

RESEARCH ARTICLE

Do Breast Cancer Risk Factors Affect the Survival of Breast Cancer Patients in Southern Sri Lanka?

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Abstract

Background: Breast cancer continues to be a major cause of morbidity among women in Sri Lanka. Possible effects of etiological risk factors on breast cancer specific survival (BCSS) of the disease is not clear. This study was designed to explore the impact of breast cancer risk factors on the BCSS of patients in Southern Sri Lanka. **Method:** This retro-prospective study included all breast cancer patients who had sought immunohistochemistry services at our unit from May 2006 to December 2012. A pre-tested, interviewer-administered questionnaire was used to gather information on risk factors. BCSS was estimated using the Kaplan-Meier model. Univariate Cox-regression analysis was performed with 95% confidence intervals using the SPSS statistical package. **Results:** A total of 944 breast cancer patients were included. Five year BCSS was 78.8%. There was a statistically significant difference between the patients who had a family history of breast cancer and no family history of any cancer in terms of the presence/absence of lymph node metastasis ($p=0.011$) and pathological stage ($p=0.042$). The majority of the premenopausal patients had associated DCIS ($p<0.001$) and large tumours ($p=0.015$) with positive lymph nodes ($p=0.016$). There was no statistically significant association between hormone receptor subtypes and hormone related risk factors. Univariate analysis revealed that breast cancer risk factors had no significant effect on the BCSS. **Conclusion:** Even though family history of breast cancer and premenopausal status are associated with poor prognostic features, they, in line with the other breast cancer risk factors, appear to have no significant effect on the BCSS of patients in Southern Sri Lanka.

Keywords: breast cancer- breast cancer specific survival- risk factors- Southern Sri Lanka

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Introduction

Breast cancer is the commonest malignancy among females worldwide and also it is the leading malignancy among females in Asian countries as well (Farley et al., 2015). In Sri Lanka, breast cancer is the commonest cancer since the year 2000, when all age groups and both females and males are taken into account (Cancer Incidence Data, 2005 and 2009). The breast cancer mortality rate has increased and it is the cause of highest cancer mortality rate for Sri Lankan females (Cancer Incidence Data, 2005 and 2009).

There are well established risk factors for breast cancer; family history of breast cancer, early age at menarche, late age at menopause, being >30 years at first full term pregnancy, nulliparity, lack of breast feeding, use of oral contraceptive pills (OCP) and use of hormone replacement therapy (HRT) (Hulka and Moorman, 2001; De Silva et al., 2010; Lodha et al., 2011).

Presence of these risk factors is associated with clinically important tumour characteristics including poor prognostic features (Lu et al., 2011).

Hence, risk factors of breast cancer may predict the survival of females with breast cancer. However the effect of the risk factors on the survival of patients who have developed breast cancer is still controversial. Late age at first birth, multiparity, recent use of OCP and high BMI (Body mass index) are reported to have a negative impact on the survival of breast cancer patients (Barnett et al., 2008; Alsaker et al., 2013; Butt et al., 2009). Contrastingly some investigators have found that use of OCP and parity had no impact on survival (Barnett et al., 2008; Lu et al., 2011). Many previous publications have described that reproductive or hormonal risk factors had no impact on the survival of patients with breast cancer (Barnett et al., 2008; Ewartz et al., 1991).

Data on risk factors of breast cancer in Sri Lankan female population is sparse and the effect of those risk factors on the survival is not available in the literature. Therefore this study was designed to determine the distribution of breast cancer risk factors among those who have developed breast cancer in the Southern Province of Sri Lanka and to analyze the effect of breast cancer risk factors on the breast cancer specific survival (BCSS) of

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the cohort.

Materials and Methods

This was a study with retrospective and prospective patient follow-up. Out of the 1068 female patients with breast cancer who had sought the services of the Diagnostic Immunohistochemistry Laboratory, Department of Pathology, Faculty of Medicine, University of Ruhuna, Sri Lanka from May 2006 to December 2012, only 944 patients gave consent to participate in the study. Our unit was the referral center for Immunohistochemistry services in the Southern Province of Sri Lanka during this period. The referrals to our unit came from the single Oncology unit in the Southern Province which receives referrals from all hospitals with surgical units in the Southern Province. The study was approved by the Ethical Review Committee of our institution.

