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Divergent breast cancer incidence trends by hormone receptor status in the state of Sarawak, Malaysia

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Abstract

Recent studies from high-risk countries such as the US, Denmark, and Ireland have shown rising incidence rates of hormone receptor (HR)-positive and falling rates of HR-negative breast cancers (BC). However, it remains unclear whether a similar pattern occurs in low-risk countries. Detailed clinical and risk factor data were collected from 2,977 female invasive BC patients (≥20 years) in Sarawak General Hospital, Malaysia, representing 93% of the population. The population-at-risk was obtained from Department of Statistics Malaysia. Secular trends in age-standardized incidence rates were assessed using estimated average annual percent changes. Associations between established BC risk factors and tumor subtypes defined by HR or joint HR/HER2 (human epidermal growth factor receptor 2) status were examined by case-case comparisons using logistic regression. From 2006-2015, incidence rates increased for HR-positive cancers by 4.46%/year (95%CI=2.19 to 6.78) and decreased for HR-negative cancers by 2.29%/year (95%CI=−4.31 to −0.24). When further stratified by HER2, the most contrasting difference in linear trends was observed between HR+/HER2− and HR−/HER2− subtypes. After controlling for potential confounders, cases with excess body weight ($OR_{overweight\ vs.\ normal}$=0.82; 95%CI=0.69-0.98; $OR_{obese\ vs.\ normal}$=0.62; 95%CI=0.48-0.80), later age at first birth ($OR_{\geq 26\ years\ vs.\ <23\ years}$=0.82; 95%CI=0.66-1.02), nulliparity ($OR_{nulliparous\ vs.\ <23\ years}$=0.74; 95%CI=0.59-0.94), and never-breastfeeding ($OR_{never\ vs.\ ever}$ =0.73; 95%CI=0.55-0.97) were less frequent among HR-negative cases than among HR-positive cases. Diverging incidence trends by HR expression were similar in Sarawak and Western countries, possibly reflecting changes in the prevalence of risk factors with opposing effects by tumor subtypes in low- and high-risk populations.

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Conflict of interests

Dr Sung is employed by the American Cancer Society, which received a grant from Merck Inc for intramural research outside the submitted work; however, her salary is solely funded through the American Cancer Society. No other disclosures were reported. The other authors declare that they have no competing interests.

Keywords

Breast cancer; Incidence trend; Hormone receptor positive cancer; Hormone receptor negative cancer; Malaysia

Introduction

Breast cancer subtypes defined by hormone receptor (HR) status are thought to be associated with different etiologic pathways.[1, 2] Therefore, temporal changes in the prevalence of risk factors are likely to have different impact on incidence rates of breast cancer by tumor subtypes. However, subtype-specific incidence trends of breast cancer are largely unknown, except for those reported in a few high-income Western countries. Studies conducted in the United States (US),[3, 4] Denmark,[5] and Ireland[6] demonstrated that rates for HR-positive cancers have been increasing, whereas rates for HR-negative cancers have been decreasing during 1980-2004., likely reflecting changes in mammography screening as well as risk factors that have heterogenous effects on HR-positive and HR-negative cancers.

Compared to high-income Western countries, incidence rates of breast cancer are still substantially lower in most transitioning countries. In 2018, incidence rate in Malaysia was 47.5 per 100,000 women compared to 84.9 in the US and 90.3 in Ireland.[7] Nevertheless, breast cancer incidence rates have been rapidly increasing in most traditionally low-risk countries, presumptively due to the adoption of a Westernized lifestyle, and breast cancer is now the most frequently diagnosed female cancer in Malaysia (33%) and in South-East Asia (26.4%).[7] Sarawak is the largest state in Malaysia. Based on the 2015 census data, the population was 2,636,000, approximately 60% of which residing in urban areas and consisting predominantly of Malays and Chinese, and a small population of urban natives of Ibans and Bidayuhs.[8] We previously reported that women in Sarawak were at lower risks for all breast cancer subtypes defined by HR or joint HR/human epidermal growth factor receptor 2 (HER2) status compared with their counterparts in the US.[9] However, secular trends in subtype-specific rates have not been reported in Sarawak or in any low-risk populations. In this study, we further examined trends in subtype-specific incidence rates of breast cancer in Sarawak. To identify risk factors that potentially account for the observed trends, we also extended our previous analysis that compared distributions of well-established breast cancer risk factors by tumor subtypes in this larger study including more patients with extended study period.[10, 11]

