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Research Article

Differences in Survival of Women with Breast Cancer from Different Ethnic Groups in Singapore- A Population Based Cancer Registry Study and an Institutional Based Review

Benita Kiat Tee Tan[1-3]*, Gek Hsiang Lim[4], Puay Hoon Tan[5], Yoon Sim Yap[6], Yong Wei Sean[1-3], Preetha Madhukumar[1-3], Ong Kong Wee[1-3] and Kee Seng Chia[7]

[1]*Singhealth Duke NUS Breast Centre*
[2]*Department of General Surgery, Singapore General Hospital, Singapore*
[3]*Division of Surgical Oncology, National Cancer Centre, Singapore*
[4]*National Registry of Diseases of Singapore, Ministry of Health Promotion Board, Singapore*
[5]*Department of Pathology, Singapore General Hospital, Singapore*
[6]*Division of Medical Oncology, National Cancer Centre, Singapore*
[7]*Saw Swee Hock School of Public Health, National University of Singapore, Singapore*

***Corresponding author**

Benita Kiat Tee Tan, Senior Consultant, Sing Health Duke-NUS Breast Centre, Department of General Surgery, Singapore General Hospital, Academia, 20 College Road, Singapore 169856, Tel: 6591868137; benita.tan.k.t@singhealth.com.sg

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Keywords

- Breast cancer
- Relative survival
- Ethnic differences
- Receptor status
- Tumour biology

Abstract

Purpose: Remarkable differences in breast cancer incidence in the three main ethnic groups in Singapore have been described, we report the survival differences.

Methods: Using the Singapore national breast cancer registry, and a local hospital registry, relative survival ratios (RSR) were used to describe prognosis. Poisson regression modelling was used to calculate relative risks for different follow-up periods, age groups, time of diagnosis, disease stages and tumour characteristics.

Results: 20517 women patients diagnosed between 1968 and 2006 were included, (Chinese: 85%, Malay: 10%, Indian: 5%). Overall 5-year RSR was highest in the Chinese (79%), followed by the Indians (72%) and the Malays (59%). Survival improved over the years for all, but the differential trend persisted in the stage-by-stage comparison. Malays were younger and had more advanced disease. Malay ethnicity, adjusted for follow-up, age and stage, has an increased risk of death. In the institutional registry, ER/PR status was similar in the 3 ethnic groups. Chinese had less high grade tumours, and were less likely to have lymphovascular and these features remained significant after adjustments for follow-up, stage, ethnicity and tumour subtype. Malay ethnicity remained a significant risk of death after including tumour characteristics (RR 1.7, CI 1.1- 2.7).

Conclusions: Ethnic differences in breast cancer survival in Singapore exist: Chinese have the best survival, followed by the Indians and the Malays. Stage of the cancer, tumour factors such as grade and lymphovascular invasion and perhaps the subtype are responsible for part of this difference. Ethnicity remained an independent risk of death.

ABBREVIATIONS

ASR:Age-Standardised Rate; BMI: Body Mass Index; BTB: Breast Tumour Board; CAP: College Of American Pathologists; CI: Confidence Interval; ER: Estrogen Receptor; FISH: Fluorescence In Situ Hybridisation; HER2: Epidermal Growth Factor Receptor 2, Previously Called HER2/Neu, Or ERBB-2; IHC: ImmunoHistoChemistry; LVI: Lymphovascular Invasion; PR: Progesterone Receptor; RR: Relative Ratio; RSR: Relative Survival Ratio; SES: Social Economic Status

INTRODUCTION

Remarkable differences in breast cancer incidence in the three main ethnic groups in Singapore: Chinese, Malays and Indians have been described [1]. Singaporean women presenting with breast cancer were younger and presented in later stage cancer [1,2] compared to the Western population. Within the region, ethnic differences in presentation and survival seen in clinical practice was reported in a recent Singaporean-Malaysian series where Malay women had the poorest outcome [3].

Breast cancer survival is affected by tumour biology, stage of disease, treatment and treatment response. Role of ethnicity in survival in the SEER data has been largely attributed to increased diagnosis of late-stage breast cancers, which could be explained by delayed diagnosis reflecting the socioeconomic status, cultural beliefs, access to healthcare [4]. Some of these factors are also related to the immigration as 1st generation migrants have been shown to have poorer survival [5]. However, ethnic differences in tumour biology [6] and other surrogate factors for other determinants, of aggressive breast carcinoma and specific cell cycle defects have been observed [7] Demicheli R et al suggested that survival differences not due to socioeconomic factors between ethnic groups was likely a result of host-tumour interaction where genetic, environmental, or behavioural traits of individuals may be affected by ethnic-related factors [8].

The three ethnic groups in Singapore have relatively similar changes in reproductive and socioeconomic changes, and equal access to heavily subsidised healthcare. Understanding the ethnic differences in disease presentation, patient demographics, tumour biology and acceptance of treatment is important for recommendations of public health education and planning to improve the outcome of these women with breast cancer in Singapore. In this study, we described for the first time, the ethnic differences in survival of women with breast cancer in Singapore using the national cancer registry, as well as the effects of tumour biology on survival, from an institutional registry.

