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EPIDEMIOLOGY

Multiparity and the risk of premenopausal breast cancer: different effects across ethnic groups in Singapore

Helena M. Verkooijen · Karen P. L. Yap · Vineta Bhalla · Khuan Yew Chow · Kee Seng Chia

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Abstract *Background* The relationship between multiparity and premenopausal breast cancer risk is different in Caucasian, African-American and Hispanic women. For Asian women, this relationship has never been well studied. *Methods* Within the Singapore Birth Registry, we selected all women who had a first child between 1986 and 2002 (169,936 Chinese, 40,521 Malay, 17,966 Indian). We linked them to the Singapore Cancer Registry data to identify those who developed breast cancer after childbirth ($n = 527$). We used multivariate Cox analysis to examine the relationship between parity, ethnicity and premenopausal breast cancer risk. *Results* Compared to Chinese, Malay women had increased and Indian women had decreased risks of premenopausal breast cancer (adjusted Hazard Ratios [HRadj] 1.25 [1.0–1.6] and 0.48 [0.3–0.8] respectively). Multiparity did not modify the risk of premenopausal breast cancer in Chinese and Indians. In Malays there was a significant risk reduction with increasing parity (P_{trend} 0.037). Malay women with one, two and ≥3 children had premenopausal breast cancer risks (HR_{adj}) of 1.86 (1.2–3.0), 1.52 (1.1–2.2) and 0.87 (0.6–1.3) respectively compared to their Chinese counterparts. *Conclusions* The impact of multiparity on premenopausal breast cancer risk differs across ethnic groups in Singapore. Increasing parity reduces the risk of premenopausal breast cancer in Malay, but not in Chinese and Indian women. Uniparous Malay women have twice the risk of premenopausal breast cancer compared to uniparous Chinese. This excess risk disappears after giving birth to ≥3 children. Indian women have lower premenopausal breast cancer risks than Chinese, regardless of their parity status.

Keywords Breast cancer · Ethnicity · Parity · Population-based · Premenopausal

Helena M. Verkooijen and Karen P. L. Yap are joint first authors.

H. M. Verkooijen (✉) · K. P. L. Yap · K. S. Chia
Centre for Molecular Epidemiology, Faculty of Medicine, National University of Singapore, 16 Medical Drive, 117597 Singapore, Singapore
e-mail: cofhmv@nus.edu.sg

H. M. Verkooijen · K. S. Chia
Department of Community, Occupational and Family Medicine, Faculty of Medicine, National University of Singapore, Singapore, Singapore

H. M. Verkooijen
Geneva Cancer Registry, Geneva University, Geneva, Switzerland

V. Bhalla
Ministry of Health, Singapore, Singapore

K. Y. Chow
National Registries of Disease Office, Health Promotion Board, Singapore, Singapore

Introduction

Breast cancer is the leading cause of cancer mortality in women world wide [1]. Incidence rates of breast cancer in Asian women are relatively low compared to those of Caucasian women in industrialized countries. Nevertheless, annual increases in breast cancer incidence and mortality rates in Asian populations are among the highest in the world [2].

Risk factors for breast cancer include low and late parity [3]. Giving birth to multiple children, starting at a young age, reduces a woman's risk of breast cancer. The impact of these reproductive factors on breast cancer risk has been well established for Caucasian populations and relates to

postmenopausal, and to a lesser extent, premenopausal breast cancer [4–8]. In other ethnic groups, the relationship between multiparity and breast cancer risk seems to be different. In Hispanics, multiparous women were reported to have similar pre- and postmenopausal breast cancer risks as uniparous women [7]. In African American women, a dual relationship between multiparity and breast cancer risk has been reported: here, increasing levels of parity are associated with lower postmenopausal, but higher premenopausal breast cancer risks [8, 9].

Evidence on the relationship between parity and premenopausal breast cancer risk in Asian populations is scarce. A small hospital-based case–control study from Singapore found no reduction in the risk of premenopausal breast cancer with increasing parity [10]. Another hospital-based case–control study, including Vietnam and Chinese premenopausal women, showed lower premenopausal breast cancer risks in parous versus nulliparous women, but the effect of multiparity as compared to uniparity was not presented [11].

Some years from now, Asians will probably represent the majority of breast cancer patients worldwide. We therefore need to improve our understanding of the relationship between 'established' risk factors for breast cancer and actual breast cancer risk in Asian populations. In this population-based study, we aim to evaluate whether multiparity reduces the risk of premenopausal breast cancer among Asian women. In addition, we will determine whether the relationship between multiparity and premenopausal breast cancer risk differs across the ethnic subgroups in Singapore.

