

## RESEARCH ARTICLE

# Passive Smoking and Breast Cancer - a Suspicious Link

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### Abstract

**Background:** Breast cancer is the most common malignancy of women in the world. The disease is caused by infectious and non-infectious, environmental and lifestyle factors. Tobacco smoke has been one of the most widely studied environmental factors with possible relevance to breast cancer. The purpose of this study was to assess the impact of tobacco smoking in breast cancer patients in a hospital based cohort and to establish prognostic implications if any. **Materials and Methods:** A retrospective audit of 100 women with pathological diagnosis of invasive breast cancer was included in this study. The verbal questionnaire elicited information on current and previous history of exposure to smoking in addition to active smoking. All analyses were adjusted for potential confounders, including stage at presentation, alcohol intake, hormonal replacement therapy, oral contraceptive intake, obesity and menopausal status. **Results:** The mean age at presentation of breast cancer was  $51.4 \pm 10.86$  years. Mean age of presentation was  $53.1 \pm 11.5$  and  $45.7 \pm 11.9$  years in never smokers and passive smokers, respectively. Age at presentation varied widely in patients exposed to tobacco smoke for >10 years in childhood from  $40.3 \pm 12.0$  years to  $47.7 \pm 13.9$  in patients exposed for >20 years as adults. Among passive smokers, 60.9% were premenopausal and 39.1% of patients were postmenopausal. In never smokers, 71.4% were postmenopausal. Expression of receptors in non-smokers vs passive smokers was comparable with no significant differences. Metastatic potential in lung parenchyma was slightly elevated in passive smokers as compared to never smokers although statistically non-significant. **Conclusions:** An inverse relationship exists between the intensity and duration of smoking and the age at presentation and poor prognostic factors. The results strongly suggest efforts should be taken to prevent smoking, encourage quitting and restrict exposure to second hand smoke in India.

**Keywords:** Breast cancer - passive smoking - link - prognosis - India

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### Introduction

Breast cancer is the most common malignancy in women worldwide and leading cause of death among women (Minatoya et al., 2013). According to the recent estimates 1.38 million women were diagnosed with breast cancer and 485,000 died worldwide in 2008 (Jemal et al., 2011). Breast cancer is one of the most frequent diagnosed cancers among women in the economically developing countries (Jemal et al., 2009; 2011; Ferlay et al., 2010). The known most important determinant factors for breast cancer included: age, family history, genetics, personal history of breast cancer, radiation to chest/ face before age 30, race/ethnicity, being overweight, pregnancy/breast feeding and menstrual history, using hormone replacement therapy (HRT), drinking alcohol, having dense breast, lack of exercise, and smoking (Das et al., 2012; Wafa et al., 2014).

The several fold difference in incidence rates between

high-incidence and low-incidence regions and changes in incidence rates over time and among migrants suggest that environmental factors can influence breast cancer risk (Nagata et al., 1997). Of the identified environmental factors with potential relevance to breast cancer, one of the most widely studied has been tobacco smoke. Many studies have reported that smoking is associated with increased risk of breast cancer (Band et al., 2002; Li et al., 2005; Reynolds et al., 2009; Luo et al., 2011). Smokers are more exposed to free radicals. These free radicals cause oxidative damage to lipids, proteins and DNA that can result in cancer. The tobacco leaf contains about 7000 toxic chemical species, 20 of which are established as mammary carcinogens (Reynolds et al., 2009).

Since, there are very less published India data about association of smoking and breast cancer, this study was to corroborate the impact of tobacco smoking in breast cancer patients and to find out the prognostic implications if any. The relation of exposure to tobacco smoke in

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women with histologically proven breast cancer with the age of presentation, menopausal status, hormone receptor status and metastatic potential to lung parenchyma was also searched.

## Materials and Methods

The study comprised of 100 biopsy proven patients of carcinoma breast who were coming for follow up in Department of Radiotherapy, Christian Medical College, & Hospital, Ludhiana between January 2011 to August 2012. A comprehensive questionnaire was used to elicit information on current and previous smoking history. Patients were categorized as “smokers” comprising both active and passive smokers and “never smokers”. We further subdivided passive smokers into three descriptors of timing of smoking initiation. Three categories were exposure of  $\geq 10$  years as children,  $\geq 20$  years at home as adults, and  $\geq 10$  years in workplace.