Translational Relevance

Ethnic differences in breast cancer survival have been attributed to late stage diagnosis reflecting socioeconomic status, cultural beliefs, and access to care. Singapore is unique with a multiracial population living in a small city state, has a good standard of living, and an efficient and accessible system of healthcare. We observed the difference in breast cancer survival amongst the ethnic groups: Chinese women experienced the best outcome and the Malays, the poorest. Stage of cancer, tumour factors such as grade, LVI and perhaps tumour subtype were responsible for part of this difference; ethnicity and related factors added significant contribution. This observation is important to guide breast cancer management: efforts on screening and health education to improve the awareness and health care seeking behaviour of Malay women with breast cancer; efforts to further study the differences in biological factors by ethnicity and identify other biological factors not yet identified could provide further insight.

MATERIALS AND METHODS

Study population

National cancer registry: All cases of invasive breast cancer diagnosed from 1 January 1968 to 31 December 2006 were obtained from the Singapore Cancer Registry, National Registry of Diseases Office (NDRO). Patients with a previous malignancy, including contra lateral breast cancer, and those diagnosed with breast cancer at autopsy (death certificate only) were excluded from the study. The cause of death was coded in accordance with the International Classification of Diseases and Causes of Death ICD9. For the comparison between ethnic Chinese, Malays and Indians in Singapore, 20517 women diagnosed between 1968 and 2006 were included in the study. Follow-up was performed and available until 31 December 2008 by matching with the national death register. The study was exempted from ethnics review by National University of Singapore Institutional Review Board as the research work was based on aggregate and anonymised data; individual patient consent was not required.

The stage of the breast cancer in the Singapore Cancer Registry was classified as localized cancer, regional spread and distant metastases based on the notification forms before 2001. Cancers are staged as local if they are confined entirely to the breast. Regional cancers are those that have extended beyond the limits of the breast directly into surrounding tissues or organs, or into lymph nodes in the region. Distant cancers are those that have spread beyond these locations. No attempt was made to access the extent of localized invasion or the number of regional lymph nodes involved.

Institutional based cancer registry: As the national registry did not collect information on tumour characteristics such as receptor status, our institutional based breast cancer registry was used. This registry prospectively records patient diagnosed and treated for breast cancer in Singapore General Hospital (SGH) and National Cancer Centre, Singapore (NCCS), through our weekly breast tumour boards since 2001. This records almost 700 new cases of breast cancers a year from the adjacent centres, and consists of a multidisciplinary team of breast surgeons, medical and radiation oncologists, and pathologists who practice in both these tertiary centres. Patient demographics, cancer histological characteristics including receptor status, tumour grade, lymphovascular (LVI) status, staging details, surgery and neoadjuvant treatment details are recorded in a computer database, maintained by an informatics team. Adjuvant treatment recommendations made at the meeting are also recorded.

A total of 2245 Chinese, Malay and Indian female Singaporean residents with unilateral primary invasive breast carcinoma recorded from 2001 to 2007 were included. Women from 2001 to 2006 in this registry would be a subset of women in the national registry. Women with a previous malignancy, including contra lateral breast cancer were excluded. Follow-up to 31 December 2010 with death information was obtained by matching with the national death register and case note reviews. Approval for the study was obtained from the Sing Health Centralised Institutional Review Board; individual patient consent was not required.

Analysis

Association of clinical variables between ethnic groups were performed using chi-square test. Two age groups (</= 50 years old and >50 years old) were used to represent the premenopausal and postmenopausal age groups in this analysis. Classifications into clinical subtypes: ER/PR positive (either HER2 positive or negative), triple negative (ER, PR and HER2 negative) and HER2 positive (ER/PR negative, HER2 positive) was performed for the institutional registry according to the ER, PR and cerbB2/HER2 status on IHC and/or FISH. Interactions between ethnicity and the age of diagnosis, and between the calendar period and the age of diagnosis, were also analysed. Descriptive prognostic comparisons between the ethnic groups were performed by relative survival analyses. Relative survival ratios were computed by taking the ratio of observed survival to expected survival, accounting for the competing causes of

death. The expected survival probabilities were calculated using Ederer II method derived from the general female population in Singapore by ethnicity, similar to the breast cancer patients in terms of attained age, ethnicity and calendar period of diagnosis. Cumulative relative survival ratios were age-standardized to the world standard cancer population [9]. Join point regression analysis was used to estimate the annual mortality trends from the five-yearly rates available for the population [10]. The cause of death information was used only to calculate the cause-specific mortality rate, which is the total of breast cancer deaths divided by the total female population of each ethnic group. Poisson regression model was used to calculate the excess hazards of death following relative survival analysis, taking into account the age, disease stage, period of diagnosis, ethnicity, years of follow-up and tumour biology: subtype, grade and lymphovascular invasion(LVI) in the respective dataset. STATA 10 (StataCorp. College Station, TX: Stata Corporation) was used for the statistical analyses.

