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## Associated risk factors in Breast cancer: A comparative Sri Lankan perspective

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### ABSTRACT

*Breast cancer (BC) is the commonest carcinoma among women in Sri Lanka. Various modifiable and non-modifiable risk factors are reported as causatives of BC, even though studies on the incidence and relevance of these risk factors to the Sri Lankan context are not comprehensively documented. Thus, objectives of the present study were to assess the odds related to the incidence of known and unknown risk factors in BC development in Sri Lanka. The risk factors including age at diagnosis of BC, age at menarche, age at menopause, parity, duration of breastfeeding, history of abortions, usage of hormonal contraceptives, smoking, involvement of exercises, frequency of consumption of selected foods etc. were collected from an interviewer-administered questionnaire from 355 participants (255 BC patients and 150 healthy women). Ethical approval for the study was obtained. The majority (63%) of the BC patients were postmenopausal and the commonest age group at diagnosis of the carcinoma was 51-60 years. A woman was observed to have 3.6 (Odds Ratio = 3.58, Confidence Interval 1.37-9.34) and 2.1 (Odds Ratio 2.13, Confidence Interval 1.0-4.95) times risk in developing BC when having first-order relatives and second-order relatives with breast cancer respectively. A woman had three times the odds (Odds Ratio = 3.02, Confidence Interval 1.59-5.75) of developing BC with the use of hormonal contraceptives for more than two consecutive years and three times the risk of having BC (Odds Ratio = 3.12, Confidence Interval 1.63-5.98) if she has had one or more spontaneous or induced abortions. Factors including consumption of selected food, use of bottled water and usage of microwave ovens with inappropriate containers (plastic containers) among BC patients were not significantly different compared to healthy. The risk factors including a woman in the age close to or soon after menopause, having a family history of BC, having used hormonal contraceptives and having experienced one or more abortions showed a higher risk compared to other factors studied.*

**KEYWORDS:** Breast cancer, risk factors, family history, abortions, menopausal status

## 1 INTRODUCTION

Breast cancer (BC) is the most frequently diagnosed carcinoma and the leading cause of cancer-related death among women globally (DeSantis et al. 2015). Similarly, BC is the commonest cancer among women in Sri Lanka (Joseph et al. 2019). Causative factors of BC are categorized as inherent and extrinsic factors. Inherent or non-modifiable risk factors include age, sex, race, reproductive history, family history of BC, and occurrence of benign proliferative lesions of the mammary gland. Extrinsic factors are modifiable risk factors conditioned by the lifestyle of an individual. Dietary habits, Smoking, consumption of alcohol, less involvement in physical exercise and long-term medical treatments such as using hormonal contraceptives or hormone replacement therapies are examples of extrinsic parameters. Identification of modifiable factors contributes to implementing prevention strategies (Kamińska et al. 2015) specific to a population.

Among the most common risk factors, having first-order or second-order relatives with BC takes precedence. Relative risks of 2, 2.3 and 3.6 are found if the mother, a sister or both mother and sister are affected respectively (Pharoah et al. 1997). Early menarche and late menopause increase the risk of BC (Bernstein 2002). The chances of developing BC increase every year younger at menarche and also every year older at menopause (Beral et al. 2012). However, contradictory results are reported in some studies indicating no association between the age at menarche with the estimated total duration of breast

mitotic activity (Chang et al. 2007). The impact of abortions on BC is reported with inconclusive results. Neither induced nor spontaneous abortion is reported to be associated with premenopausal BC (Michels et al. 2007).

Women who give birth before the age of 25 years show a 36% reduced risk of breast cancer compared with women who give birth at an older age. Women with late first birth, never breastfed are reported to be associated with an increased risk of the disease condition. The risk of breast cancer is increased by 13% for each five-year increment in age at first birth among women with two or more parities (Lambe et al. 1996). Nulliparous women are at increased risk of developing breast cancer (Britt et al. 2007).

Hormonal contraceptives and hormone replacement therapy have various impacts on BC incidence. Hormonal contraceptives used could be combined oral contraceptives or progestin-only contraceptives which can be used as injections, oral preparations (pills), implants and also as hormone-releasing intrauterine devices (Kumle et al. 2002). The use of oral contraceptives for more than four years before the first full-term pregnancy is reported to be associated with an increased risk of BC (Fentiman 2002). Long-term users of oral contraceptives are at significantly increased risk of developing BC than those who have never used hormonal contraceptives. Similarly, the use of combined oral contraceptives and progestin-only pills results in a similar impact on developing BC (Kumle et al.