Women who reported a natural menopause or B/L oophorectomy at cohort enrollment were considered post menopausal, regardless of age at hysterectomy or use of hormonal replacement therapy. A detailed analysis was carried out with respect to age, menopausal status, disease stage, surgery performed, histopathology, and hormone receptor status. The potential confounders such as alcohol intake, obesity, use of hormone replacement therapy and oral contraceptive intake were taken into consideration at

the time of enrollment. All parameters were entered into a computerized database.

All data were analysed statistically by ‘t’ test and ‘Chi-square test’ by using SPSS version 16 and Open Epi version 2.1.1. software. Any p value  $<0.05$  were considered statistically significant.

## Results

This study was conducted in post treated breast cancer patients who were coming for follow up. A total of 100 breast cancer patients were taken for analysis who were treated by various treatment modalities in various combinations. Out of 100 cases of primary breast cancer patients, 77 patients were in never smokers while 23 patients had history of passive smoking. No patient was having history of active smoking. Age at presentation of 100 patients was  $51.4 \pm 10.86$  years. Mean age at presentation in passive smokers group was  $45 \pm 11.9$  years that was earlier than never smokers group of  $53 \pm 11.5$  years (p value = 0.038).

Amongst the passive smokers most patients are in premenopausal state at time of presentation while majority of never smokers are postmenopausal. In passive smokers group, 60.86% patients were premenopausal whereas 28.57% patients were premenopausal in never smokers group (p value = 0.05).

In stage wise distribution of patients, 60.9% patients

**Table 1. Clinico-pathological Characteristics of Patients and Association with Smoking Habits**

Breast cancer patients	Passive smoker (n=77)	Never smoker (n=23)	P value (n=100)
Mean age (In years)	45.7 $\pm$ 11.9 (30-79)	53.1 $\pm$ 11.5 (34-74)	0.038
Menopausal status			
Premenopausal	14 (60.9%)	22 (28.6%)	0.05
Postmenopausal	9 (39.1%)	53 (71.4%)	
Stage at presentation			
Stage I	0 (0.0%)	1 (1.3%)	0.189
Stage II	6 (26.1%)	34 (44.2%)	
Stage III	14 (60.9%)	28 (36.4%)	
Stage IV	3 (13.0%)	14 (18.2%)	
Histology			
IDCA	22 (95.6%)	68 (88.3%)	0.446
Other histology (ILCA, Medullary, Carcinosarcoma)	1 (4.4%)	9 (11.7%)	
Hormonal receptor status			
Luminal A (ER+,PR+,Her-2 neu -)	12 (52.2%)	36 (46.7%)	0.981
Luminal B (ER+,PR+,Her-2 neu +)	2 (8.7%)	7 (9.1%)	
Basal type (ER-,PR-,Her-2 neu -)	7 (30.4%)	23 (29.8%)	
Her-2 neu type (ER-,PR-,Her-2 neu +)	2 (8.7%)	10 (12.9%)	
Metastasis			
Present to any site (n=19)	5 (26.3%)	14 (73.7%)	0.999
Pulmonary (n=10)	3 (30.0%)	7 (70%)	

**Table 2. Distribution According to Age at Initiation and Duration of Passive Exposure to Tobacco Smoke and its Co-relation with Poor Prognostic Markers of Breast Cancer Patients in Hospital Based Cohort**

Passive smokers (N=23)	$\geq 10$ years of exposure in childhood n=8 (34.8%)	$\geq 20$ years exposure in adults n=15 (65.2%)	p-value
Age at presentation (years)	40.3 $\pm$ 12.0	47.7 $\pm$ 13.9	0.218
Menopausal status at time of presentation			
Premenopausal	5 (62.5%)	10 (66.7%)	0.999
Postmenopausal	3 (37.5%)	5 (33.3%)	

presented in stage III where as 26.1%) and 13.0% were in stage II and stage IV respectively in passive smokers group. Out of 77 never smokers 44.2% were in stage II while 36.4%, 18.2% and 1.3% were in stage III, stage IV and stage I respectively. There was no significant difference in stage at presentation and exposure to second hand smoke (p value = 0.189).

Majority of patients were of Infiltrating Ductal Carcinoma (IDCA). 95.6% patients in passive smokers and 88.3% in never smokers group were diagnosed as of Infiltrating Ductal Carcinoma (IDCA). Remaining 4.34% in passive smokers and 11.6% in never smokers had a different histopathology. No Statistically significant relation was observed in smoking exposure and disease histology (p value = 0.446).