RESULTS

Descriptive data

Table 1 presents the characteristics of the Singaporean women diagnosed with invasive breast cancer, recorded in the national cancer registry and our institutional breast cancer registry. Two thirds of the women in the national registry were born in Singapore, Chinese 68%, Malays 62% and Indians 42%. The distribution of stage of the cancer was similar by the country of birth. Malay women tended to be younger and were diagnosed in a later stage compared to the Chinese and Indians. Over the calendar periods, there was an improvement in the stage of diagnosis as more were diagnosed with local stage cancer, with the Chinese showing the most improvement. Fewer Malay women presented with regional stage cancer over the calendar periods but the proportion with metastatic cancer remained the same. The institutional registry, where the period of diagnosis was similar to the later calendar period of 2000-2006, had more

Table 1: Characteristics of Singaporean women with breast cancer by ethnicity.

Characteristic	Chinese		Malays		Indians		Total		p value
		%		%		%		%	
National cancer register, from 1968 to 2006*									
Frequency	17499	85	2007	10	1011	5	20517	100	
Period of diagnosis									0.042
1968-1989	4157	86	420	9	230	5	4807		
1990-1999	6012	85	693	10	341	5	7046		
2000-2006	7330	85	894	10	440	5	8664		
Non-immigrants									<0.005
1968-1989	2353	57	287	68	89	39	2729	57	
1990-1999	4070	68	393	57	153	45	4616	66	
2000-2006	5499	75	556	62	247	56	6302	73	
Age group									<0.005
1968-1989									
≤50	2082	50	246	59	125	54	2453		
>50	2075	50	174	41	105	46	2354		
1990-1999									
≤50	3075	51	441	64	150	44	3666		
>50	2937	49	252	36	191	56	3380		
2000-2006									
≤50	3313	45	516	58	189	43	4018		
>50	4017	55	378	42	251	57	4646		
Stage** (% complete)	3658	76	4250	60	6622	76	14530	71	<0.005
1968-1989									
Local	1497	47	106	34	84	47	1687	46	
Regional	1386	44	157	50	81	45	1624	44	
Distant	281	9	52	16	14	8	347	9	
1990-1999									
Local	1977	54	168	42	99	46	2244	53	
Regional	1393	38	170	42	102	47	1665	39	

Distant	262	7	64	16	15	7	341	8	
2000-2006									
Local	3567	64	316	47	187	56	4070	61	
Regional	1652	29	257	38	120	36	2029	31	
Distant	396	7	99	15	28	8	523	8	
Deaths	6518	37	993	49	426	42	7937	39	<0.005
Breast cancer deaths	4736	27	795	40	311	31	5842	28	<0.005
Institutional cancer register, from 2001 to 2007‡									
Frequency (%)	1940	(86)	192	(9)	113	(5)	2245		
Age group (%)									<0.005
≤50	753	39	105	55	54	48	912	41	
>50	1187	61	87	45	59	52	1333	59	
Stage ‡ (% complete)	1925	99	191	99	113	100	2229	99	<0.005
Local	1085	56	73	38	58	51	1216	55	
Regional	768	40	101	53	51	45	920	41	
Distant	72	4	17	9	4	4	93	4	
Deaths	324	17	54	28	21	19	399	18	<0.005
Breast cancer deaths	283	15	48	25	19	17	35	16	<0.005

Women with first diagnosis of unilateral breast cancer and no history of previous other cancers
* Follow up till 31 December 2008
† Follow up till 31 December 2010
** Staging is likely a combination of clinical and pathological staging
‡Staging is based on pathological staging except for 7% of cases with neoadjuvant chemotherapy and 4% with metastatic disease.

Table 2: Tumour characteristics by ethnicity.

Characteristic (%)	**Chinese**		**Malays**		**Indians**		**Total**		**p**
Receptor status									
ER (% available)	1910	98	192	100	111	98	2213	99	
Positive	1300	68	127	66	70	63	1497	68	0.493
Negative	610	32	65	34	41	37	716	32	
PR (% available)	1901	98	191	99	111	98	2203	98	
Positive	1108	58	110	58	66	59	1284	58	0.951
Negative	793	48	81	42	45	41	919	42	
HER2 (% available)	1624	84	167	87	100	88	1891	84	
Positive	390	24	47	28	20	20	457	24	0.3
Negative	1234	76	120	72	80	80	1434	76	
Grade of tumour (% available)	1837	95	187	97	109	96	2133	95	
1	329	18	27	14	12	11	368	17	0.015
2	701	38	57	30	40	37	798	37	
3	807	44	103	55	57	52	967	45	
LVI (% available)	1695	87	170	89	100	58	1965	88	
No	1205	71	102	60	65	65	1372	80	0.006
Yes	409	29	59	40	35	35	593	30	
Subtype classification									
Frequency (% available)	1604	83	165	86	100	88	1869	83	0.298
ER/PR positive	1162	72	120	73	68	68	1350	72	
HER2-	959	60	92	56	56	56	1107	59	
HER2+	203	12	28	17	12	12	243	13	
Triple negative	258	16	26	16	24	24	308	16	
HER2 positive	184	11	19	12	8	8	211	11	

ER/PR positivity is based on 10% or more of invasive tumour cells staining with an intensity of at least 2+.HER2 positivity is based on cerbB2 by IHC: 65% had raw scores of intensity of 3+, 35% were recorded as positive without details of raw scores; IHC 0/1+: negative: IHC 2+: equivocal.
LVI: lymphovascular invasion; HER2 positive: ER-, PR-, HER2+; triple negative: ER-, PR-, HER2-

women with regional disease in all the ethnic groups, maintaining the similar differential trend. This is likely reflecting the patient selection in a tertiary centre. All cause and breast cancer death was highest amongst the Malays during the follow-up period.