Data on risk factors were collected at the first interview with the patient using an interviewer administered questionnaire. All breast cancer patients who were alive were interviewed at the clinic or at their residences. If the patient was dead, by the time of the study was commenced, the closest relative of the dead patient was interviewed to obtain information on risk factors. A few patients who neither attended the clinic nor consented for home visits, were interviewed over the phone.

The information on potential breast cancer risk factors; family history of breast cancer or ovarian cancer or other types of cancer up to 4th degree and history of benign breast diseases were collected. Menstrual and reproductive history was taken which included age at menarche, age at menopause, menopausal status at the diagnosis of the disease, number of children born alive, age at first live birth and breast feeding practices. Measuring the body weight and calculation of body mass index were not done as the patients were enrolled retrospectively. Pre- and postmenopausal status of the subjects was defined as follows (Butt et al., 2012). The patients who had natural menopause (absence of menstruation for at least six months before the diagnosis of breast cancer) or who had bilateral oophorectomy before the diagnosis of breast cancer or who had hysterectomy alone (without oophorectomy) and were more than 55 years of age at the time of the diagnosis of breast cancer were considered post-menopause. The patients who were still having menstrual cycles or attained menopause during the period of receiving chemotherapy or females who have had a hysterectomy without bilateral oophorectomy and were aged <55 years at the time of the diagnosis of breast cancer were considered as pre-menopause.

The duration of breast feeding was calculated in months. The total number of months of breastfeeding was calculated as a summation of duration of breast feeding to all live births of a subject (De Silva et al., 2010). A study subject was considered to have exposure to passive smoking if she had a family member who is a smoker living in the same house. The study population was analyzed for the risk factors according to the high and low risk categories defined by Hulka and Moorman (2001) (Table 1).

Collection of these data was based on patient's recall memory. If they were unable to recall, those data on risk factors were considered as missing/unknown data.

Association of breast cancer risk factors with tumour characteristics

The study subjects were categorized into two groups; patients with a family history of cancer and those who have no family history of cancer. The patients with a family history of cancer were subdivided; patients with a family history of breast cancer and patients with a family history of other malignancies.

The histopathological features were compared between groups of patients as follows;

- family history of cancer versus no family history of cancer
- family history of breast cancer versus no family history of cancer
- family history of other malignancies versus no family history of cancer

All the study subjects were divided into two groups; premenopausal and postmenopausal, based on their menstrual history. The histopathological features of each of the two groups were compared.

Statistical analysis

The chi-square test was performed to compare the categorical variables in the different groups. The BCSS was estimated using the Kaplan-Meier model and differences were examined using the log rank test.

The BCSS time was calculated from the date of diagnosis of the disease to the date of death. Patients who died of breast cancer or who died with breast cancer (progression/metastasis) were included (Rakha, 2013). Patients died of other causes or from unknown causes were censored to the date of death. The cause of death of the patient was obtained from the death certificate issued by the Department of Registrar General.

The univariate analysis was performed using Cox proportional hazards model with 95% CI. All covariates which had a p value <0.100 were to be taken for multivariate analysis. Multivariate analysis was done with Cox proportional hazards model with backward stepwise factor retention method.

All p values <0.05 were considered statistically significant and all analyses were performed using the SPSS statistical package.

Results

A total of 944 breast cancer patients were included in this study. Descriptive data on risk factors are given in the Table 2.

The mean age at menarche of the study population was 13.9 (SD±1.6). The mean age at menarche of high risk, normal and low risk groups were 11.65 (SD±0.7), 13.6 (SD±0.5) and 15.4 (SD±0.9) respectively.