2002). Lactating and breastfeeding for prolonged durations are reported to reduce BC risk (Lipworth 2000). In contrast, a negative association between breastfeeding and BC is reported (Tryggvadottir 2001)

Psychological stress induced by major life events is evidenced to be strongly associated with increased BC risk (Antonova et al. 2011). For example, a divorce or a separation could impact BC by 2.26 times risk and the death of a husband, death of a close relative or a friend could increase the risk twice and 1.36 times respectively (Lillberg 2003). Physical activity imparts a favourable influence on BC incidence and outcome (Chlebowski 2013).

Studies have revealed a stronger impact of physical activity amongst postmenopausal women, women who are of normal weight, have no family history of breast cancer and are parous. Physical activity decreases BC risk via multiple biochemical pathways which are interrelated which might be due to adiposity-related secretions, sex hormones, insulin resistance, adipokines, and chronic inflammatory reactions (Lynch et al. 2011).

Many of the cancer-causing substances (polycyclic hydrocarbons, aromatic amines, and N-nitrosamines ) found in tobacco smoke are found in the fluid in the breasts of women who smoke (Terry & Rohan 2002). Thus, it is suspected that smoking could increase breast cancer risk. Meta-analyses reveal, current and former

smoking are weakly associated with breast cancer risk and a stronger association is observed in women who initiated smoking before first birth. These results support the hypothesis that active smoking is associated with increased breast cancer (Gaudet et al. 2013).

Diet-related factors are thought to account for about 30% of cancers in developed countries (Key et al. 2002). Therefore, to prevent recurrence and improve the survival of breast cancer survivors not only consuming a diet rich in vegetables and fruits but also adopting a modernized Mediterranean diet is recommended (Lorgeril & Salen 2014). Research suggests low-fat diet may play a role in breast cancer prevention (Wang et al. 2008). Nevertheless, there is weak evidence on the relationship between trans fatty acids and breast cancer risk (Thompson et al. 2008). However, detailed studies are not found in abundance on the impact of various food consumption on the risk of developing breast cancer.

As the BC incidence is increasing unprecedentedly it is timely to study associations of possible risk factors, and incidence of known risk factors to increase awareness specially among women to reduce the disease burden.

The present study intended to analyze the incidence of known and unknown risk factors among women diagnosed with BC compared to apparently healthy age-matched females.

## **2 RESEARCH METHODOLOGY / MATERIALS AND METHODS**

### **2.1 Voluntary participants**

Women who were diagnosed with BC (n=255) and those who consented to participate in the present study were selected from Apeksha Hospital (National Cancer Institute Maharagama). Healthy, age-matched females who consented to participate (n=150) were selected for the control group.

### **2.2 Data collection**

Data on risk factors were collected using an interviewer administered questionnaire which was validated and pretested. Data on age, age at first diagnosis of carcinoma, marital status, educational background, employment and monthly income, information on events that caused stress within the past ten years including death or separation from the husband, death of parents, siblings and close relative, stress due to low income (when the household expenses could not be covered from the income), stress at workplace (higher responsibilities and heavy workload at working place), stress due to family related matters and stress due to health-related issues (when suffering from various diseases before the diagnosis of carcinoma and intake of medications and the fear of future complications) were collected.

Information on the history of illnesses (breast lumps, dyslipidemia, diabetes, thyroid-related diseases, other known diseases, family history of BC and family history of any other carcinomas) was

collected using the same questionnaire. If patients had comorbidities and were on treatment, data on the type of drugs used, and history of treatment (past 3 months, one year, two years, etc.) were obtained.

Data on reproductive history including the age at menarche, age at menopause, marital status, number of children, age at first childbirth, duration of breastfeeding for each child, number of abortions (induced and spontaneous), usage of oral contraceptives and duration were collected.

Further, information on smoking (active or passive), history of hormone therapy, level of physical activity, and knowledge of self-assessment of breast lumps, using a microwave oven for heating/cooking, and the type of containers used and regular use of plastic containers for food and water (single-use plastics) storage were also obtained.

### **2.3 Data Analysis**

Data were analyzed using the SPSS version 20.0 (2007, SPSS for Windows, SPSS Inc., Chicago, IL, USA) package. The quantitative data that were normally distributed were presented as mean $\pm$ 1 standard deviation (SD) and quantitative data with skewed distribution were presented as median (Inter quartile range). The qualitative data were expressed by calculating the frequency and percentage. A *p* value of less than 0.05 ( $p < 0.05$ ) was considered as significant. The significant associations that exist among categorical variables were studied by chi-square test

and independent sample t-test and paired sample t-test were used for parametric variables. Non-parametric variables were presented as median with interquartile range and their significances were analyzed using the Mann-Whitney U test.

## **2.4 Ethical clearance**

Ethical approval for the study (selection of newly diagnosed BC patients and selection of age-matched healthy females) was obtained from the Ethics Review Committee, Faculty of Medical Sciences, University of Sri Jayewardenepura ((No 651/12, 28/14). Informed written consent was obtained from the participants after explaining the purpose of the study.

