diseases Office	1980-2014	Singapore General Hospital/ National Cancer Centre Singapore	4832	2010-2014

Taiwan	Taiwan Cancer Registry	1979-2013	National Taiwan University Hospital	3408	2010-2014
United States	National Cancer Institute, Surveillance, Epidemiology, and End Results (SEER) Program	SEER 9: 1973-2013 SEER 11: 1990-2010	National Cancer Institute, SEER Program	244819	SEER 18: 2010-2013

Figure legends

Figure 1. Age-specific incidence rates of female breast and colorectal cancers in East Asia and the US, and in SEER Asian Americans and non-Hispanic white Americans

(A). The observed age-specific incidence rates of female breast cancer in East Asia (*n* = 253840) and the US (*n* = 66230) for years 2011−2014. **(B)**. The observed age-specific incidence rates of female colorectal cancer in East Asia (*n* = 184055) and the US (*n* = 17688) for years 2011−2014. **(C)**. The estimated age-specific incidence rates of female breast cancer in East Asia and the US for years 2011−2014. **(D)**. The estimated age-specific incidence rates of female colorectal cancer in East Asia and the US for years 2011−2014. The estimated age-specific incidence rates shown in (C) and (D) were based on the fitted multiple linear regression models in **Supplementary Table 1**. **(E)**. The observed age-specific incidence rates of female breast cancer in SEER Asian Americans (*n* = 25665) and non-Hispanic white Americans (*n* = 683164) for years 1990−2010. **(F)**. The observed age-specific incidence rates of female colorectal cancer in SEER Asian Americans (*n* = 11982) and non-Hispanic white Americans (*n* = 240286) for years 1990−2010.

Figure 2. Observed age-specific probabilities of ER+, HER2+, TNBC, and Histological grade III female breast cancer in East Asia and the US

Age-specific clinicopathological characteristics of female breast cancer were determined based on 18008 cases from hospital data in East Asian countries/regions and 244819 cases from US SEER data for years 2010-2014. Abbreviations: ER+, Estrogen receptor positive; HER2+, Human epidermal growth factor receptor 2 positive; TNBC, Triple negative breast cancer; BCH, Beijing Cancer Hospital; PWH, Prince of Wales Hospital; WCD, West Cluster Database; KUH, Kyorin University Hospital; NCCHE, National Cancer Center Hospital East; SNUH, Seoul National University Hospital; SGH, Singapore General Hospital; NCCS, National Cancer Centre Singapore; NTUH, National Taiwan University Hospital; and SEER, Surveillance, Epidemiology, and End Results program.

Figure 3. Conditional effect plots of estimated age-specific probabilities of ER+, HER2+, TNBC, and Histological grade III female breast cancer in East Asia and the US for years 2010-2014

The estimated age-specific clinicopathological characteristics of female breast cancer were determined based on the fitted multiple logistic regression models of 18008 cases in East Asians and 244819 in Americans (**Supplementary Table 2**).

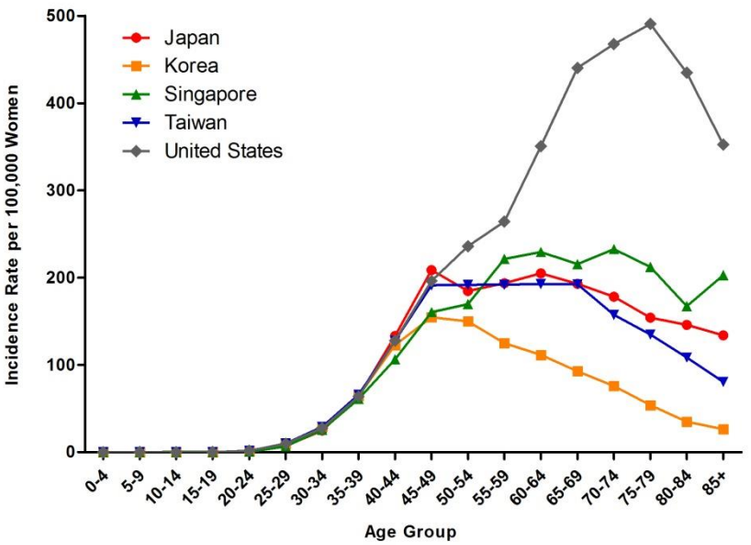
Abbreviations: ER+, Estrogen receptor positive; HER2+, Human epidermal growth factor receptor 2 positive; and TNBC, Triple negative breast cancer.