The majority (60%) of the patients were postmenopausal. The mean age of the premenopausal group was years 42.3 years (SD ± 6.3) while it was 59.6 years (SD ± 8.1) in the postmenopausal group. The mean

Table1. Risk Factors of Breast Cancer

Factor	High-risk	Low-risk
Family history of breast cancer	Yes	No
History of benign breast diseases	Yes	No
Age at first full-term pregnancy#	>30 years	<20 years
Age at menarche#	<12 years	>14 years
Age at menopause#	>55 years	<45 years
Parity#	Nulliparous	Multiparous
Breast feeding#	None/<12 months	>24 months
Recent use of hormonal contraceptives (OCP)*	Yes	No
Hormone replacement therapy- recent and long-term use (HRT)*	Yes	No
Alcohol consumption	Yes	No
Smoking	Active smoking	No

*The use OCP or HRT for at least a period of one month within the 10 years before the diagnosis of the disease was considered a risk (Trivers et al., 2007); #The patients who fall within the intermediate group are considered to have a risk comparable to the general population and not included in neither high nor low risk group

age at menopause was 48.3 years (SD±3.8) for the study population. The mean age at menopause of high risk (>55 years=4%), normal (45-55years=84%) and low risk (<45 years=12%) groups were 55.5 (SD±1.1), 48.9 (SD±2.6) and 41.2 (SD±2.6) years respectively. The majority (84%) of the study population was parous and 31% had more than three children.

The mean age at first full term pregnancy was 27

years (SD±6). The mean age of high risk (>30 years), normal (20-30 years) and low risk (<20 years) groups were 33.9 years (SD±3.4), 24.7 years (SD±2.9) and 18.2 years (SD±1.1) respectively. The majority of the parous women (70%) had breast fed for more than 24 months and only 1.3% had not breast fed.

The majority of the study population (90 %) had no history of benign breast diseases. Those who had a history

Table 2. Distribution of Risk Factors among the Study Cohort

Risk factor	Frequency n (%)	Risk factor	Frequency n (%)
Family history of cancer		Parity	
Breast cancer	77 (8)	Parous	794 (84)
Other cancer	206 (22)	Nulliparous	150 (16)
Both	32 (3.4)	Number of children	
No cancer	627 (66.6)	>3	244 (31)
Unknown	2	03-Jan	550 (69)
Age at menarche		Breast feeding	
Low Risk (>14 years)	260 (30.7)	Yes	782 (83)
Normal (12-14 years)	443 (52.3)	No	162 (17)
High Risk (<12 years)	144 (17)	Duration of breast feeding	
Unknown	97	>24 months	664 (86)
Menopausal state		<=12 months	49 (6)
Premenopausal	352 (40)	13-24 months	57 (7)
Postmenopausal	538 (60)	Unknown	12
Unknown	54	History of benign breast diseases	
Age at menopause		Presence	95 (10)
Low risk (<45 years)	58 (11)	Absence	843 (90)
Normal (45-55 years)	427 (85)	Unknown	6
High risk (>55 years)	21 (4)	Use of OCP	
Unknown	32	Yes	114 (12)
Age at first full term pregnancy		No	814 (88)
Low risk (<20 years)	92 (12)	Unknown	16
Normal (20-30 years)	433 (55)	Smoking	
High risk (>30 years)	263 (33)	Passive	333 (35)
Unknown	6	None	609 (65)

n, number; %, percentage; OCP, oral contraceptive pills

Table 3. Profile of the Tumour Characteristics of the Study Cohort

Tumour features	Frequency n (%)	Tumour features	Frequency n (%)
Age at presentation		Lymph node stage	
<=35 years	64 (7)	Stage 0	404 (45)
36-60 years	661 (70)	Stage 1	223 (25)
>60 years	219 (23)	Stage 2	173 (19)
Presence of associated DCIS		Stage 3	99 (11)
Presence	331 (36)	Unknown	45
Absence	599 (64)	TNM stage	
Unknown	14	I	165 (19)
Tumour size		II	415 (47)
<20mm	294 (33)	III	286 (32)
>20-50mm	523 (59)	IV	14 (2)
>50mm	67 (8)	Unknown	64
Unknown	60	Expression of ER	
Nottingham grade		Positive	320 (40)
Grade 1	96 (12)	Negative	485 (60)
Grade 2	355 (45)	Unknown	139
Grade 3	339 (43)	Expression of PR	
Unknown	154	Positive	334 (42)
Lympho-vascular invasion		Negative	462 (58)
Presence	260 (28)	Unknown	(148)
Absence	667 (72)		
Unknown	17		

n, number; %, percentage; DCIS, ductal carcinoma insitu; TNM, tumour-node-metastasis; ER, oestrogen receptor; PR, progesterone receptor

of benign breast disease, either had it on the same side as the breast cancer (8%), or in the contra-lateral breast (2%).