As the national register did not record details of tumour characteristics, these were studied using the institutional registry (Table 2). The proportions of ER positive, PR positive and HER2 positive tumours were similar between the ethnic groups. The HER2 receptor positivity was more common amongst the Malays although this was not statistically significant. When the tumours were classified into clinical subtypes based on the receptor status, there appears to be more triple negative tumours amongst the Indians but this was not statistically significant (p=0.298). There were higher grade tumours and tumours exhibiting LVI amongst the Malays, followed by the Indians; the Chinese had the lowest proportion. Within each ethnic group, there was no significant change in ER and PR positivity and LVI by age groups; but in the Chinese, proportion of grade 3 tumours decreased with increasing age (p=0.042), this trend was also present in the Malays, though not significant (p=0.234), while the numbers were too small amongst the Indians. Consistent with known literature [11], review of the tumour factors show that ER and PR negative tumours were more likely high grade; HER2 positive tumours were more likely LVI positive. There was a shift in the later 3 years towards more ER/PR+ tumours compared to the initial 4 years (Supplementary information, Table 1).

Treatment information was not available in the national registry and incomplete in the institutional registry for consideration; surgical treatment was available for the latter registry. Ninety-six per cent of the women in the institutional registry had surgery, with either a mastectomy or breast conservation and axillary surgery (Supplementary information, Table 2). Detailed information on adjuvant therapy such as chemotherapy, hormonal therapy, targeted therapy (Trastuzumab) and radiotherapy were not available in the database, but were available as Tumour Board recommendations, as intention to treat.

Survival Analysis

The overall relative survival for women diagnosed with breast cancer from 1968 to 2006 in the national registry was better amongst the Chinese, with the Malays showing the poorest survival (Figure 1). The overall age-standardized 5-year relative survival for the Chinese, Malays and Indians was significantly different at 79%, 59% and 72%, respectively. This trend persisted when the women were stratified by period and stage of diagnosis. Within each ethnic group, there was improvement in survival across the calendar period of diagnosis where the Malay women with regional disease diagnosed in the later calendar period making the largest improvement (Table 3A).

The institutional registry showed similar trend where the Chinese constantly outperformed the Malays and the Indians. The overall age-standardized 3-year relative survival for the Chinese, Malay and Indian women in the institutional registry was at 90%, 76% and 75% respectively. The Chinese women also performed better when stratified by stage in the institutional cohort, the 3-year RSR amongst the Chinese women with localised cancer was 105% (see discussion); however, the Malay women with regional disease in the institutional registry appeared to do better when compared to the national registry (Table 3B). However, the 95% confidence interval is wider amongst the Malays and Indians, likely due to the small numbers.

Overall prognosis by subtype classification (Figure 2A) showed that women with ER and/or PR positive tumours have excellentsurvival, those whose tumours were also HER2 negative performed better than those HER2 positive. Womenwith triple negative (ER/PR/HER2-) and ER/PR-, HER2+ tumours fared poorer (p<0.05). As the numbers amongst the Malays and Indians were small, the subtype classification was regrouped into 2 groups: ER/PR+ and ER/PR-, regardless of the HER2 status. There is substantial difference in the 3-year relative survival amongst the Malays, the p-value was borderline significant (p=0.056, Figure 2B); with smaller difference among the Chinese. This is likely a reflection of the substantially smaller sample size of Malay women. The number of events was still too few amongst the Indians to show any discernible estimates.

Poisson regression: excess risk of death

Table 4a presents the risk of death of the Singaporean women in the national registry taking age, disease stage, period

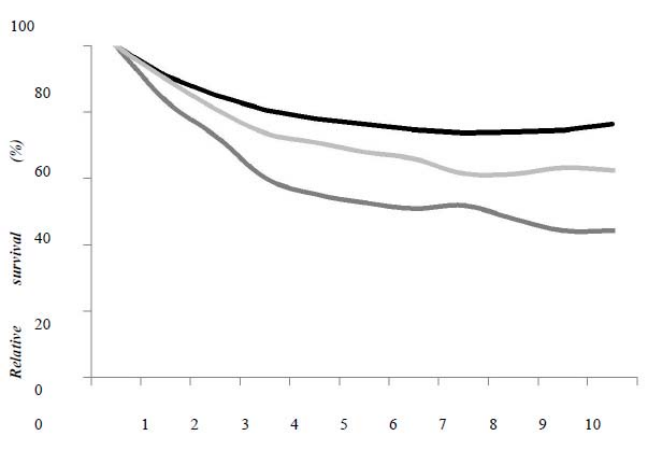

Figure 1 Age-standardized RSR by Ethnicity Years since diagnosis.