Figure 4. Observed age-specific proportions of ER+, HER2+, TNBC, and Histological grade III female breast cancer in SEER Asian Americans and white Americans for years 2010-2013

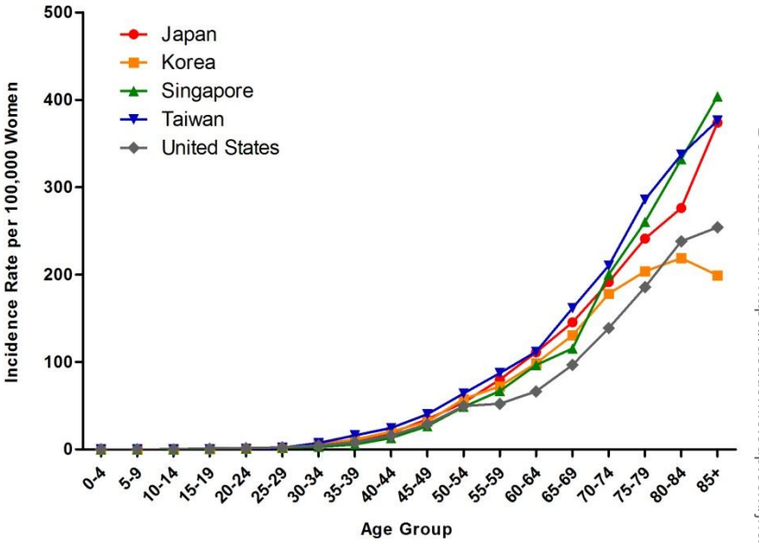
The age-specific proportions of ER+, HER2+, TNBC, and Histological grade III between 7185 C-J-K Asian Americans and 194524 white Americans were compared using two-sided pointwise two-sample z tests. The figures show the exact *P* values when *P* value is less than .05. Abbreviations: ER+, Estrogen receptor positive; HER2+, Human epidermal growth factor receptor 2 positive; TNBC, Triple negative breast cancer; and C-J-K, Chinese-Japanese-Korean.