A 12% of the total study population had used OCPs and had commenced at different ages before the diagnosis of breast cancer. The use of OCP is considered as a risk factor, if it has been used within the 10 years before the diagnosis of the breast cancer (Trivers et al., 2007). A 4% of the subjects had used OCP within this period and can be considered having had a higher risk.

Only a 35.3% had been exposed to passive smoking and there were no active smokers. There were only two patients who had consumed alcohol out of the total study population. The majority of the patients had at least one risk factor (65.7%). Almost one third of patients did not have a single risk factor of breast cancer.

Association of breast cancer risk factors with tumour characteristics

The tumour characteristics of the study cohort are given in the Table 3. There was no statistically significant difference between the patients with and without family history of cancer and, the patients with a family history of other malignancies and patients with no family history of any cancer, with regard to any of the tumour characteristics considered for this study.

However, there was a statistically significant difference between the patients who had a family history of breast cancer and no family history of any cancer in terms of the presence or absence of lymph node metastasis ($p=0.011$) and pathological stage of the tumour ($p=0.042$)

(Table 4). Patients with a family history of breast cancer had higher prevalence of lymph node metastasis and higher pathological stage compared to the patients without a family history of any cancer.

In the present study, majority of premenopausal patients had associated DCIS ($p<0.001$) and large tumours ($p=0.015$) with positive lymph nodes ($p=0.016$) (Table 5) compared to the postmenopausal patients.

Depending on the status of ER and PR, patients were categorized into three groups; ER or PR positive, ER and PR positive, and ER and PR negative. The prevalence of hormone related risk factors within the above three sub groups was compared. There was no statistically significant association between the hormone receptor subtypes and the hormone related risk factors among the study subjects.

The effect of breast cancer risk factors on the BCSS

The five year BCSS of the study cohort was 78.8%. The impact of breast cancer risk factors on the BCSS was analyzed using Cox proportional hazards model. The number of patients presented with a history of HRT ($n=14$) and alcohol consumption ($n=2$) were minimal. Therefore, these factors were not considered in the univariate analysis. Five year BCSS rates for subgroups of risk factors and the results of the univariate analysis with hazards ratio for the risk factors are given in the Table 5.

Patients with a family history of any cancer or breast cancer or other malignancies, earlier age at menarche, late age at menopause and late age at first full term

Table 4. Comparison of Histopathological Features between the Patients Having a Family History of Breast Cancer and No Family History of Any Cancer

Histopathological feature	Family history of breast cancer (n=109)	No family history of any cancer (n=627)	p value
Presence of associated DCIS			0.919
Yes	39 (36%)	221 (36%)	
No	68 (64%)	394 (66%)	
Unknown data	2	12	
Tumour size			0.786
T1 (≤20 mm)	34 (33%)	205 (35%)	
T2 (>20-≤50 mm)	59 (58%)	346 (58%)	
T3 (>50 mm)	9 (9%)	41 (7%)	
Unknown data	5	35	
Nottingham grade			0.3
Grade 1	14 (14%)	66 (13%)	
Grade 2	49 (51%)	226 (44%)	
Grade 3	34 (35%)	225 (43%)	
Unknown data	12	110	
Presence of LVI			0.101
Yes	37 (35%)	166 (27%)	
No	70 (65%)	452 (73%)	
Unknown data	2	9	
Lymph-node metastasis			0.011
Yes	69 (66%)	315 (53%)	
No	35 (34%)	281 (47%)	
Unknown data	3	31	
Lymph-node stage			0.053
0	35 (34%)	281 (47%)	
1	27 (26%)	144 (24%)	
2	26 (25%)	108 (18%)	
3	16 (15%)	63 (11%)	
Unknown data	3	31	
Nottingham prognostic index			0.217
≤3.4	9 (10%)	83 (17%)	
3.4-5.4	50 (54%)	253 (51%)	
>5.4	33 (36%)	155 (32%)	
Unknown data	17	136	
Pathological stage			0.042
I	13 (13%)	120 (21%)	
II	44 (43%)	277 (47%)	
III	44 (43%)	176 (30%)	
IV	1 (1%)	12 (2%)	
Unknown data	7	42	

n, number; p, significance; DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ; LVI, lympho-vascular invasion; unknown data, information was not available

pregnancy had poor survival compared to the other relevant subgroups of patients with a particular risk factor. The fourth degree relationship of the family history had a better survival compared to the first, second and third degrees of relationship. The patients who had a history of benign breast diseases, ever use of OCP and exposure to passive smoking had an improved prognosis. However,

the effect of the use of OCP within the 10 years before the diagnosis was not further analyzed as the number of such patients was smaller.

