RESEARCH ARTICLE

Passive Smoking and Breast Cancer - a Suspicious Link

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Abstract

<u>Background</u>: 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 wiith 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. <u>Materials and Methods</u>: 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. <u>Results</u>: The mean age at presentation of breast cancer was 51.4 ± 10.86 years. Mean age of presentation was 53.1±11.5 and 45.7±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± 12.0 years to 47.7± 13.9 in patients exposed for > 20years as adults. Among passive smokers, 60.9% were premenopausal and 39.1% of patients were postmenopausal. In never smokers, 71.4% were post menopausal. Expression of receptors in non-smokers vs passive smokers was comparable with no significant differences. Metastatic potential in lung parenchyma was slightlyelevated in passive smokers as compared to never smokers although statistically non-significant. <u>Conclusions</u>: 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

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 results 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 ≥ 10 years as children, ≥ 20 years at home as adults, and ≥ 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 ± 10.86 years. Mean age at presentation in passive smokers group was 45±11.9 years that was earlier than never smokers group of 53±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±11.9 (30-79)	53.1±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 Smoke and its Co-relation with Poor Prognostic Markers of Breast Cancer Patients in Hospital Based Cohort

Passive smokers (N=23)	≥10 years of exposure in childhood n=8 (34.8%)	≥ 20 years exposure in adults n=15 (65.2%)	p-value
Age at presentation (years)	40.3± 12.0	47.7± 12.9	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 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 ≥ 10 years during childhood whereas 65.2% patients were exposed for ≥ 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 ≥10 years of exposure in childhood and ≥ 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 ≤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 ≥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 ≤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 found 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 .

References

Abdullah, Aini N, Mahiyuddin, et al (2013). Survival rate of breast cancer patients in malaysia: a population-based study. *Asian Pac J Cancer Prev*, **14**, 4591-4.

Ahern TP, Lash TL, Egan KM, Baron JA (2009). Lifetime tobacco smoke exposure and breast cancer incidence. *Cancer Causes Control*, **20**, 1837-44.

Band PR, Le ND, Fang R, Deschamps M (2002). Carcinogenic and endocrine disrupting effects of cigarette smoke and risk of breast cancer. *Lancet*, **360**, 1044-49.

Cancer Research UK. (2002, January 2014). Breast Cancer. Retrieved 20 May, 2014, from http://www.cancerresearchuk.org/cancer-info/cancerstats/types/breast/

Collaborative Group on Hormonal Factors in Breast Cancer (2002). Alcohol, tobacco and breast cancer-collaborative reanalysis of individual data from 53 epidemiological studies, including 58 515 women with breast cancer and 95 067 women without the disease. *Br J Cancer*, **87**, 1234-45.

Das S, Sen S, Mukherjee A, et al (2012). Risk factors of breast cancer among women in eastern India: A tertiary hospital based case control study. *Asian Pac J Cancer Prev*, **13**, 4979-81.

Ferlay J, Shin HR, Bray et al (2010). GLOBOCAN 2008 version 2.0. Cancer incidence and mortality worldwide: IARC cancer base No 10. Lion, France. Interl Agency Res Cancer, http://globocan.iarc.fr. Accessed May 2011.

Gao CM, Ding JH, Li SP, et al (2013). Active and passive smoking, and alcohol drinking and breast cancer risk in Chinese women. *Asian Pac J Cancer Prev*, **14**, 993-6.

Gram IT, Braaten T, Terry PD, et al (2005). Breast cancer risk among women who start smoking as teenagers. *Cancer Epidemiol Biomarkers Prev*, **14**, 61-6.

Ha M, Mabuchi K, Sirgurdson AJ, et al (2007). Smoking cigarettes before first childbirth and risk of breast cancer. *Am J Epidemiol*, **166**, 55-61.

Hulka BS, Moorman PG (2001). Breast cancer: hormones and other risk factors. *Maturitas*, **38**, 103-6.

Hunter DJ, Hankinson SE, Hough H, et al (1997). A prospective study of NAT2 acetylation genotype, cigarette smoking, and risk of breast cancer. *Carcinogenesis (Lond.)*, **18**, 2127-32.