Figure 1

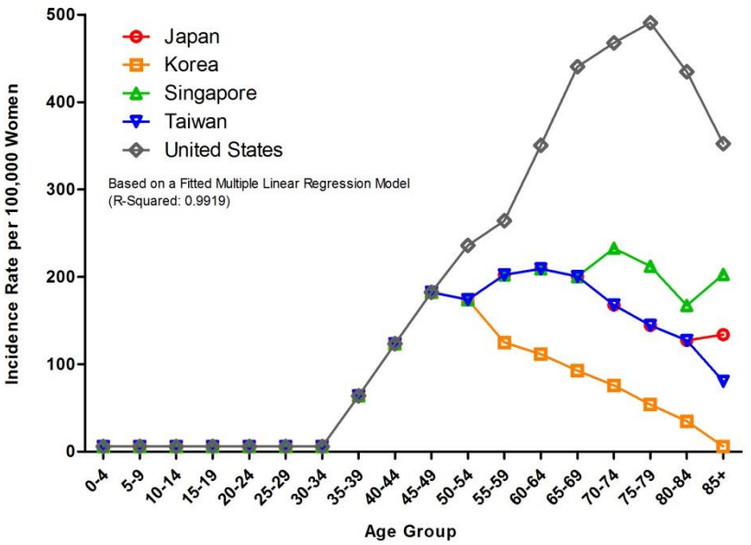
A. Breast cancer, observed



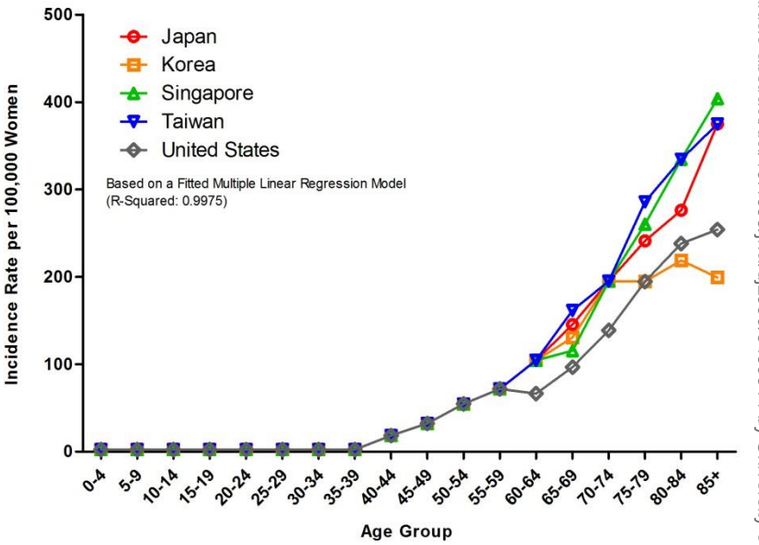
B. Colorectal cancer, observed