Material and Methods

Study population

Breast cancer cases were diagnosed and treated in the Department of Radiotherapy and Oncology of the Sarawak General Hospital, where about 93% of all newly diagnosed breast cancer cases in Sarawak, Malaysia, are treated.[10] We included 2,977 cases (≥20 years) who were diagnosed with invasive breast cancer between 2003 and 2015. Demographic factors and breast cancer risk factors were collected using a standardized questionnaire at the time of breast cancer diagnosis, including age at diagnosis, height and weight for the calculation

of body mass index (BMI), family history of breast cancer among first-degree relatives, age at menarche, age at first birth, parity (yes or no), number of children, and breastfeeding (yes or no; cumulative duration in month). Clinical characteristics of cancers were extracted from pathology reports and medical records, which included TNM stage (0, I, II, III, IV), grade (well differentiated, moderately differentiated, poorly differentiated), and expression status of three tumor makers including estrogen receptor (ER), progesterone receptor (PR), and HER2. ER and PR expression were assessed with immunohistochemical (IHC) staining of formalin-fixed, paraffin-embedded tissue sections, while HER2 expression was measured by IHC and fluorescence *in situ* hybridization (FISH, for HER2 IHC 2+ or 3+).[10] Details on the reliability of IHC staining were described previously.[9] We defined HR-positive (HR+) cancers as ER-positive or PR-positive; HR-negative (HR−) as ER-negative and PR-negative; and remaining as HR-unknown. Subtypes by joint HR/HER2 status were defined as: HR+/HER2−, HR+/HER2+, HR−/HER2+, and HR−/HER2−.[12-14] The study protocol was approved by the National Ethics Committee, Ministry of Health of Malaysia and exempted from review by the National Institutes of Health Office of Human Subject Research (OHSRP#: 5410).

Statistical Analysis

We restricted the trend analysis to cases diagnosed in 2006-2015 because of the incomplete marker data collection in earlier years (Supplementary Figure 1). To estimate population-based subtype-specific incidence rates of breast cancer, we counted observed number of cases for each subtype by age at diagnosis (20-24, 25-29, …, 80-84, 85+) and calendar year of diagnosis (2006, 2007, … 2015), and adjusted the observed number of cases to the expected total population by dividing the observed number of cases by population coverage factor, 0.93.[10] We obtained data on population at-risk by age (5-year age groups) in Sarawak from Department of Statistics Malaysia (Supplementary Table 1).[15] We estimated subtype-specific age-standardized incidence rates (ASR) of breast cancer overall and by age groups (20-49, 50+ years) using the World Health Organization's new World Standard Population (WHO 2000-2025) as a reference population. The linear trend in ASRs was summarized as average annual percent change in the ASR, which was calculated by weighted log-linear regression under the assumption of a Poisson distribution.[16]

We used case-case analyses to test heterogeneity in associations of established breast cancer risk factors (family history of breast cancer, obesity, age at menarche, age at first birth, parity, breastfeeding) by tumor subtypes.[17] We conducted unconditional logistic regression analyses to calculate odds ratios (ORs) for risk factor differences in HR-positive and HR-negative patients using HR-positive as the reference. Polytomous logistic regression was used to calculate ORs for HR+/HER+, HR−/HER2+, HR−/HER2− subtypes using HR+/HER2−, the most common subtype, as the reference. We tested family history of breast cancer (yes or no), BMI (<25, 25-29.9, 30+ kg/m^2), age at menarche (<13, 13, ≥13 years), age at first birth (<23, 23-25, 26+ years, nulliparous) in mutually adjusted models in all cases or in cases stratified by age groups (20-49, 50+ years). Number of children (1-2, 3-4, or ≥5 children) and breastfeeding (ever, never) were additionally tested in parous women only. All ORs were adjusted for age (5-year interval) and year at diagnosis (2003-2006, 2007-2010, 2011-2013, 2014-2015) and ethnicity (Chinese, Malay, others). Statistical

analyses were performed using SAS (Version 9.4, The SAS institute, Cary, NC) and MATLAB® R2017b (The MathWorks Inc., MA). All p-values were two-sided and considered statistically significant at $p < 0.05$.

Ethics approval and consent to participate

All study participants provided written informed consent and the project was approved by the Ethics Committee of the National Institutes of Health, Malaysia. The study was also exempted from review by the Office of Human Subject Research Protections at the National Institutes of Health (NIH) since NIH investigators do not have the access to the personal identifying information.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Results

Characteristics of study participants

There were 2,977 invasive cases diagnosed between 2003 and 2015 in Sarawak, Malaysia, with the majority being Chinese (48.6%) and 40-69 years old (67.4%), and having Stage II (42.1%), moderately differentiated (55.8%), and HR-positive (65%) cancers. HR-positive cases tended to have earlier stage and lower grade cancers than HR-negative cases ($P_{\text{Mantel-Haenszel Chi-Square}}<0.0001$, Table 1). While the frequencies of family history of breast cancer, age at menarche, and menopausal status were similar between HR-positive and HR-negative patients, Chinese ethnicity, higher BMI, delayed first birth, and shorter duration of breastfeeding were more common among HR-positive patients than HR-negative patients (Table 1).