There was no survival difference between parous and nulliparous and premenopausal and postmenopausal groups of patients. Number of children did not influence the survival of the breast cancer patients. Breastfed and

Table 5. Comparison of Histopathological Features between Pre- and Postmenopausal Breast Cancer Patients

Histopathological feature	Postmenopausal (n=538)	Premenopausal (n=352)	p value
Presence of associated DCIS			<0.001
Yes	159 (30%)	147 (42%)	
No	370 (70%)	200 (58%)	
Unknown data	9	5	
Tumour size			0.015
T1 (≤ 20 mm)	171 (34%)	107 (32%)	
T2 (>20 – ≤ 50 mm)	303 (61%)	191 (57%)	
T3 (>50 mm)	27 (5%)	36 (11%)	
Unknown data	37	18	
Nottingham grade			0.66
Grade 1	58 (13%)	33 (11%)	
Grade 2	197 (45%)	139 (46%)	
Grade 3	183 (42%)	128 (43%)	
Unknown data	100	52	
Presence of LVI			0.1
Yes	128 (24%)	103 (29%)	
No	396 (76%)	247 (71%)	
Unknown data	14	2	
Lymph-node metastasis			0.016
Yes	260 (51%)	202 (59%)	
No	250 (49%)	138 (41%)	
Unknown data	28	12	
Lymph-node stage			0.067
0	250 (49%)	138 (41%)	
1	118 (23%)	95 (28%)	
2	89 (17%)	74 (22%)	
3	52 (10%)	32 (9%)	
Unknown data	29	13	
Nottingham prognostic index			0.358
≤ 3.4	68 (16%)	38 (13%)	
3.4-5.4	219 (53%)	150 (52%)	
>5.4	127 (31%)	100 (35%)	
Unknown data	124	64	
Pathological stage			0.128
I	102 (20%)	61 (18%)	
II	240 (48%)	157 (47%)	
III	145 (29%)	115 (34%)	
IV	11 (2%)	2 (1%)	
Unknown data	40	17	

p, significance; DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ; LVI, lympho-vascular invasion; Unknown data, information was not available

never breastfed patients had a similar survival pattern.

Even though there were survival differences between the subgroups of patients with some risk factors, the differences between the survival curves of none of the aforesaid breast cancer risk factors were statistically significant. The analysis was repeated amalgamating low risk and no risk categories together against the high risk categories which yet did not reveal any effect on the BCSS. Multivariate analysis was not done as no risk factor

was found to have a statistically significant effect on the survival in the univariate analysis.

Although the subset of patients with family history of breast cancer had poor prognostic tumour characteristics compared to the patients without a family history of any cancer, no survival difference was identified between the two groups ($p=0.139$). The subset of postmenopausal patients too had no survival advantage over the premenopausal patients contrary to the observed