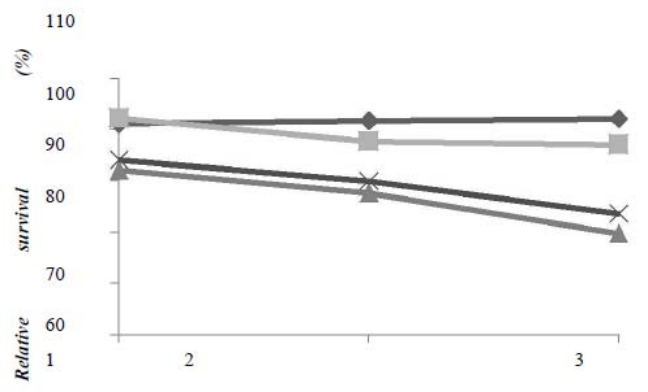

Figure 2a Age standardized RSR by tumour subtype Year since diagnosis.

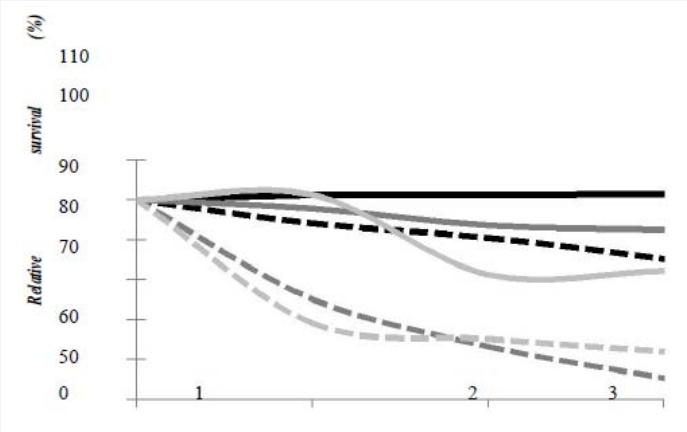

Figure 2b Age standardized RSR by Ethnicity and Subtype Years since diagnosis.

of diagnosis, years of follow-up and ethnicity. As expected, the stage of cancer is an important predictor of survival. The risk of death was decreased in the later calendar period of diagnosis but it remained the highest amongst the Malay women. The immigration status and country of birth did not affect the risk of death (results not shown).

As the survival for ER/PR+/HER2+ and ER/PR+/HER2- were similar in this study likely because of the small numbers of Malay and Indian women in the study, they were grouped as ER/PR+ in the univariate and multivariate analysis; age was not a significant factor. On multivariate analysis, as expected, the stage of cancer is an important predictor of survival. Tumour subtype, grade, LVI and ethnicity remained as independent prognosticators for overall survival. Malay women had a 70% increase in the risk of death compared to the Chinese women (Table 4b).

DISCUSSION

Singaporean women with breast cancer present differently and experience differential survival between ethnic groups. Malay women were younger and were with later stage cancer. Chinese women had the best overall survival compared to the Indian and Malay women. This was partially contributed by more Chinese women presenting in earlier stage breast cancer and favourable tumour biology such as lower grade and absence of lymphovascular invasion. In contrast, Malay women presented in later stage of breast cancer and more had poorer tumour biology. Consistent with literature, Singaporean women with early stage cancer and tumours of better biology perform better with similar trends. However, after taking the various clinical parameters that contribute to the risk of death: period of diagnosis, stage and tumour biology, ethnicity remained as independent risks factors of death.

Survival from breast cancer is dependent various factors, but namely biology of the tumour, stage of the cancer at diagnosis and the treatment received. In Asian populations, breast cancers in premenopausal young women were associated with higher grade, lymph node involvement and LVI even when majority of tumours were ER and PR positive, and associated with a higher proportion of cerbB2-positive tumours compared to SEER data [12]. Malay women presenting younger with higher mortality are also reminiscent of the premenopausal breast cancers among the women in United States. Malay women tended to have more children compared to Indians and Malays, where 60% of them had 3 or more children [13]. Multiparty could have contributed to a decrease in post-menopausal breast cancer amongst the Malays, reducing the median age of women with breast cancer in Malays; this itself could have been the reason of higher grade cancers amongst the Malays. In addition, earlier age of the first birth and