Time trend in age-standardized breast cancer incidence rates by tumor subtypes

Figure 1 shows overall and subtype-specific incidence rates between 2006 and 2015. Rates for overall breast cancer increased from 33.8 (95% CI=29.0-38.5) in 2006 to 47.7 (95% CI=42.8-5.27) in 2015 at a rate of 2.48% on average per year (95% CI=0.15-4.87). During the same period, the rate for HR-positive cancers increased from 21.1 (95% CI=17.3-24.9) to 34.7 (95% CI=30.5-39.0) with an average increase of 4.46% per year (95% CI=2.19-6.78), but decreased for HR-negative cancers from 12.6 (95% CI=9.70-15.6) in 2006 and 15.0 (95% CI=11.9-18.1) in 2007 to 12.3 (95% CI=9.80-14.8) in 2015 with an average decrease of 2.29% per year (95% CI= −4.31 to −0.24) (Figure 1A; **see** Supplementary Table 2 **for numbers**). When further stratified by HER2 status (Figure 1B), the increase of HR-positive cancers was accentuated in HR+/HER2− subtype (5.46%/yr; 95% CI=3.52-7.44) but was not prominent in HR+/HER2+ cancers. For HR-negative cancers, the decrease appeared to be more pronounced for HR−/HER2− cancers but the trend was not statistically significant (−3.45%/yr; 95% CI= −7.10 to 0.34). Analyses by HR (Figure 2; Supplementary Table 3) and HR/HER2 (Supplementary Table 3) subtypes according to age groups (20-49 years, ≥50 years) showed similar trends in younger and older

women with a slightly greater annual percent change estimated in older than younger women, although none of the trends in HR-negative tumors were statistically significant.

Association of breast cancer risk factors with tumor subtypes

Table 2 shows associations of BMI and selected reproductive factors with HR-status that remained statistically significant in multivariable models. We found that nulliparity ($OR_{\text{nulliparous vs. <23 years}}$=0.74; 95% CI=0.59-0.94) and later age at first full term birth ($OR_{\geq 26 \text{ vs. } <23 \text{ years}}$=0.82; 95% CI=0.66-1.02) were less frequent among HR-negative cases than among HR-positive cases after controlling for potential confounders. Among parous women, never-breastfeeding was also less common among HR-negative cases ($OR_{\text{never vs. ever}}$=0.73; 95% CI=0.55-0.97). In addition, excess body weight was less frequent among HR-negative cases than among HR-positive cases with OR of 0.82 (95% CI=0.69-0.98) for overweight and 0.62 (95% CI=0.48-0.80) for obesity. These associations were similar in older and younger women, but the magnitude of the associations was generally stronger among older women. When HR-positive cases were further stratified by HER2 status (Supplementary Table 4), breast cancer risk factors did not vary between HR+/HER2− and HR+/HER+. Excess body weight and delayed first birth were less frequently observed among cases with HR−/HER2+ and HR−/HER2− cancers than among those with HR+/HER2− cases.

Discussion

In Sarawak, Malaysia, breast cancer incidence rates increased for HR-positive cancers but decreased for HR-negative cancers from 2006-2015. Further stratification by HER2 status suggested that the increasing HR-positive trend and the decreasing HR-negative trend was driven by HR+/HER2− and HR−/HER2− cancers, respectively. Frequencies of excess body weight and reproductive factors, particularly age at first birth and breastfeeding, varied by subtypes, which may partly account for rising rates for HR-positive cancers and falling rates for HR-negative cancers in Sarawak. The pattern of divergent trends by HR status in Sarawak is similar to what was previously reported in the US, Denmark, and Ireland.[3, 5, 18] This suggests similar changes in the prevalence of common risk factors that may have opposing effects on HR-positive and HR-negative breast cancers, despite the substantial variation in overall incidence rates across populations.[19]

Although results in different studies were not directly comparable due to differences in study periods, design, and approaches, the annual increase estimated for HR-positive cancers was greater in Sarawak (4.5%/yr from 2005-2014) compared to those in the US (1.2%/yr from 1992-2008), Denmark (3.0%/yr from 1993-2010), and Ireland (2.2%/yr from 2004-2013), whereas there was little variation in annual declines for HR-negative cancers across countries (range, 2.1-3.4%/yr).[4-6] While the recent stabilizing trend of overall breast cancer incidence rates in some high-risk countries may reflect the superimposition of the two opposing trends (HR-positive and HR-negative cancers) with similar magnitudes, the greater increase in HR-positive cancers shown in Sarawak, Malaysia, implies that sustained rapid increases of overall breast cancer incidences in historically low-risk regions are driven by increases in HR-positive cancers rather than by HR-negative cancers. In our previous study,

the overall ASR for breast cancer was 22.0 per 100,000 women for 1998-2009 in Sarawak[10] as compared to 40 per 100,000 women for 2006-2015 estimated in the current study, showing a rapid increase of breast cancer incidence in recent years. Despite the potential impact of improved case ascertainment on cancer incidence rates, especially in transitioning countries, the decline of HR-negative cancers as opposed to the incline of HR-positive cancers implies that the increase of HR-positive cancers may not be solely explained by changes in the cancer registry practice.