Table 6. Univariate Analysis of Breast Cancer Risk Factors

Risk factor	Five-year BCSS	Log-rank test	HR	95% CI	Risk factor	Five-year BCSS	Log-rank test	HR	95% CI
Family history of cancer					Age at first full term pregnancy				
Presence	76%	0.204	1.229	0.894 - 1.690	High risk (>30 years)	77%	0.124	0.923	0.549 - 1.552
Absence	80%		Reference		Normal (20-30 years)	81%		0.666	0.403 - 1.102
Family history of breast cancer					Low risk (<=20 years)	78%		Reference	
Presence	71%	0.139	1.397	0.895 - 2.182	Parity				
Absence	80%		Reference		Parous	79%	0.999	Reference	
Family history of other cancers					Nulliparous	78%		1	0.657 - 1.520
Presence	78%	0.495	1.14	0.782 - 1.662	Parous				
Absence	80%		Reference		1-3 kids	79%	0.949	0.988	0.689 - 1.417
Degree of relationship					>3 kids	77%		Reference	
1st degree	76%	0.94	1.311	0.534 - 3.220	Breast feeding				
2nd degree	77%		1.309	0.522 - 3.284	Yes	80%	0.76	Reference	
3rd degree	77%		1.316	0.494 - 3.506	No	79%		1.06	0.729 - 1.541
4th degree	77%		Reference		Duration of breast fed				
Age at menarche					≤12 months	85%	0.592	Reference	
High Risk (<12 years)	82%	0.339	1.381	0.786 - 2.425	13-24 months	71%		1.472	0.580 - 3.740
Normal (12-14 years)	86%		0.954	0.594 - 1.531	>24 months	81%		1.095	0.509 - 2.355
Low Risk (>14 years)	87%		Reference		History of benign breast diseases				
Menopausal state					Yes	80%	0.563	0.834	0.450 - 1.546
Premenopausal	82%	0.762	Reference		No	79%		Reference	
Postmenopausal	82%		1.057	0.738 - 1.514	Use of OCP				
Age at menopause					Yes	87%	0.126	0.651	0.375 - 1.132
High risk (>55 years)	80%	0.674	1.47	0.367 - 5.878	No	79%		Reference	
Normal (45-55 years)	83%		1.46	0.629 - 3.392	Smoking				
Low risk (<45 years)	91%		Reference		Passive	81%	0.475	0.888	0.640 - 1.231
					None	77%		Reference	

BCSS, breast cancer specific survival; p, significance; HR, hazard ratio; CI, confidence interval; OCP, oral contraceptive pills

significant difference in the prevalence of some good prognostic features among the postmenopausal patients.

Discussion

The aim of this study was to determine the prevalence of established breast cancer risk factors among those who have developed breast cancer and its impact on/or association with the BCSS of females with breast cancer in the Southern Province of Sri Lanka. The results of this study revealed that one third of the breast cancer patients did not have a single risk factor although they had a breast cancer. In the present study, the majority of the patients; did not have a family history of cancer; were parous; had breast fed; had not attained menarche at an early age; did not have late menopause; did not have a late first full term pregnancy; had not used OCP within the 10 years before the diagnosis of the breast cancer; had not used HRT, alcohol and not exposed to active or passive smoking.

Epidemiological studies conducted on different populations have identified different combinations of well-established risk factors to be more significant for the development of breast cancer in their populations. Most of these studies were case-controls and there are very few studies done on cases of breast cancer alone, in the literature.

There is only one case-control study done on breast cancer to find out the risk factors for breast cancer in Sri Lanka. They found that lack of breastfeeding, having a family history of breast cancer, being postmenopausal, having had a previous abortion and exposure to passive smoking are significant risk factors for breast cancer while age at menarche, BMI, age at first full term pregnancy, use of OCP for more than five years are not significant risk factors in the Sri Lankan population (De Silva et al., 2010). Information on previous abortions and BMI were not collected for the present study. The majority of the patients in the present study did not have aforesaid risk factors except being a postmenopausal female (57%). However, the prevalence of the following risk factors; nulliparity, late age at first full term pregnancy and passive smoking were higher among the present study population while early age at menarche, family history of breast cancer and lack of breastfeeding were lower than in the study done by De Silva and colleagues (2010).

In the present study, patients with a family history of breast cancer was less prevalent compared to the Western countries and similar to the other Asian countries (Leong et al., 2010). First degree relative with a breast cancer is one of the recognized risk factors for breast cancer (Hulka and Moorman, 2001). Later, it was found that family history is a prognostic factor rather than a simple risk factor for breast cancer patients (Atri et al., 2002). Presence of family history indicates inheritance of genetic alterations that modify the risk of developing breast cancer (Cipollini et al., 2004). Therefore females with breast cancer may carry different genetic alterations which may affect the tumour characteristics. The present study demonstrated that family history of breast cancer was associated with a higher prevalence of lymph node metastasis and advanced pathological stage. Similar to the present study, some

investigators have found that patients with a family history of breast cancer had a high prevalence of lymph node involvement (Tazzite et al., 2013).