Hormone receptor status was analyzed in terms of molecular biology in breast cancer. A majority of patients were Luminal A type. Among passive smokers and never smokers, 52.2% and 46.7% cases were Luminal A type respectively. This was followed by 30.4% and 29.8% of Basal type in passive smokers and never smokers group respectively. No significant association was noted with exposure to tobacco smoke and receptor status.

In this study out of 19 patients who presented with metastatic disease 5 (21.7%) were passive smokers and 14 (18.2%) were never smokers. In patients with pulmonary metastasis, 13% had history of passive smoking while 9.1% patients were never exposed to tobacco smoke. There exists no significant relation between exposure to tobacco smoke and presentation of metastatic disease in specific to lungs (p value= 0.999).

Out of 23 passive smokers, 34.8% patients had exposure to tobacco smoke for  $\geq 10$  years during childhood whereas 65.2% patients were exposed for  $\geq 20$  years in adulthood. Mean age at presentation of carcinoma breast was 40.2 years in patients who were exposed to smoking since childhood while it was 47.7 years in patients who were exposed to second hand smoke in adulthood. It was seen that patients who were exposed to tobacco smoke at an earlier age; they were diagnosed with breast cancer 7 years earlier in comparison to patients who were exposed to tobacco smoke in adulthood. It was statistically not significant but it was clinically relevant. Among passive smokers, 62.5% and 66.7% patients were premenopausal in  $\geq 10$  years of exposure in childhood and  $\geq 20$  years exposure in adults group respectively. There was no difference in menopausal status at presentation based on timing of onset of exposure to second hand smoke.

## Discussion

Breast cancer is the most common malignancy in women in the world. In year 2012 more than 1.5 million new cases of breast cancer were reported globally and the incidence has increased by 20.0% (Cancer, 2014). Overall, women from UK and US were observed to be at a higher risk, with age standardize rate of more than 120 in 100,000 populations (Cancer Research UK, 2002; Siegel et al., 2014). In contrast, India, China and South Africa have considerably lower incidence rate of about 30 in 100,000 population . Overall, a five year survival rate is observed

among the 80-90% of the UK and US patients (Cancer Research UK, 2002), which is up to 50-60% among the patients from India, Thailand and Malaysia (Abdullah et al., 2013). The disease is caused by multiple genetic defects that can be due to infectious and noninfectious factors, environmental and lifestyle factors, e.g. diet, physical inactivity, obesity, alcohol consumption, tobacco smoking (Hussain et al., 2003; Nahleh et al., 2011). There are a number of studies which proves that carcinogens present in smoke are the major risk factor in the development of breast cancer (Band et al., 2002; Jhonson et al., 2011; Gao et al., 2013). Another study suggested that smoke increased the risk of breast cancer in former smokers (Ilic MC et al., 2013).

Most observational studies on association between cigarette smoking and breast cancer have failed to find a strong association. For example, Moore and Sobue (2010) in a study on strategies for cancer control in the various regions of Asia reported that cigarette smoking can play a minor role in breast cancer risk. The previous reanalysis of 53 epidemiological studies (Collaborative Group on Hormonal Factors in Breast Cancer, 2002), focusing on smoking status, also concluded that tobacco has no effect on overall risk of breast cancer, but its effect on certain subgroups of women could not be excluded. Analysis of findings of the latter studies on this topic indicates that the link of smoking with breast cancer may be dependent on several factors including age of smoking initiation, duration, amount of cigarette smoking per day, genotype, estrogen level, suggesting that early age at smoking initiation, longer duration of smoking and greater numbers of cigarettes are linked with increased risk (Hulka and Moorman, 2001; Reynolds et al., 2004; Gram et al., 2005; Olson et al., 2005; Terry and Goodman, 2006; Ha et al., 2007; Ahern et al., 2009; Pieta et al., 2009; Young et al., 2009; McKenzie et al., 2013).

Passive Smoking: Khuder et al examined the association between passive smoking and breast cancer risk and suggested the possibility of a weak positive association but also noted that causality has not been established (Khuder et al., 2000). Nitrosamines and other carcinogens found in tobacco smoke appear to be more concentrated in passive smoke as compared to mainstream smoke but researchers did not found of association between passive smoking from husbands and BC risk for any of the ER/PR subtypes (Kruk, 2014). Nevertheless, it is possible that passive smoking of long duration may be associated with increased risk, whereas active smoking of shorter duration may not.