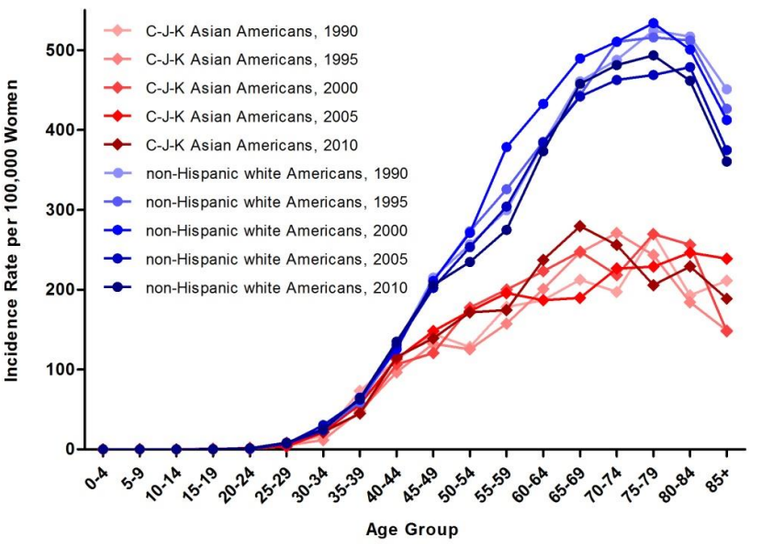
C. Breast cancer, estimated



D. Colorectal cancer, estimated



E. Breast cancer, observed



F. Colorectal cancer, observed