multiparty at a young age are risk factors to the development of tumours with poorer biology of higher grade and presence of LVI. Singaporean Indians appear to have a higher proportion of triple negative cancers, also seen in the African Americans [14], although this was not statistically significant; but this may be limited by selection bias in a single tertiary institution not reflective of the national population. Ethnic groups found to have tumours of more aggressive biology related to ethnicity and differences in gene expression patterns between the ethnic groups have been reported [15–17]. Genetic loci newly associated with breast cancer had been reported in East-Asians [18] though genetic differences accounting for the difference in breast cancer tumour biology in Singapore have not been reported. However, reports on difference in gene polymorphisms for cell toxicity pathways, drug metabolism and lipid metabolism between the ethnic groups in Singapore have been reported [19–21]and perhaps there will be breast cancer related genetic differences between the ethnic groups that could account for the difference we observe. Other biological factors not seen by the ER, PR or HER2 phenotype, grade and lymphovascular invasion that may exist between the ethnic groups have yet to be identified. Other risk factors such as BMI, diet, and other behavioural or environmental differences are not available in this study. But Singapore have few women who smoke 3.2% (2004 National Health Survey statistics) [22]. Only about 6% of postmenopausal women in Singapore are on hormonal replacement therapy for menopause [23]; Chinese women have a high intake of soy and consume the lowest amount of dietary fat [24] while Malay women are less likely to consume alcohol. Prevalence of obesity (BMI>/=30kg/m2) is highest in Malay women (24%), compared to the Chinese (8%) and Indians (17%) as reported in the National Health Survey 2010 [13] and this may also be contributory.

Table 3: Relative and observed survival of Singaporean women by ethnicity and stage.

		Relative survival ratio (CI)					**Observed survival rate (CI)**			
A) National registry (1968-2003*) 5-year age-standardized survival										
		1968-1989								
Chinese	Local	83	81	-	86		75	73	-	77
Malays		62	52	-	72		58	48	-	67
Indians		73	61	-	82		68	57	-	76
Chinese	Regional	50	47	-	53		44	42	-	47
Malays		35	27	-	43		33	26	-	40
Indians		45	34	-	57		42	31	-	53
Chinese	Distant	22	17	-	28		19	14	-	24
Malays		8	3	-	18		8	2	-	17
Indians		23	6	-	48		21	5	-	45
		1990-2003								
Chinese	Local	97	96	-	98		90	89	-	91
Malays		86	81	-	90		82	77	-	86
Indians		94	88	-	99		87	81	-	91
Chinese	Regional	76	73	-	78		70	68	-	72
Malays		64	57	-	69		60	54	-	66
Indians		72	63	-	79		67	59	-	73
Chinese	Distant	32	27	-	37		28	24	-	33
Malays		22	14	-	31		20	13	-	29
Indians		21	9	-	37		20	8	-	36
B) Institutional registry (2001-2007) 3-year age-standardized survival										
		Relative survival ratio (CI)					**Observed survival rate (CI)**			
Chinese	Local	105	98	-	108		96	91	-	98
Malays		77	58	-	82		74	56	-	78
Indians		80	73	-	82		77	71	-	79
Chinese	Regional	93	81	-	101		86	75	-	92
Malays		84	62	-	98		78	57	-	91
Indians		78	66	-	81		76	64	-	79
Chinese	Distant	52	22	-	79		49	21	-	74
Malays		32	2	-	62		30	2	-	58
Indians		**								

*Women with breast cancer diagnosed up to 2003 were included to provide a minimum 5 years of follow up to calculate the 5 year survival rate.
Observed survival rate is the percentage of women alive
Relative survival is the ratio of observed survival to the expected survival rate of the population

Table 4: Poisson regression analysis for excess risk of death for relative survival ratio.

A. National Registry

	HR	95% CI		p			HR	95% CI		p
Period of diagnosis										
1968-1989						**1990-2003**				
Year of follow-up						**Year of follow-up**				
1	1.0	(reference)				1	1.0	(reference)		
2	1.1	1.0	1.3	0.162		2	1.3	1.1	1.6	0.001
3	1.0	0.9	1.2	0.979		3	1.3	1.1	1.6	0.002
4	0.7	0.6	0.9	0.002		4	1.2	1.0	1.5	0.028
5	0.7	0.5	0.8	<0.005		5	1.0	0.8	1.3	0.785
Age group						**Age group**				
<35	1.0					<35	1.0			
35-54	0.7	0.6	0.8	<0.005		35-54	0.8	0.6	1.0	0.072
45-54	0.8	0.7	1.0	0.035		45-54	0.7	0.6	0.9	0.013
55-64	0.9	0.8	1.1	0.49		55-64	0.9	0.7	1.2	0.63
65-74	0.8	0.6	1.0	0.026		65-74	0.9	0.7	1.2	0.475
75+	0.9	0.6	1.3	0.451		75+	1.0	0.7	1.4	0.94
Stage						**Stage**				
Local	1.0	(reference)				Local	1.0	(reference)		
Regional	3.2	2.8	3.7	<0.005		Regional	5.1	4.2	6.0	<0.005
Distant	9.5	8.0	11.2	<0.005		Distant	23.3	19.3	28.2	<0.005
Ethnicity						**Ethnicity**				
Chinese	1.0	(reference)				Chinese	1.0	(reference)		
Malay	1.7	1.5	2.0	<0.005		Malay	1.6	1.3	1.8	<0.005
Indian	1.1	0.8	1.4	0.623		Indian	1.3	1.1	1.7	0.015