## **3 RESULTS & DISCUSSION**

The majority (63%) of women with BC were postmenopausal. The average ages of premenopausal and postmenopausal women with BC were  $42\pm 7$  and  $63\pm 7$  years respectively. Incidence of was commonest in the age group 51-60 years. Women in the age group 41- 50 years and 61-70 years also showed a higher incidence. Considering marital status, the majority (> 85%) of BC patients and healthy females were married (92%). Nearly 55% of BC patients and 65% of healthy women were residing in urban areas of the country. The majority of women diagnosed with BC in the study group were near to or within 10 years of menopause. These findings are also in parallel to studies that reveal, the disease presenting was most common among postmenopausal which could be due to the hormonal changes that occur in

a woman near and after menopause.

Considering the educational background of women with BC one-fifth had attended school up to grade 8 or lower, 45.5% up to General Certificate of Education, Ordinary Level and 26% up to General Certificate of Education, Advanced Level. The majority of the control group of the study had studied up to General Certificate of Education, Advanced Level and a significantly higher percentage of healthy women have had tertiary education. However, the awareness of modifiable and non-modifiable risk factors/ possible causatives of BC was not satisfactory among all the study participants. Thus, more attention must be paid to increase the awareness of the general public on the same.

Nearly 25% recollected depressing family matters to have occurred a few years before the diagnosis of BC. A significant number of patients (71%) reported either one or more of the studied stress-related factors (low income, death of husband, loss of close relatives, stress due to other family matters, high workload and other stress at working place etc.) to have caused stress when compared to healthy ( $p<0.05$ ). Confirming the same, the serum cortisol concentration among the BC patients was significantly elevated compared to healthy (unpublished data). Apparent links between psychological stress and cancer arise in several ways. People under stress may develop certain behaviours, such as smoking, overeating, or drinking alcohol, which further increase a person's risk of developing cancer.

When considering comorbidities, nearly one-third (30%) of the patients were either hypercholesterolemic or were diagnosed with diabetes. Intermediate risk factors associated with BC (hypercholesterolemia, diabetes, thyroid abnormalities, previous breast lumps) were observed in 40% of the

BC patients and significantly higher compared to apparently healthy ( $p < 0.05$ ). The history of BC among the participants is illustrated in Table 1. Nearly one-fifth of the BC patients had first-order or second-order relatives with BC.

**Table 1.** Family history of diagnosed breast cancers or any other cancers

	Women with BC (n= 255)		Healthy women (n= 150)	
	Frequency	Percentage	Frequency	Percentage
First-order relatives with BC	52	20 <sup>a</sup>	9	6 <sup>b</sup>
Second-order relatives with BC	46	18 <sup>c</sup>	14	9 <sup>d</sup>
Blood-related other relatives with any cancer	77	30 <sup>e</sup>	38	25 <sup>e</sup>

Different superscripts along each row indicate the significant differences at a 95% confidence interval.

Having first or second-order relatives with BC was significantly high among BC patients ( $p < 0.05$ ) compared to healthy. However, having a blood relative with any other cancer was not a not significant observation ( $p > 0.05$ ) among BC patients compared to apparently healthy women.

reducing/minimizing the modifiable risk factors including obesity, smoking, consumption of high-fat diets, sedentary lifestyle etc. among women having first and second-order relatives with BC to reduce the disease burden and social impact. The mean age of menarche, menopause, and age at first childbirth were not significantly different among the two groups (table 2).

These findings are indicative of the importance of at least

**Table 2.** Reproductive history of the participants.

	Women with BC (n=255)	Healthy female (n=150)
The mean age of menarche (years)	13± 1.5 <sup>a</sup>	13± 1.5 <sup>a</sup>
The mean age of menopause (years)	49± 3 <sup>b</sup>	50 ±3 <sup>b</sup>
Parity Nulliparous	n=13 (5%) <sup>c</sup>	n=1 (1%) <sup>c</sup>
Number of children (mean)	2±1 <sup>d</sup>	2±1 <sup>d</sup>
Mean age at first childbirth	27±6 <sup>e</sup>	29±3.5 <sup>e</sup>

Different superscripts along each row indicate significant differences at 95% confidence interval.

Usage of oral contraceptives for more than twelve consecutive months was more common ( $p < 0.05$ ) among BC patients (34%) compared to apparently healthy women. Women using hormonal contraceptives for more than 24 consecutive months showed a three times higher risk (Odds Ratio = 3.02, Confidence

Interval 1.59-5.75) in developing BC when compared to apparently healthy. The parity or duration of breastfeeding was not significant among the two groups (Table 3). The majority of study participants (BC and healthy) have breastfed for more than 2 years.