Studies examining subtype-specific trends of breast cancer are lacking in other low-risk countries and/or regions. Notwithstanding the existence of high-quality long-term cancer registry data in several Asian countries such as Japan, Korea, Singapore, and Taiwan, incidence trends by HR status have not been reported in Asia due to the lack of tumor marker information in cancer registries. A report from Korea based on hospital-based cancer registry showed that the percentage of ER-positive cancers increased from 58% in 2002 to 74% in 2015,[20] which is consistent with the rising trend of HR-positive cancers observed in our study. Following sociocultural changes towards a more Westernized lifestyle, Asian women have experienced rapid changes in their lifestyle and reproductive factors, characterized by earlier onset of menarche, delayed childbirth and fewer children, less breastfeeding, increasing body weight, and less physical activities.[21, 22] It is notable that some of these factors are known to have differential associations with HR-positive cancers and HR-negative cancers. For example, while earlier age at first birth and multiparity are protective for HR-positive cancers, they were associated with increased risk of HR-negative cancers, especially triple-negative cancers.[1, 23-29] Consistent with these findings, our case-case comparisons showed cases with HR-positive cancers were more likely to be nulliparous or to have delayed their first births compared to cases with HR-negative cancers. In Malaysia, the mean age at first marriage, which could be considered as a proxy for age at first birth, increased from 21.6 years old in 1970 to 25.1 years in 2000.[30] The total fertility rate (births per woman) also decreased from 6.5 children per woman in 1960 to 2.0 in 2017.[31] Data from a case-control study conducted in Selangor, Malaysia, also showed that women of each ethnic group experienced significant reduction in parity and increase in age at first full term pregnancy across birth cohorts from before 1950 to after 1970.[32] The increasing prevalence of delayed childbirth and fewer number of children, which may have opposing effects on breast cancer risk by subtypes, may at least in part explain the observed diverging trend of breast cancer defined by HR status.

Given the declining frequency and duration of breastfeeding during recent decades in Malaysia,[33] the observed lower frequency of breastfeeding in HR-positive cases compared to HR-negative cases is also consistent with the rising HR-positive cancers in contrast to the falling HR-negative cancers. However, the association of breastfeeding with cancer subtypes in our study is contradictory with results based on a systematic review summarizing 27 studies that reported a stronger protective effect of breastfeeding for HR-negative cancers (especially for triple-negative cancer) compared to HR-positive cancers.[34] Conflicting results exist particularly for non-white women. For example, a previous study using a similar case-only design as our study among women of Mexican descent reported lower prevalence of breastfeeding in luminal A cases vs. triple-negative cases;[35] and a multiethnic study showed a significantly shorter duration of breastfeeding among triple-negative breast cancer

cases in White, Hispanic and African American but not among Asian women.[36] The discrepancies are possibly due to differences in study design, the adjustment of multiparity, definition of HR-positive tumors (based on ER or joint ER/PR), as well as race/ethnicity.[37] Large studies, especially those with population-based design and optimally controlling for other parity-related variables, are needed to further investigate the relationship between breastfeeding and breast cancer subtypes in diverse populations/ethnic groups.

Excess body weight has been consistently associated with increased risk of HR-positive breast cancers, particularly among postmenopausal women.[38-41] Increasing trends of HR-positive cancers may be partially due to a rapid increase of the obesity prevalence in Malaysia in recent decades. Age-standardized prevalence of obesity (BMI≥30 kg/m^2) among women (≥20 years) increased more than 8-fold from 2.3% in 1975 to 18.5% in 2016 in Malaysia, making Malaysia the most obese country in East and South East Asia.[42] Although excess body weight has been associated with reduced risk of premenopausal breast cancer and increased risk of postmenopausal women in Western countries,[38-41] studies conducted in Asian countries or immigrant Asian women showed that excess body weight was associated with increased breast cancer risk regardless of menopausal status in Asian women.[39, 43] We found a slightly faster increase in HR-positive cancers among older than younger women (4.8%/yr versus 4.0%/yr), which is consistent with the greater effect size of the obesity association among postmenopausal women.[39, 43]

Increasing access to mammography screening may have also contributed to the rise of HR-positive cancers as screening mammography preferentially detects ER-positive cancers with higher sensitivity than ER-negative cancers.[44, 45] In Malaysia, a subsidized screening program has been carried out since 2007 by the National Population and Family Development Board Malaysia mammogram screening program.[46] However, very few women are eligible to attend this screening, and screening uptake in the general population is low. According to studies conducted in urban and sub-urban localities of Terengganu, Selangor and Kuala Lumpur, screening uptake was between 11% and 32% in the general population of those areas.[46] Therefore, mammographic screening may not have major impact on breast cancer incidence changes in Malaysia as it does in high-income Western countries.