In the present study cohort, the difference in the tumour characteristics has not made any significant effect on the survival of patients with family history of breast cancer. Therefore patients presented with a family history of breast cancer did not have a significant difference in the BCSS compared to the patients with no family history of cancer. Previous studies that compared the survival between breast cancer cases with and without family history reported inconsistent results (Thalib et al., 2004; Cao et al., 2011). The recent most publication on this subject tallies well with our study and it has been concluded stating that family history per se is not an independent prognostic feature for recurrence and death in breast cancer patients (Eccles et al., 2015).

Family history of other malignancies had no significant association with the histopathological features of breast cancer in the current study. Although many researchers have found an association between histopathological factors and family history of breast cancer (Molino et al., 2004; Tazzite, et al., 2013), only a few studies have commented on the relationship between histopathological factors and family history of other malignancies (Atri et al., 2002). Atri and colleagues (Atri et al., 2002) found that patients with a family history of other malignancies have a significant association with tumour grade and lymphatic invasion, but the present study did not demonstrate any such relationship.

Being a postmenopausal woman is a significant risk factor for developing a breast cancer (De Silva et al., 2010). In the present study, majority of the study subjects were postmenopausal. Menopausal status is an important factor considered in deciding on a specific endocrine treatment plan for hormone sensitive breast cancer patients (De vos et al., 2012). However there were hardly any reports on the association of histopathological tumour characteristics and menopausal status. There are reports to indicate that breast cancers in postmenopausal women are generally better differentiated (Zavango et al., 2000).

In the present study, premenopausal patients had larger tumours with associated DCIS and metastatic lymph nodes compared to the postmenopausal patients. In contrast, Zavango and colleagues, (2000) have found that the premenopausal patients had smaller tumours compared to the postmenopausal and had no difference in axillary lymph node status. The discrepancies of these findings could be due to the mean age of the sample in these studies. In the present study; the mean age of the premenopausal group was less compared to the study done by Zavango and colleagues, (2000).

Even though several parameters were significantly different between the pre- and postmenopausal women, menopausal status did not influence the BCSS in the present study. Menopausal status is an age dependent factor (Zavango et al., 2000). Therefore the age may be confounding the effect of menopausal status on the BCSS. It has been identified that age has a qualitative interaction conferring benefit for one subgroup and harm another. Epidemiologic studies have shown that breast cancer

demonstrates age specific heterogeneity that transcends a simple or single cut point such as menopausal status (Anderson, Jatoi and Sherman, 2009).

Hormone related risk factors which include early age at menarche, late age at menopause, late age at first full term pregnancy and nulliparity increase the duration of exposure to oestrogen hormone during the life time of a female. Therefore the patients with those risk factors have a higher risk of developing a breast cancer compared to the others. However, the majority of the study population did not have menarche at an early age and menopause or first full term pregnancy at a late age. The prevalence of early age at menarche in our cohort was less compared to the others (Lodha et al., 2011; Lee et al., 2014). Nulliparity was more prevalent in our study population compared to the Indian and Chinese breast cancer patients (Lodha et al., 2011; Lee et al., 2014).

Many recent studies have demonstrated significant associations between hormone related risk factors of breast cancer and IHC subgroups defined by ER and PR status. Hormone related risk factors were found to be associated with ER/PR positive breast cancers (Setiawan et al., 2009; Yang et al., 2011). Multiparity and lack of breast feeding are also associated with ER/PR negative breast cancers (Work et al., 2014). However, previous studies have reported contradictory findings in terms of association between hormone related risk factors of breast cancer and IHC subgroups (Setiawan et al., 2009; Bao et al., 2011; Turkoz et al., 2012). The results of the present study did not demonstrate a significant association between the hormone related risk factors and the ER/PR status of the breast cancer.

Most previous studies have failed to demonstrate an effect of age at menarche, age at menopause and menopausal status on the survival of breast cancer patients similar to the current study (Barnett et al., 2008; Orgéas et al., 2008; Song et al., 2015). Similar to many published reports, the current study revealed that survival was similar in parous and nulliparous females (Barnett et al., 2008). Some previous studies have found that survival was poor with multiparity and higher age at first birth (Barnett et al., 2008; Alsaker et al., 2013). Contrastingly the prognosis was not influenced by the number of children and late age at first full term pregnancy in the present study. The inconsistency in results may be due to the lack of uniformity in the parameters used and differences in the ethnicity among the individual studies.