Methods

Within the Singapore Birth Registry we identified all women who gave birth to a first child between 1986 and 2002 ($n = 228{,}548$). All births in Singapore are legally required to be registered with the Singapore Birth Registry. At the time of registration, information on the date of birth of the mother, mother's ethnicity and date(s) of birth of child(ren) are captured. All birth records became electronic from 1986.

We linked these women with the Singapore Cancer Registry to identify those who were diagnosed with breast cancer between 1986 and 2002, as well as their date of diagnosis. The Singapore Cancer Registry is a well-documented nationwide registry, and was founded in 1968. Since then, it receives notifications of incident cancers from all medical practitioners and pathology laboratories as well as reviews of all hospital discharges and death certificates. The completeness of reporting was 99% between 1993 and 1997 [12]. Pre-menopausal breast cancer was defined breast cancer occurring in women under 50 years (average age of menopause occurrence), as the Singapore Cancer Registry does not capture date of menopause.

For all individuals, information on vital status was obtained from the Death Registry. All record linkages were performed at the National Registries of Disease Office and researchers had no access to the personal information of the individuals.

For the current study, we excluded women who had breast cancer before they ever gave birth ($n = 40$) and women with incomplete information on parity ($n = 84$). The final study population included 228,423 individuals.

Variables of interest included mother's age at first birth, mother's age at last birth and ethnicity (Chinese, Malay, Indian). Parity was calculated as the number of children given birth to between 1986 and 2002. For women who gave birth after they had been diagnosed with breast cancer ($n = 36$) we calculated parity based on the number of children given birth to before breast cancer diagnosis. We had no detailed information on tumor characteristics, such as hormone receptors status and grade. Person-years were calculated from date of last birth until death, breast cancer occurrence, departure from Singapore or end of follow up (31st December 2002) depending whichever came first.

The study was approved by the Institutional Review Board of the National University of Singapore.

Statistical analysis

We used multivariate Cox analysis to calculate risks (Hazard Ratio [HR]) of premenopausal breast cancer associated with parity. Uniparous women (women who gave birth to one child) were taken as a reference category. We adjusted HR's of premenopausal breast cancer for age at first birth (categorized as $\leq$20, 21–25, 26–30, 31–35, 35+ years), age at last birth (continuous) and ethnicity. Presence of effect modification was tested by stratification as well as tests for interaction. We calculated premenopausal breast cancer risks within five years after last pregnancy as well as more than five years after last pregnancy. All 95% confidence intervals (CIs) are two-sided. We used SPSS software (15.0) to perform the analyses.

Results

Of the 228,423 women included in this study, 169,936 (74%) were of Chinese, 40,521 (18%) of Malay and 17,966 (8%) of Indian ethnicity. Malay women had on average more children and earlier mean age at first birth than Chinese and Indian women (Table 1). The mean follow up was 4.3 years (range 1 day to 16.8 years), giving rise to a total of 982,003 person years, during which 527 cases of

Table 1 Parity, age at first birth, breast cancer occurrence and age at breast cancer diagnosis according to ethnicity in the 228,425 women from the Singapore Birth Registry

	Chinese $N = 169,936$ (74%)	Malay $N = 40,521$ (18%)	Indian $N = 17,966$ (8%)	P value
Parity				
1 child	59,735 (35%)	9,287 (23%)	6,067 (34%)	<0.000
2 children	76,670 (45%)	13,019 (32%)	7,257 (40%)	
3 children	28,905 (17%)	11,854 (29%)	3,713 (21%)	
4+ children	4,626 (3%)	6,359 (16%)	929 (5%)	
Age at first birth (mean and range)	28.2 (12–48)	24.8 (13–45)	26.3 (14–49)	<0.000
Breast cancer	422 (0.25%)	88 (0.22%)	17 (0.095%)	<0.000
Age at diagnosis (mean and range)	37.9 (23–51)	35.5 (27–50)	36.1 (27–43)	<0.000