Data source from Sarawak offered a unique opportunity, for the first time to our knowledge, to examine subtype-specific incidence trends of breast cancer in a historically low-risk population. The data covered 93% of the target population and subtype information was nearly complete (missing [%], 0 to 2.3% by year for HR status; 0 to 5% by year for HR/HER2 status; Supplementary Figure 1). Further to enhance our understanding of the observed trend, we examined the associations between well-established breast cancer risk factors and HR subtypes, which demonstrated that breast cancer risk factors might act differentially on different subtypes. However, our study has several important limitations. First, breast cancer subtype information was available only for the recent 10 years, which limited our ability to examine a long-term incidence trend by subtype. As additional data, especially from other low-risk populations, become available over time, future analyses are needed to confirm and expand our findings. Second, although our findings on divergent trends of breast cancer accompanied by risk factor analysis may provide important insights

on the presence of risk factors with opposing effects by tumor subtypes, our results do not inform a causal relationship of the risk factors on the observed incidence trends. In addition, our study did not assess the impact of changing prevalence of risk factors on the diverging incidence trends. Addressing these limitations in future studies, which require longitudinal collection of risk factor data, would further improve our understanding of the observed trend. Third, our findings were based on a single hospital in the state of Sarawak, which may not be generalizable to the rest of the population in Malaysia considering the heterogeneous ethnic composition across states. In addition, although tumor markers have been measured consistently in a single institution using the same threshold over the 10 years of the study period, it is unknown whether the improved sensitivity in assay techniques to measure tumor markers over time may have affected the observed subtype-specific trend. Lastly, Sarawak is a multiethnic state comprising three major ethnic groups namely Malays, Chinese, and Natives, with varied breast cancer incidence rates and distinct lifestyles in each ethnic group.[10] However, our study was not powered to investigate the incidence trends by HR status in each ethnic group separately.

In conclusion, breast cancer incidence rates in Sarawak, Malaysia, have shown diverging trends by HR status. We also showed that risk factors, including nulliparity, late age at first birth, never-breastfeeding, and excess body weight, were more prevalent among HR-positive than HR-negative cancers. The burden of HR-positive breast cancers relative to HR-negative cancers is expected to continue to increase with time, given the rising prevalence of risk factors that are more relevant to the risk of HR-positive cancers. Future studies are warranted to investigate subtype-specific incidence trends in other low-risk populations and further identify factors contributing the trends.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ASR	age-standardized incidence rates
BC	breast cancers
BMI	body mass index
CI	confidence interval
ER	estrogen receptor
HER2	human epidermal growth factor receptor 2
HR	hormone-receptor

IHC	immunohistochemical
OR	odds ratio
PR	progesterone receptor

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Novelty and Impact

Using data from Sarawak, Malaysia, we first report incidence trend of breast cancer by tumor subtype in a low-risk region. Between 2007 and 2015, incidence rates for hormone-receptor (HR)-positive cancer increased (4.46%/year), while rates for HR-negative cancer decreased (2.29%/year), similar to what previously reported in a few high-income Western countries. Reasons for the divergent trend remain unclear, however, may reflect changes in the prevalence of risk factors with opposing effects on HR-positive vs. HR-negative cancers.