Smoking before or after a First Full-term Pregnancy: Kelsey et al. (1993) hypothesized that a relatively early age at first full-term pregnancy is associated with reduced breast cancer risk due to terminal differentiation of the breast epithelium that occurs late in the first trimester. Hunder et al. (1997) found greater susceptibility of breast tissues to the carcinogenic chemicals found in tobacco smoke before rather than after terminal differentiation of breast epithelium. In our study, age at first child birth is similar in the three study groups which had exposure to passive tobacco smoking. Olson et al. (2005) reported increased breast cancer risk by 27% in women who started

smoking before the first delivery and by 39% in those who started smoking between first menarche.

**Age at Presentation:** There is a growing body of literature suggesting that tobacco use does increase the risk of breast cancer, especially in younger women. Mathew et al, 2010 found smoking was associated with a younger age at diagnosis of breast cancer. In our study results have been replicated with earlier mean age at presentation in smokers as compared to non smokers which was statistically significant ( $p$  value =0.038). A recent small study (191 cases, 191 controls) conducted in Serbia reported significantly increased breast cancer risk among former smokers (Ilic et al., 2013). The group showed that breast cancer risk was increased in women who quit smoking at  $\leq 50$  years of age (OR=3.29, 95%CI=1.07-5.24) and in those who stop smoking  $< 5$  years before diagnosis of the disease (OR=5.46, 95%CI=1.34-22.28) when compared with nonsmokers.

**Menopausal status:** Most of the studies that have examined cigarette smoking in relation to breast cancer risk among both premenopausal and postmenopausal women have not shown meaningful differences in risk according to menopausal status. Palmer et al. (1991) corroborated that cigarette smoke contains known carcinogens, and the developing breast is especially susceptible to cancer initiation. Our findings also raise the hypothesis that exposure to cigarette smoke during adolescence may increase a woman's risk of breast cancer earlier in their premenopausal years ( $p$  value 0.005). According to study by Kruk (2014), both premenopausal and postmenopausal active smokers experienced increased risk for the intensity of smoking  $\geq 10$  cigarettes/day as compared with non-smokers (OR=2.55, 95%CI=1.81-3.60, OR=1.78, 95%CI=1.33-2.37, respectively).

**ER and PR Status:** A few epidemiological studies have examined the association between quantitative measures of cigarette smoking and breast cancer risk according to ER status. Manjer J et al, 2001 found a statistically significant 160% increased risk of ER- tumors but no clear association with ER+ tumor. A study by Morabia et al, 2000 did not show any clear difference in the association with smoking intensity according to ER status. The overall findings suggest that smoking may increase risk through pathways other than those mediated by estrogen or perhaps that ER- tumors have evolved from ER+ tumors and therefore have common risk factors. In our study, receptor status reviewed in 100 breast cancer patients showed no significant difference between never smokers and passive smokers. In a recent case control study carried out in Japan (1,263 cases and 3,160 controls), Nishino et al. (2014) found no significant relationship between history of smoking and BC risk for any ER/PR subtype. However, the authors observed the significantly increased risk among postmenopausal women with ER- / PR- status who started to smoke at ages of  $\leq 19$  years (OR=7.01, 95%CI=2.07-23.73). Further, the results of their analysis indicated that intensity of smoking, duration of smoking, and start of smoking before the first birth were not associated with the risk independently on the receptor subtype. Also, the researchers did not find of association between passive smoking from husbands and BC risk for

any of the ER/PR subtypes.

**Metastasis to Lung:** Smokers have been found to have an increased rate of death from breast cancer in several epidemiological studies. A potential explanation for this manifests that smoking causes a host of changes in the lung, including increased permeability (Sundram et al, 1995) and altered local immune function (Kuschner et al, 1996), that adversely affects the natural history of lung diseases. Scanlon and colleagues in 1995, suggested that cigarette smoking is a risk factor for the development of metastatic pulmonary involvement among women with breast cancer. In our study, slightly higher incidence of pulmonary metastasis between never smokers and passively smoking breast cancer patients were noted, however it was not statistically significant.

In conclusion, an increased risk of developing cancer at an earlier age was observed among women exposed to tobacco smoke for more than 20 years. Moreover, considering the mean age at presentation, breast cancer occurs on an average eight years earlier in smokers than in non-smokers. This finding could support the hypothesis of a direct carcinogenic effect of tobacco. A larger prospective study with adequate power, comparing breast cancer cohort and control group along with the ability to control other potentially confounding lifestyle factors, and a longer follow up should be performed to establish the relative risk of breast cancer with cigarette .

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