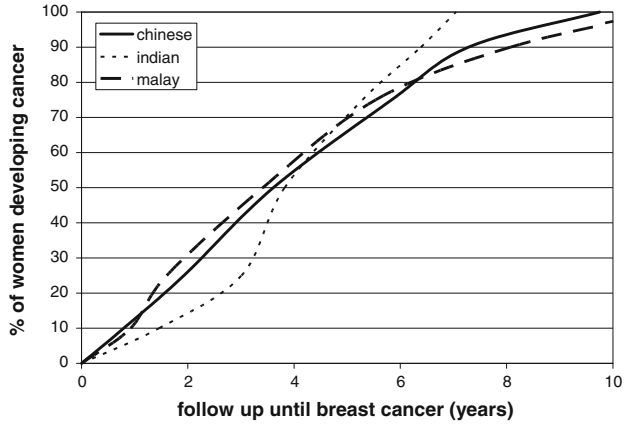

Fig. 1 Distribution of duration of follow up until breast cancer (for women who developed breast cancer) since last birth

premenopausal breast cancer were diagnosed. The distribution of duration of follow-up until breast cancer (among those who developed breast cancer) was similar among the three ethnic groups (Fig. 1).

Overall, multiparity did not have a statistically significant impact on premenopausal breast cancer risk. Compared to uniparous women, adjusted HR's of premenopausal breast cancer risks for those with 2 or ≥3 children were 1.08 (95% CI: 0.8–1.4), 0.89 (95% CI: 0.6–1.2) respectively. However, the impact of multiparity on premenopausal breast cancer risk was significantly different across ethnic groups (test for interaction between ethnicity and multiparity (yes versus no), $P = 0.037$). In Chinese and Indian women, multiparity did not modify the premenopausal breast cancer risk (Table 2). Malay women had reduced premenopausal breast cancer risks with increasing levels of parity (P_{trend} 0.037), even though not all strata-specific risk estimates (HR_{adj}) were statistically significant.

When we further stratified into breast cancers occurring within versus more than 5 years since the last birth, a similar trend of reduced premenopausal breast cancer risk with increasing parity was seen in the Malays (P_{trend} 0.216 for breast cancer risk within 5 years after last birth and P_{trend} 0.044 for breast cancer risk more than 5 years after last birth) (Table 2). There was no change in risk with increasing parity in Chinese women after stratification. The number of cases among the Indians was too small for stable Hazard Ratio's to be calculated.

Compared to Chinese, the premenopausal breast cancer risk (adjusted for parity, age at last birth and age at first birth) was higher in Malays (adjusted HR 1.25, 95% CI: 1.0–1.6) and significantly lower in Indians (adjusted HR 0.48, 95% CI: 0.3–0.8). After stratification by parity, uniparous Malay women had a 1.86 (95% CI 1.2–3.0) fold increased risk of premenopausal breast cancer compared to uniparous Chinese women (Fig. 2). Malay women with two children had a fifty percent higher risk of premenopausal breast cancer than their Chinese counterparts (HR_{adj} 1.52, 95% CI 1.1–2.2). Only after having given birth to three or more children, Malay women were no longer at increased premenopausal breast cancer risks compared to Chinese (HR_{adj} 0.87, 95% CI: 0.6–1.3). Indian women had lower premenopausal breast cancer risks than Chinese, regardless of the number of children they had given birth to.

Discussion

The results of this study show that ethnicity modifies the relationship between multiparity and premenopausal breast cancer risk in the well defined population of Singapore. We demonstrated this by means of two main comparisons. Firstly, we showed that Chinese and Indian women did not have reduced premenopausal breast cancer risks with increasing number of live births, whereas Malay women had significantly lower premenopausal breast cancer risks with increasing parity. This phenomenon was present within the first five years after last birth as well as more than five years after last birth.

Secondly, uniparous Malay women had almost twice the risk of premenopausal breast cancer compared to uniparous Chinese, but similar breast cancer risk when having given

Table 2 Breast cancer cases, person years and adjusted hazard ratios of premenopausal breast cancer according to ethnicity and period of diagnosis