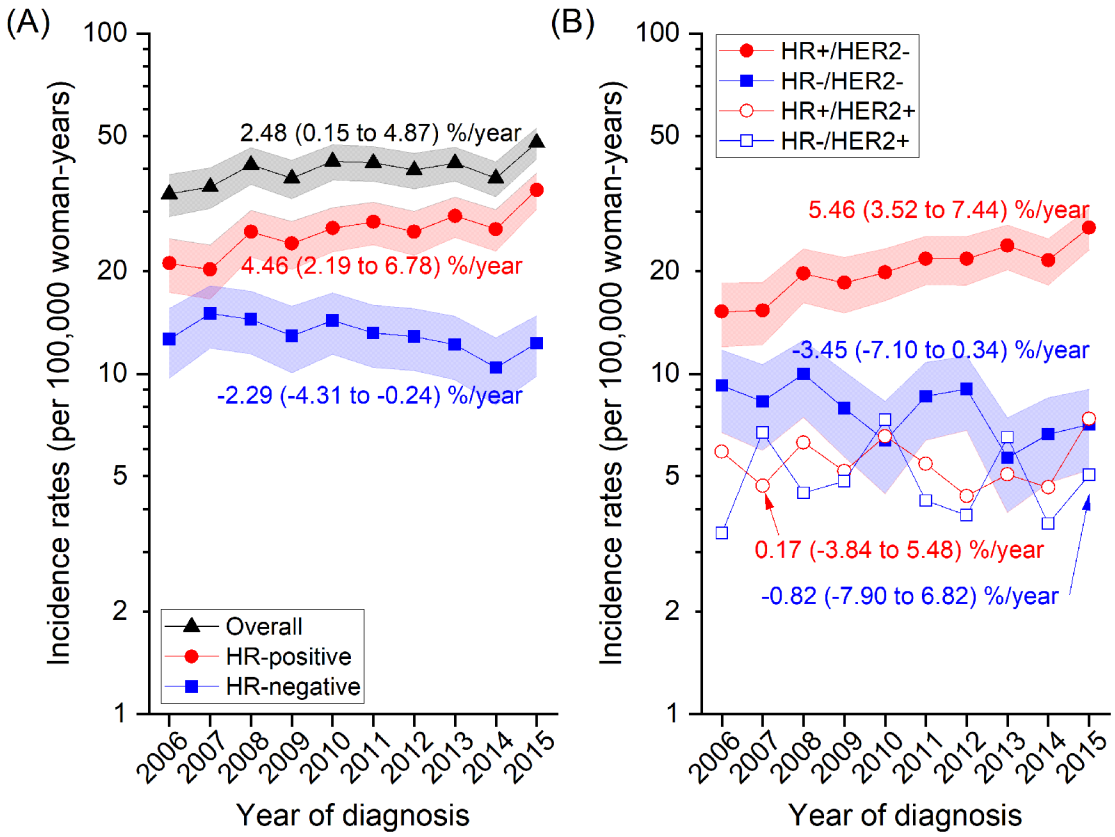

Figure 1. Trends in breast cancer incidence rates and average annual percent changes (% per year) by (A) HR and (B) HR/HER2 status between 2006 and 2015 in Sarawak, Malaysia

Symbols represent annual rates adjusted to the World Health Organization's new World Standard Population (WHO 2000-2025) and 95% confidence intervals (CIs) are indicated by shaded bands. Annual rates (95% CI) for HR+/HER2+ and HR−/HER− subtypes are presented in Supplementary Table 1.

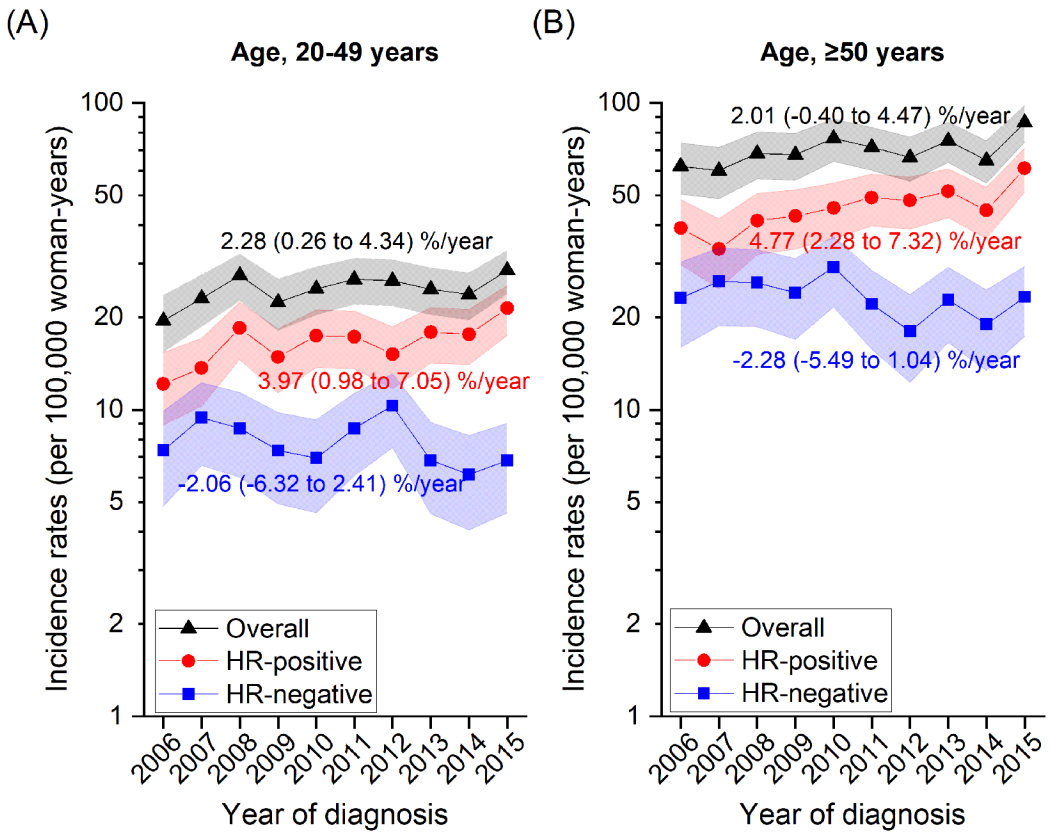

Figure 2. Trends in breast cancer incidence rates and average annual percent changes (% per year) by HR status for women aged (A) 20-49 years and (B) 50-89 years between 2006 and 2015 in Sarawak, Malaysia