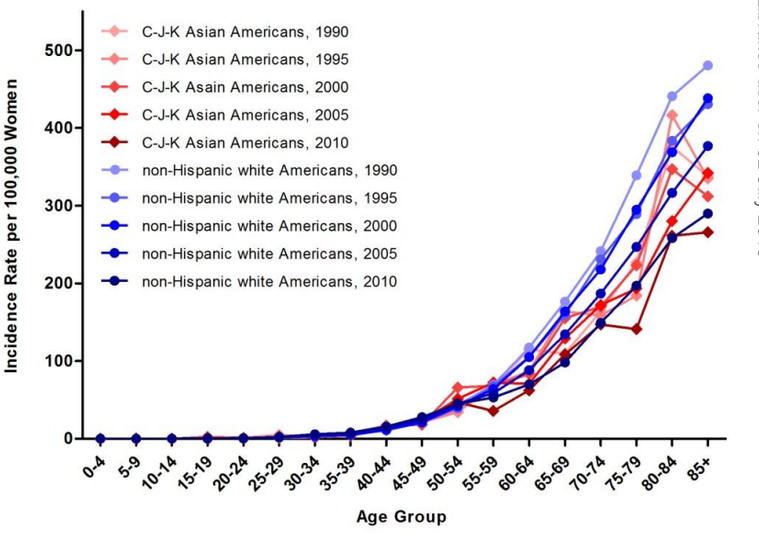


Figure 2

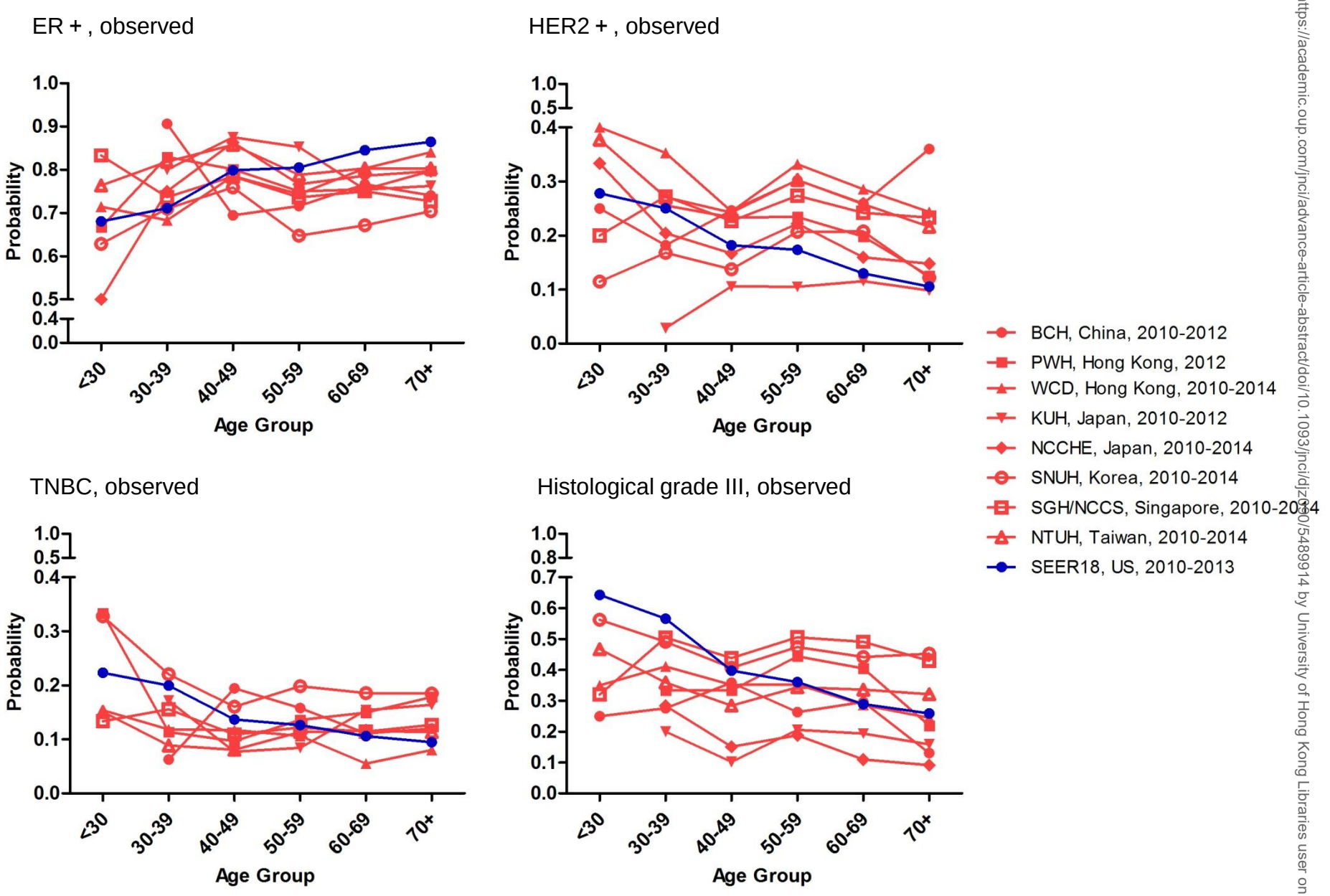


Figure 3

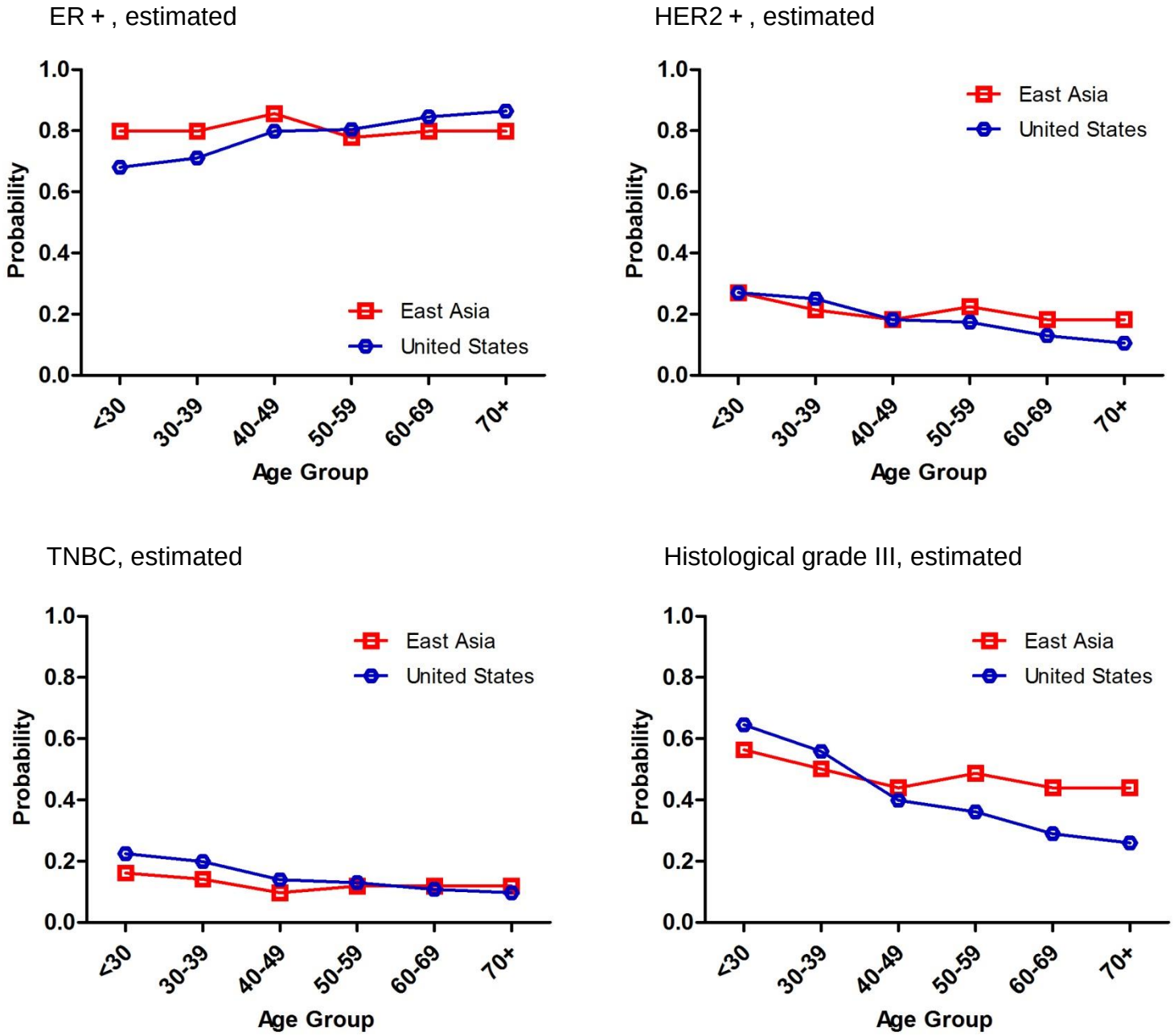


Figure 4