	All		≤5 years after last birth		>5 years after last birth	
	Cases/person years	Adjusted hazard ratio (95% CI)	Cases/person years	Adjusted hazard ratio (95% CI)	Cases/person years	Adjusted hazard ratio (95% CI)
Chinese						
Parity						
Uniparous	99/217,514	1 (ref)	72/176,160	1 (ref)	27/41,354	1 (ref)
2 Children	215/363,964	1.11 (0.8–1.4)	138/276,358	1.01 (0.7–1.4)	77/87,606	1.37 (0.8–2.3)
3+ Children	108/142,561	1.02 (0.7–1.5)	79/124,552	1.01 (0.7–1.6)	29/38,254	1.10 (0.6–2.1)
Age at first birth	422/744,284	1.03 (0.8–1.3)	289/577,070	1.00 (0.7–1.3)	133/167,214	1.14 (0.8–1.7)
Malay						
Parity						
Uniparous	19/31,459	1 (ref)[a]	13/25,444	1 (ref)[b]	6/6,014	1 (ref)[c]
2 Children	36/55,101	0.84 (0.4–1.6)	24/43,069	0.90 (0.4–1.9)	12/12,032	0.65 (0.2–2.0)
3+ children	33/51,769	0.46 (0.2–1.0)	26/60,093	0.58 (0.2–1.5)	7/14,203	0.23 (0.05–1.0)
Age at first birth	88/160,856	0.92 (0.6–1.4)	63/128,606	1.10 (0.7–1.8)	25/32,249	0.54 (0.2–1.3)
Indian						
Parity						
Uniparous	3/22,005	1 (ref)	1/17,923	1 (ref)	2/4,082	1 (ref)
2 Children	10/33,655	1.54 (0.4–6.4)	8/25,598	3.5 (0.4–31.2)	2/8,057	0.70 (0.1–7.0)
3+ Children	4/17,437	0.72 (0.1–4.8)	3/16,581	1.30 (0.1–17.7)	1/4,621	0.77 (0.01–21.8)
Age at first birth	17/76,856	0.81 (0.3–2.1)	12/60,102	0.68 (0.2–1.9)	5/16,760	1.93 (0.2–17.7)

[a] *P* Trend: 0.037; [b]*P* trend: 0.216; [c]*P* trend: 0.044

Age at 1st birth was categorized into the following categories: ≤20, 21–25, 26–30, 31–35, 35+ years and analyzed as ordinal variable

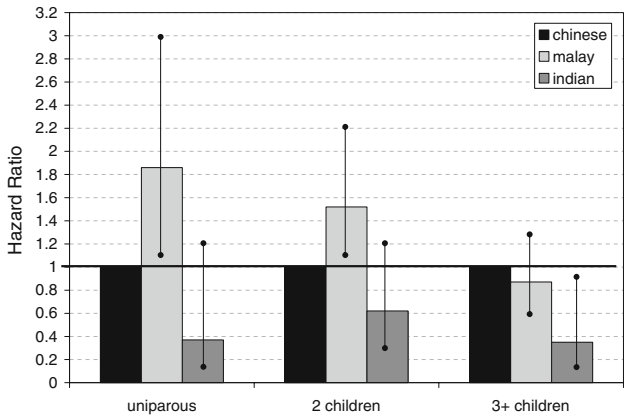

Fig. 2 Hazard Ratio's and 95% Confidence Intervals, representing the risk of premenopausal breast cancer according to ethnicity within parity categories. Chinese women are taken as reference. Hazard ratios are adjusted for age at first birth and age at last birth

birth to ≥3 children. Indian women had lower breast cancer risks than Chinese, regardless of their number of life births.

Breast cancer is a growing problem in Singapore, where incidence rates have almost tripled between 1968 and 2002, from 19.9 to 54.9 new cases per 100,000 person years [12]. This increase affected both pre- and postmenopausal women. The resident population of Singapore (4.2 million inhabitants) is built up of 77% Chinese, 14% Malays, 8% Indians and 1.4% other ethnicities. In the early 1970s, breast cancer rates were highest in Indian women, but today highest breast cancer rates are seen in Chinese [13]. In Indian women, breast cancer incidence rates increase with age and rates are highest among the oldest age groups. In contrast, Malay and Chinese women have increasing breast cancer rates up until the age of 49 years, which level off afterwards [13]. These ethnic differences in incidence trends and age distribution suggest ethnic differences in risk factor exposure or ethnic differences in response to changing risk factors.

The increase in breast cancer incidence in Singapore may be related to Singapore's transition from a developing to a developed country, bringing about changes in lifestyle in the population. Socioeconomic status has increased, diets and exercise levels have changed and more women participate in paid employment. This, together with family planning campaigns, have led to delayed childbearing and smaller family sizes.

Increasing numbers of full term pregnancies reduce the risk of postmenopausal breast cancer, and to a lesser extent, premenopausal breast cancer in Caucasian women [4–8]. During the first years after pregnancy, this protective effect

of parity is transiently reduced, more strongly in uniparous than in multiparous women [14].