Symbols represent annual rates adjusted to the World Health Organization's new World Standard Population (WHO 2000-2025) and 95% confidence intervals (CIs) are indicated by shaded bands. Annual rates (95% CI) by HR/HER2 status according to age groups are presented in Supplementary Table 2.

Table1.

Characteristics of female invasive breast cancer cases diagnosed between 2003 and 2015 in Sarawak, Malaysia, by hormone receptor status

	Total (n=2977)		HR-positive (n=1925)		HR-negative (n=981)		HR-unknown (n=71)		*P*[b]
	n	%	n	%	n	%	n	%	
ASR per 100,000 (SD)[a]	40.0	(0.78)	28.1	(0.68)	12.9	(0.44)	0.5	(0.09)	
Race									
Chinese	1448	48.6	977	50.8	444	45.3	27	38.0	0.02
Malay	722	24.3	448	23.3	258	26.3	16	22.5	
Others	807	27.1	500	26.0	279	28.4	28	39.4	
Age at diagnosis									
Mean (SD)	51.6	(11.1)	51.6	(10.9)	51.4	(11.5)	51.8	(11.0)	0.62
20-40	367	12.3%	216	11.2	144	14.7	7.0	9.9	0.77
40-49	1006	33.8%	686	35.6	299	30.5	21	29.6	
50-59	911	30.6%	578	30.0	305	31.1	28	39.4	
60-89	693	23.3%	445	23.1	233	23.8	15	21.1	
Year of diagnosis									
2003-2005	481	16.2	273	14.2	169	17.2	39	54.9	<.0001
2006-2009	841	28.3	521	27.1	313	31.9	7	9.9	
2010-2012	779	26.2	508	26.4	256	26.1	15	21.1	
2013-2015	876	29.4	623	32.4	243	24.8	10	14.1	
Stage									
I	414	14.1	315	16.5	97	10.0	2	2.9	<.0001
II	1238	42.1	828	43.5	395	40.8	15	21.7	
III	931	31.7	566	29.7	343	35.4	22	31.9	
IV	359	12.2	196	10.3	133	13.7	30	43.5	
Unknown	35		20		13		2		
Grade									
Well differentiated	310	10.7	267	14.1	40	4.2	3	5.5	<.0001
Moderately differentiated	1622	55.8	1171	61.8	420	43.8	31	56.4	
Poorly differentiated	977	33.6	456	24.1	500	52.1	21	38.2	
Unknown	68		31		21		16		
Molecular subtype									
HR+/HER2−	1411	52.2	1411	78.8	-	-	-	-	
HR+/HER2+	379	14.0	379	21.2	-	-	-	-	
HR−/HER2+	343	12.7	-	-	343	37.5	-	-	
HR−/HER2−	571	21.1	-	-	571	62.5	-	-	
Unknown	273		135		67		71		
Family history									
No	2496	85.3	1613	85.2	824	85.3	59	86.8	0.95
Yes	431	14.7	280	14.8	142	14.7	9	13.2	

	Total (n=2977)		HR-positive (n=1925)		HR-negative (n=981)		HR-unknown (n=71)		P^b
	n	%	n	%	n	%	n	%	
Unknown	50		32		15		3		
BMI (kg/m^2)									
Mean (SD)	24.8	(4.7)	25.0	(4.7)	24.5	(4.6)	24.6	(4.2)	0.01
<25	1612	56.0	1008	54.1	565	59.7	39	57.4	0.001
25-29.9	876	30.4	579	31.1	276	29.2	21	30.9	
30+	390	13.6	277	14.9	105	11.1	8	11.8	
Unknown	99		61		35		3		
Age at menarche									
<13	909	30.8	606	31.7	277	28.5	26	37.7	0.18
13	1003	34.0	634	33.2	345	35.5	24	34.8	
13+	1040	35.2	670	35.1	351	36.1	19	27.5	
Unknown	25		15		8		2		
Menopausal status									
Pre	1396	46.9	906	47.1	458	46.7	32	45.1	0.85
Post	1581	53.1	1019	52.9	523	53.3	39	54.9	
Parity/Age at first birth									
<23	891	29.9	554	28.8	319	32.6	18	25.4	0.01
23-25	619	20.8	387	20.1	214	21.8	18	25.4	
26+	807	27.1	539	28.0	250	25.5	18	25.4	
Nulliparous	659	22.1	445	23.1	197	20.1	17	23.9	
Unknown	1				1				
Number of children[c]									
1-2	742	32.1	482	32.7	251	32.1	9	16.7	0.09
3-2	1032	44.7	677	45.9	323	41.4	32	59.3	
5+	537	23.2	317	21.5	207	26.5	13	24.1	
Unknown	7		4		3				
Breastfeeding[c]									
Never	341	14.7	233	15.7	96	12.2	12	22.2	0.01
1-5 Months	802	34.6	522	35.3	267	34.1	13	24.1	
6-12 Months	704	30.4	446	30.1	241	30.7	17	31.5	
13+ Months	471	20.3	279	18.9	180	23.0	12	22.2	