**Table 3.** Incidence of selected factors among BC and healthy females

		Incidence among BC patients	%	Healthy females' Incidence	%
Using hormonal contraceptives	<2 year	7	2.7 <sup>f</sup>	15	10 <sup>g</sup>
	>2 year	87	34 <sup>h</sup>	38	25 <sup>i</sup>
Duration of breastfeeding	<1 year	25	10 <sup>j</sup>	22	14.6 <sup>k</sup>
	1-2year	72	28 <sup>l</sup>	60	40 <sup>m</sup>
	>2 years	158	62 <sup>o</sup>	68	45.4 <sup>p</sup>
Incidence of abortions	0	154	60 <sup>q</sup>	125	83 <sup>r</sup>
	1	61	24 <sup>s</sup>	14	9 <sup>t</sup>
	2	38	15 <sup>u</sup>	12	8 <sup>v</sup>
	3	2	1	0	0
Incidence of using hormone replacement therapies		0	0	0	0

Different superscripts along each row indicate significant differences at a 95% confidence interval.

The association of abortion and BC risk is subjected to scrutiny as abortions can interrupt the normal cycle of hormones during pregnancy. Hormonal changes that occur in an abortion could leave the breast epithelium in a proliferative state with an increased susceptibility to breast carcinogenesis (Erlandsson et al. 2003). Among the BC patients, the incidence of having one or more abortions was 40%. Apparently, healthy participants showed a lower (22 %) incidence of having

abortions. Thus, women who have had one or more abortions showed a 3 times risk of developing BC (Odds Ratio = 3.12, Confidence Interval 1.63-5.98) compared to healthy.

The majority of BC patients (84%) were not engaging in any physical exercise. Only 16% of BC patients engaged in exercises. Jogging/walking were the commonest exercises engaged in by patients as well as healthy women (Table 4).

**Table 4.** Involvement in physical activities

	Women with breast cancer		Healthy females	
	Frequency	Percentage	Frequency	Percentage
Involvement in physical exercises	45	17.7	28	18.6
I. Exercise machine	7	2.7	12	8
II. Jogging/walking	36	14	25	17

Antioxidant defense system improves upon physical activity via an exercise-induced increase in the antitumour immune defense system even though the extent to which exercise induces changes in oxidant defenses is unknown (Friedenreich et al. 2002). However, the majority of BC patients (84%) were not engaging in any physical exercise. They were of the belief that routine household activities provided adequate exercise per day. The majority (95%) were unaware of the fact that exercises could reduce the risk of developing BCs. Thus the sedentary lifestyle might have contributed to BC formation with the other factors as most of BC patients were obese in comparison control group (Akalanka et al. 2018). The majority of women in both groups were non-vegetarians. Farvid et al. (2014) report high red meat consumption could be a risk factor for breast cancer. But nearly 80% of both groups have never consumed beef or pork. Thus, red meat consumption cannot be considered a risk in the present study sample. Nearly 70% of both groups have not consumed cheese and butter more than once a week.

The majority of breast cancer patients and healthy women (>94%) were not aware of when and how the breast self-examination should be done. Most have identified the

breast lump randomly. Thus, further awareness programs on breast self-examination will be beneficial to society in detecting BC at its initial stages. It is an exercise that could be introduced in schools which will reduce mortality due to late diagnosis.

Considering the other behavioural risk factors, none of the BC or healthy women smoked and a negligible percentage (0.8%) with BC (7.4%) and 10 healthy women (7%) considered them to be frequent consumed alcohol. However, 19 women passive smokers ( $p > 0.05$ ). Thus the contribution of smoking in the development of BC was not identified as a significant contributor as reported in some studies (Gaudet et al. 2013).

The minority was using a microwave oven for heating and cooking, Heating food with polythene wrappers, or in plastic containers which are not -microwave compatible was not a frequent practice among both groups. The usage of disposable plastic bottles to drink and store water was also not common among the two groups ( $p > 0.05$ ).



#### 4 CONCLUSION & RECOMMENDATIONS

According to the study findings, the commonest risk factors among Sri Lankan BC patients were age (close to or just after menopause), having first-order or second-order relatives with BC, having a history of abortions, history of using hormonal contraceptives for two or more consecutive years and experiencing a stressful lifestyle. The majority of BC patients as well as healthy women were unaware of when and how to conduct self-breast examinations for the early detection of BC.

Thus, more awareness programs on BC risk factors, proper breast self-examination procedures and the importance of routine checkups of BC will be beneficial for early diagnosis of carcinoma. The knowledge of risk factors and BC prevention methodologies will also be helpful to reduce the risk of developing BC by adopting appropriate lifestyle changes.

#### ACKNOWLEDGMENTS

Grants obtained from the University of Sri Jayewardenepura  
ASP/06/RE/MED/2012/20 and  
ASP/06/RE/MED/2013/30 are  
acknowledged.

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