Adjusted for year of follow-up, age, stage and ethnicity

HR: hazard ratio; CI: confidence interval

B. Institutional Registry

Variable	HR	95% CI		p		Variable	HR	95% CI		p
Univariate*						**Multivariate****				
Clinical						**Clinical**				
Ethnicity						Year of follow up				
Chinese	1.0	(reference)		<0.005		1	1.0	(reference)		
Malay	2.5	1.6	6.3	<0.005		2	2.2	1.2	4.0	0.011
Indian	0.9	0.3	2.5	0.891		3	2.4	1.3	4.4	0.004
Age						Ethnicity				
</= 50	1.0	(reference)				Chinese	1.0	(reference)		<0.005
>50	0.9	0.6	1.3	0.461		Malay	1.7	1.1	2.7	0.023
						Indian	0.7	0.3	1.8	0.488
Stage						Stage				
Local & Regional	1.0	(reference)				Local & Regional	1.0	(reference)		
Distant	12.3	7.9	19.1	<0.005		Distant	6.9	3.5	13.6	<0.005
Tumour						**Tumour**				
Subtype						Subtype				

ER/PR positive	1.0	(reference)				ER/PR positive	1.0	(reference)		
Triple negative	4.4	2.7	7.0	<0.005		Triple negative	3.4	2.2	5.3	<0.005
HER2 positive	3.5	2.0	6.0	<0.005		HER2 positive	2.1	1.3	3.4	0.003
Grade						Grade				
1 and 2	1.0	(reference)				1 and 2	1.0	(reference)		
3	1.6	1.0	2.2	<0.005		3	1.7	1.1	2.6	0.028
LVI						LVI				
Yes	1.0	(reference)				Yes	1.0	(reference)		
No	0.2	0.1	0.3	<0.005		No	0.4	0.3	0.6	<0.005
*Adjusted for years of follow up, ethnicity, age, stage, tumour subtype, grade and LVI										
**Adjusted for years of follow up, ethnicity, stage, tumour subtype, grade and LVI										
HR: hazard ratio; CI: confidence interval										

The consistent overall decreased risk of death in all ethnic groups across the study period coincides with the economic restructuring and improvements in Singapore the 1980s and 1990s, decades [25]. There are improved living standards, improved education and presumably better awareness of the disease and better healthcare. Singapore enjoys a large network of affordable primary healthcare services that refer to heavily subsidized hospital and specialist care services. This is also reflected in the time trend towards less advanced tumours being diagnosed, where a small but definite increase in women with localized disease and a corresponding decrease in women with regional disease. There was a shift towards more ER-positive disease during the latter part of the study period which could reflect screening practices and influence survival [26]. This is also supported by the finding of an increase in incidence of ductal carcinoma in situ from 0.4% in 1983 to 1989 to 8.1% in 1999, to (Singapore Cancer Registry statistics), an indicator of increased mammographic screening. Earlier diagnosis by screening can cause lead-time bias and falsely depict better survival. Uptake of screening differs between the ethnic groups as reported in the National Health Survey where fewer Malay women had knowledge of mammograms or had ever had a mammogram. We could then expect more Chinese women with slow-growing breast cancers with good prognosis such as tumours of a lower grade being diagnosed lending to a better outcome [27]. This is echoed by the differences in stage distribution of breast cancer amongst the ethnic groups where the more Chinese women presented in early stage. The overall response rate to the national breast screening is low at about 30%; hence the contribution of screening to over diagnosis may be low, but still an important consideration. However, this is difficult to quantify without a randomized trial.

Malays in Singapore tended to have poorer SES, Singapore Population Census [28] and this is also associated with lower education and together, these could affect their awareness and understanding of the disease, seeking of medical attention including screening and their choice of accepting recommended treatment. This is supported by the higher proportion of more advanced stage cancer in this study, likely synonymous with delay in seeking treatment. Cultural and religious beliefs that affect relationships with men, perceived risk, differences in coping mechanisms that our women have when faced with the fear of being diagnosed with breast cancer, may also affect their attitude to the disease, and hence delay diagnosis and treatment. Several studies from our neighbouring Malaysia showed that fear of surgery, influence by friends, belief that alternative therapy works, bad experience in hospital, financial problems, fear of inability to work after the mastectomy, lack of time, having young children, believing that prayer was sufficient, were reasons for delaying medical attention and treatment, and choosing alternative therapy were especially prevalent amongst the Malays [29,30]. A report in 2007 studying women who present with late disease revealed that a fatalistic view of cancer may be a reason for women not wanting to have treatment [31]. Use of alternative therapy was another observation in this group, which included oral preparations, applications and spiritual prayers. These psychosocial factors due to the similar cultural and religious beliefs in the ethnic groups may be the reason for the disparity seen in Singapore.

A relative survival greater than 100% indicates better survival among the Chinese women with localized breast cancer than in the general population. This may be observed when statistics are based on small numbers of cases, unlikely in this study; or competing mortality is lower in these women as compared with the general population. This may be due selection bias of Chinese women with lower comorbidity with tumours that are indolent, nonlethal and do not limit their survival. This may also be due to a 'healthy patient effect', whereby these patients experience lower mortality due to other causes as a result of having greater than average contact with the health system, change in lifestyle and health habits after breast cancer diagnosis which alters death rates from other diseases. This is similar to a study where a relative survival >100% was seen in men with low-grade prostate cancer, regardless of treatment, at least during the first 5 years [32].