Prolonged breastfeeding is a protective factor against development of breast cancer and if the female has not breastfed it becomes a risk factor (De Silva et al., 2010). A high prevalence of this protective factor is observed in our cohort of breast cancer patients too. It is on par with data from the Asian countries and deviates from the Western countries (Lodha et al., 2011; Butt et al., 2012; Lee et al., 2014). In this study population 70% of patients had breast fed for more than 24 months and carried a protective factor. However, breastfeeding has not influenced the survival of breast cancer patients. This finding is consistent with other reports (Trivers et al., 2007; Song et al., 2015).

A history of benign breast disease is a risk for developing a breast cancer (Hulka and Moorman, 2001;

Dorjgochoo et al., 2008). The present study population had a lower prevalence of history of benign breast diseases compared to the Shanghai breast cancer study (Dorjgochoo et al., 2008). There was no significant difference between the BCSS of patients with and without history of benign breast cancers.

The exogenous hormones like hormonal contraceptives (eg: use of OCP) and HRT are breast cancer risk factors (De Silva et al., 2010; Hadjisavva et al., 2010). The majority of the study subjects had never used OCP. Only a few of the study subjects, who had used, had been on OCP within the 10 years before the diagnosis of the disease. The prevalence of ever use of OCP was compared with other populations. It was similar to other Asian countries, but less than the non-Asian countries (Barnett et al., 2008; Lodha et al., 2011). Only 1.5% of breast cancer patients in this study had used HRT and the frequency of patients who had used HRT is very much lower than the previous publications (Barnett et al., 2008; Hadjisavvas et al., 2010). Low prevalence of use of HRT may be related to the cultural factors.

Even though some previous reports have stated that the use of OCP had no impact, some investigators have found that recent users of OCP had a higher risk of death compared with non-users (Trivers et al., 2007; Barnett et al., 2008; Lu et al., 2011). Furthermore an earlier study has found a significant trend of decreasing risk of death with increasing time since last use of OCP (Reeves et al., 2007). In this study population, majority of the patients who had used OCP, have used it within/more than 10 years before the diagnosis of the disease. Although our study revealed that patients who had ever used OCP had better survival compared to the others (HR, 0.65; 95% CI, 0.375-1.132), there was no statistical significance (p=0.12) between the two groups.

Alcohol consumption is very rare among Sri Lankan females due to the cultural and spiritual beliefs. Although there were no active smokers, exposure to passive smoking was prevalent in our study cohort. Exposure to passive smoking is a significant risk factor for breast cancer in Asian population (De Silva et al., 2010; Gao et al., 2013; Wada et al., 2015). An improved prognosis with passive smoking was noted which is contradictory to the previous publications (Sajiv et al., 2007). This association did not have any statistical significance. The present study did not collect data on the number of cigarettes used per day at home and hours of exposure to passive smoking which limited the further assessment of the observation. It is possible that the apparent relationship was due to mere chance.

As described above, except for parity all the other risk factors had an impact on the BCSS, none of which were statistically significant. A similar finding has been brought up by Ewertz and colleagues in 1991. Later, researchers have developed studies considering one or two risk factors at a time and found out some impact of them on the survival of breast cancer patients. They have obtained inconsistent results on the association between survival and risk factors as mentioned earlier.

Since this is a retrospective study weight of the patient at presentation was not available. Therefore BMI was

not calculated and could not be considered in the study. Information on all risk factors was gathered based on recall memory of the patient. Older patients may not have given the exact age at menarche as they were too old memory to recall. Information on the risk factors of the patients who were already dead by the time of data collection was not available. These limiting factors may have affected the final results of some risk factors.

The prevalence of risk factors among the cohort of breast cancer patients included in this study is less compared to the West. Only a two third of patients had at least one risk factor. A significant proportion of them have protective factors as well; deviating from the global pattern. The results of the present study highlight the need to investigate on factors other than the major established risk factors on the development of breast cancer in Sri Lankan women.

Out of all breast cancer risk factors considered for the study only the family history of breast cancer and premenopausal status were associated with poor prognostic features. Being in line with the other breast cancer risk factors, family history of breast cancer and premenopausal status had no significant effect on the BCSS of patients in the Southern Sri Lanka.

Conflicts of interest disclosure

All authors declare that they have no conflict of interest.

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