ASR, Age-standardised rate; BMI, body mass index; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; SD, standard deviation

[a] ASR per 100,000 woman-years for breast cancer diagnosed from 2006-2015.

[b] *P*-value for HR-positive versus HR-negative comparison based on Student's t-test, Chi-Square test, or Mantel-Haenszel Chi-Square test whichever appropriate

[c] Among parous women

Table 2.

Associations between breast cancer risk factors and hormone receptor status by age group in Sarawak, Malaysia

	HR-positive (n=1925)		HR-negative (n=981)		HR-negative vs. HR-positive	*P*
	n	%	n	%	OR (95% CI)	
BMI (kg/m^2)[a]						
Overall						
<25	1008	54.1	565	59.7	Ref.	
25-29.9	579	31.1	276	29.2	0.82 (0.69- 0.98)	0.03
30+	277	14.9	105	11.1	0.62 (0.48- 0.80)	2.5E-04
P_{trend}					1.2E-04	
20-49 years						
<25	492	55.9	246	57.5	Ref.	
25-29.9	264	30.0	124	29.0	0.92 (0.70- 1.21)	0.55
30+	124	14.1	58	13.6	0.84 (0.58- 1.21)	0.35
P_{trend}					0.33	
≥50 years						
<25	516	52.4	319	61.6	Ref.	
25-29.9	315	32.0	152	29.3	0.76 (0.60- 0.97)	0.03
30+	153	15.6	47	9.1	0.44 (0.30- 0.64)	1.6E-05
P_{trend}					9.7E-06	
Parity/Age at first birth[a]						
Overall						
<23	554	28.8	319	32.6	Ref.	
23-25	387	20.1	214	21.8	0.95 (0.76- 1.19)	0.66
26+	539	28.0	250	25.5	0.82 (0.66- 1.02)	0.07
Nulliparous	445	23.1	197	20.1	0.74 (0.59- 0.94)	0.01
P_{trend}					5.4E-03	
20-49 years						
<23	275	30.5	145	32.8	Ref.	
23-25	164	18.2	93	21.0	1.18 (0.84- 1.66)	0.34
26+	232	25.7	103	23.3	0.95 (0.68- 1.32)	0.75
Nulliparous	231	25.6	101	22.9	0.81 (0.58- 1.13)	0.21
P_{trend}					0.16	
≥50 years						
<23	279	27.3	174	32.3	Ref.	
23-25	223	21.8	121	22.5	0.80 (0.59- 1.09)	0.16
26+	307	30.0	147	27.3	0.70 (0.52- 0.94)	0.02
Nulliparous	214	20.9	96	17.8	0.64 (0.46- 0.88)	0.01
P_{trend}					3.1E-03	
Breastfeeding[b]						

	HR-positive (n=1925)		HR-negative (n=981)		HR-negative vs. HR-positive	*P*
	n	**%**	**n**	**%**	**OR (95% CI)**	
Overall						
Ever	1247	84.3	688	87.8	Ref.	
Never	233	15.7	96	12.2	0.73 (0.55- 0.97)	0.03
20-49 years						
Ever	578	86.1	300	87.7	Ref.	
Never	93	13.9	42	12.3	0.87 (0.56- 1.37)	0.56
≥50 years						
Ever	669	82.7	388	87.8	Ref.	
Never	140	17.3	54	12.2	0.65 (0.45- 0.95)	0.03

BMI, body mass index; CI, confidence interval; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; OR, odds ratio

[a]Model included year of diagnosis, race (Chinese, Malay, or others), age (5-year), BMI (<25, 25-29.9, or 30+), family history of breast cancer (yes or no), age at menarche (<13, 13, or ≥13 years), and parity (parous or nulliparous) as explanatory variables

[b]Among parous women, model included year of diagnosis, race (Chinese, Malay, or others), age (5-year), BMI (<25, 25-29.9, or 30+), family history of breast cancer (yes or no), age at menarche (<13, 13, or ≥13 years), age at first birth (<23, 23-25, or 26+), number of children (1-2, 3-4, or ≥5 children), and breastfeeding (ever or never) as explanatory variables.