Other confounding factors such as such as registry completeness, stage migration and distribution and immigration

have to be considered when analysing trends in cancer survival. The strengths of our study include the large number of cases from a population-based registry that report a high level of reliability [33,34]. Singaporeans have individual unique national registration numbers as citizens and permanent residents that allow for accurate personal data collection. Women with bilateral breast cancers, previous breast cancer or multiple cancers and those diagnosed with breast cancer at autopsy (death certificate only) can be excluded from the study. Contribution of immigration and emigration is low in Singapore, where migrations were from China, India and the archipelago surrounding Singapore [35,36]. In this cohort in the national registry, 67% of the women were born in Singapore, hence at least 2nd generation citizens (supplementary data, Table 3). The study also extends over three decades, which was probably long enough to observe differences and allow the study of trends. This is also the first nation-wide study of ethnic differences in survival of women with breast cancer. The single institution based database has limitations of selection bias, being a tertiary centre which may treat patients with different medical attention seeking behaviour and treatment preferences; completeness of the database and sample size. However, being the largest institution in Singapore, it still recorded a large number of cases, treating about 700 cases of breast cancer a year. The clinic-pathological information in the database enabled the study of factors otherwise not available in the population database during the same period. The number of Indian and Malay women was small compared to the Chinese and this has potential sample size bias with decreased predictive potential with less than steady trends when associations with various covariates were studied.

Incomplete disease stage information for one-third of women in the national registry is a limitation that could affect stage distribution. To our knowledge, every effort has been put in to ensure the completeness of cancer reporting over the years. Clinical staging information, which used to be reported voluntarily, could contribute to the lack of information. There is now a follow-up mechanism by the registry to obtain detailed clinical information from the clinical case notes. The proportion of unknown disease stage was hence worst in the early 1990s, only 52% with complete clinical staging for cases in 1990 to 1994 ($p < 0.001$), and this improved in the last 5 years of the study. This incomplete staging is probably random; however, as the age-standardized survival for the Singaporean women with unknown disease stage was comparable with the overall survival of those with stage information (data not shown). It is possible that, in the earlier years, node-positive tumours were under diagnosed with less thorough axillary dissection or histological assessment and falsely classified as being localized, and hence appeared to have poorer survival; the proportion of such cases is unknown in this study, but is probably small. Active screening for distant metastases at the time of initial diagnosis, a practice routinely adopted in Singapore can induce stage migration and increase the stage-dependent survival in all stages but this is likely consistent across ethnic groups. The completeness of tests on tumour characteristics such as receptor status, LVI and grade were not available in 5 to 17% of the cases in the institutional registry. This was inevitable as some of these tumours were too small to assess these parameters or the IHC tests failed on the sample. Study of these early cancers in relation to their receptor status would be diminished, but fortunately these did not contribute a large number. Exclusion of unknown cases when there was a selection criteria applied for the assessment of these parameters, for example, selection based on expected mortality or on other clinical parameters on the HER2 may introduce bias for complete case analysis [37]. In this series where complete receptor status, i.e., all 3: ER, PR and cerbB2 were not available was mainly due to the indeterminate or unknown HER2 status (74%), as cerbB2 by IHC or HER2 status by FISH was not routinely performed till 2007 when the use of tratzutamab became standard adjuvant therapy; the rest were not assessable because of a small invasive focus or in post-neoadjuvant cases. This by itself would introduce a similar selection bias as referenced, but perhaps to a lesser degree as more than 80% of the tumours had known HER2 status, either positive or negative. In this study, the relative survival for the unknown group was very similar to the ER+/PR+/HER2- group i.e., of good prognosis and account for about 16% of all the cases, of which two thirds were ER/PR positive. When these cases were reviewed and compared against the various parameters, they were comparable by stage, ethnicity and age, hence in risk stratification against these variables, the bias if present is unlikely significant. Treatment information is not available except for surgery in the institutional registry is also a limiting factor as confounding due to differences in treatment between the groups may impact the survival outcome.

CONCLUSION

In conclusion, we demonstrated the difference in breast cancer survival amongst the ethnic groups in Singapore, with Chinese women experiencing the best outcome and the Malays with the poorest outcome. Stage of the cancer, tumour factors such as grade, LVI perhaps tumour subtype were responsible for part of this difference. Psychosocial factors related with ethnicity likely contribute to differences in health seeking behaviour and this difference; hence efforts on health education to improve the awareness and health care seeking behaviour would be important in improving the outcome of Malay women with breast cancer. Biological factors such as genetic factors not yet identified could contribute to this ethnic difference, hence further efforts to identify these biological factors provide further insight to this observation and guide further improvements in breast cancer management in Singapore.

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Authors' contributions

BT and CKS conceived of the study, BT and LGH participated in its design analysis and carried out the statistical analysis. BT and CKS contributed to the epidemiological aspects and

participated in the interpretation of data. All authors contributed to the writing of the manuscript. All authors read and approved the final manuscript. All authors have given final approval of the version to be published

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