In other ethnic groups, the impact of multiparity on breast cancer risk has been less well investigated. In a population-based case–control study including Hispanic women, multiparity was not associated with a reduced risk of pre- nor postmenopausal breast cancer [7]. In a large prospective cohort study, including 56,725 African American women, multiparity was associated with a reduced risk of postmenopausal breast cancer, but an increased risk of premenopausal breast cancer [9]. A similar dual relationship between parity and breast cancer risk in African American women was observed by Hall et al. [8]. A smaller case–control study showed an inverse relationship between parity and premenopausal breast cancer risk for both African American and Caucasian women, but the effect of multiparity was less strong in African Americans [15]. There are only few studies addressing the relation between parity and premenopausal breast cancer risk in Asian populations living in Asia. In a hospital-based case–control study from Singapore, including only Chinese women, mulitparous women did not have lower premenopausal breast cancer risk as compared to uni- or nulliparous women [10]. Another hospital-based case–control study from Vietnam and China showed significantly lower risks of premenopausal breast cancer in parous than in nulliparous women [11]. However, the effect of multiparity as compared to uniparity could not be derived from this study.

We acknowledge that our study suffers from several limitations. Since the Singapore Birth Registry provided no information on women who never gave birth, we were only able to estimate the effect of multiparity on premenopausal breast cancer risk among parous women. Electronic data on births are only available from 1986 onwards, hence it was not possible to have an accurate estimate of the number of nulliparous women. Also, the mean follow up time was rather limited (4.3 years) and we have therefore covered only a part of the premenopausal period for most women. Even though our sample size was large enough to determine the relationship between multiparity and premenopausal breast cancer risk occurring more than 5 years after last pregnancy, longer follow up is needed to better estimate breast cancer risk during the entire premenopausal period. Finally, we recognize that the amount of variables in the birth registry is rather limited, preventing us from adjusting for some other risk factors for breast cancer, in particular breast feeding practices and body mass index (BMI).

Singapore Muslim women are 6.7 and 2.4 times more likely to breast feed their children at 2 and 6 months respectively compared to Buddhist/Taoist women [16]. Since in Singapore around 50% of Chinese women are Buddhist/Taoist and practically all Malay women are Muslims, it can be assumed that Malay women breast feed more and longer than Chinese. Nevertheless, since the protective effect of breast feeding is rather small (relative risk reduction of 4.3% for every 12 months of breast feeding [3]), it is unlikely that differences in breast feeding practices completely explain the risk difference.

Obesity and overweight have a dual impact on breast cancer risk. In premenopausal women, higher BMI scores are inversely related to breast cancer risk, while in postmenopausal women, breast cancer risks increase with increasing BMI [3]. In Singapore, there is an association between ethnicity and overweight/obesity, with highest rates of overweight/obesity in Malays [17]. In addition, parity has a weak positive association with overweight [18]. Therefore, the effect of ethnicity on the relation between parity and breast cancer risk may (partly) be mediated through overweight and obesity. In other words, if Malay women would gain more weight with increasing number of life births than Chinese women, every additional birth may protect them more strongly from developing premenopausal breast cancer.

It has been hypothesized that ethnic differences in pregnancy levels of α-fetoprotein may explain ethnic differences in breast cancer risk [19]. Alpha-fetoprotein binds estradiol and suppresses estrogen dependent growth of breast cancer cells, and may therefore possess anti-carcinogenic properties [20–21]. Serum levels of α-fetoprotein rise sharply during pregnancy and higher pregnancy levels of α-fetoprotein are associated with a lower risk of breast cancer later in life [19, 22]. Lambe et al. compared pregnancy levels of α-fetoprotein between Chinese women from Shanghai and Caucasian women from Boston [23]. After adjustment for gestational length, prepregnancy weight, parity, offspring's sex and maternal age, α-fetoprotein levels around the 16th week of gestation were substantially higher in Chinese women compared to US Caucasian women. This difference could explain (part of) the lower breast cancer risk in Chinese compared to Caucasian women. Future research, comparing serum hormone levels between pregnant Malay, Chinese and Indian women may provide further insight in this matter.

Increasing parity has been shown to particularly reduce the risk of estrogen receptor (ER) and progesterone receptor (PR) positive breast cancer, but not that of ER- and PR-breast cancer [24]. Differences in baseline risk of ER/PR positive breast cancer between ethnic groups in Singapore could therefore also (partly) explain the difference in impact of parity on breast cancer risk between Malay and Chinese women. Unfortunately, we did not have access to detailed information on tumor characteristics.

In summary, our study is the first to show different effects of multiparity on premenopausal breast cancer risk in three Asian ethnic subgroups. Prospective studies, with

detailed information on pregnancy hormone levels and other breast cancer risk factors are needed to unravel the complex relationship between ethnicity, multiparity and premenopausal breast cancer risk in Asia.

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