Hussain SP, Hofseth LJ, Harris CC (2003). Radical causes of cancer. *Nature Rev Cancer*, **3**, 276-85.

Nahleh Z, Bhatti NS, Mal M (2011). How to reduce your cancer risk: mechanisms and myths. *Int J General Med*, **4**, 277-87.

Ilic M, Vlajinac H, Marinkovic J (2013). Cigarette smoking and breast cancer: a case-control study in Serbia. *Asian Pac J Cancer Prev*, **14**, 6643-47.

Jemal A, Bray F, Center MM, et al (2011). Global cancer statistic. *CA Cancer J Clin*, **61**, 69-90.

Jemal A, Sigel R, Ward E, et al (2009). Cancer statistics, 2009. *CA Cancer J Clin*, **59**, 225-49.

Johnson KC, Miller AB, Collishaw NE, et al (2011). Active smoking and secondhand smoke increase breast cancer risk: the report of the canadian expert panel on tobacco smoke and breast cancer risk (2009). *Tob Control*, **20**, 2.

Kelsey JL, Gammon MD, John EM (1993). Reproductive factors and breast cancer. *Epidemiol Rev*, **15**, 36-47.

Khuder SA and Simon VJ (2000). Is there an association between passive smoking and breast cancer? *Eur J Epidemiol*, **16**, 1117-21.

Kruk J (2014). Lifestyle Components and Primary Breast Cancer Prevention. *Asian Pac J Cancer Prev*, **15**, 10543-55.

Kruk J (2014). Health and economic costs of physical inactivity. *Asian Pac J Cancer Prev*, **15**, 7499-503.

Kuschner WG, D'Alessandro A, Wong H, et al (1996). Dose dependent cigarette smoking-related inflammatory responses in healthy adults. *Eur Respir J*, **9**, 1989-94.

Manjer J, Malina J, Berglund G, et al (2001). Smoking associated with hormone receptor negative breast cancer. *Int J Cancer*, **91**, 580-84.

Mathew CA, Tianyu L, Monica M, et al (2010). History of Smoking is associated with Younger Age at diagnosis of breast cancer. *The Breast Journal*, **16**, 344-49.

McKenzie F, Ellison-Loschmann L, Jeffreys M, et al (2013). Cigarette smoking and risk of breast cancer in a New Zeland multi-ethnic case-control study. *PLOS ONE*, **8**, 63132.

Minatoya M, Kutomi G, Asakura S, et al (2013). Equol, adiponectin, insulin levels and risk of breast cancer. *Asian Pac J Cancer Prev*, **14**, 2191-9.

Moore MA, Sobue T (2010). Strategies for cancer control on an organ-site basis. *Asian Pac J Cancer Prev*, **10**, 149-64.

Morabia A, Bernstein M, Ruiz J, et al (1998). Relation of smoking to breast cancer by estrogen receptor status. *Int J Cancer*, **75**, 339-42.

Nagata C, Kawakami N and Shimizu H(1997). Trends in the incidence rate and risk factors for breast cancer in Japan. *Breast Cancer Res Treat*, **44**, 75-82.

Nahleh Z, Bhatti NS, Mal M (2011). How to reduce your cancer risk: mechanisms and myths. Int J General Med, **4**, 277-87.

Nishino Y, Minami Y, Kawai M, et al (2014). Cigarette smoking and breast cancer risk in relation to joint estrogen and progesterone receptor status: a case-control study in Japan. *Springer Plus*, **3**, 65.

Olson J, Vachon C, Vierkant R, et al (2005). Pregnancy exposure to cigarette smoking and subsequent risk of postmenopausal breast cancer. *Mayo Clin Proc*, **80**, 1423-8.

Pięta B, Samulak D, Opala T, et al (2009). Women's lifestyle and the risk of breast tumors. *Eur J Gynaecol Oncol*, **30**, 186-9.

Reynolds P, Hurley S, Goldberg DE, et al (2004). Active smoking, household passive smoking, and breast cancer: evidence from the California teacher study. *J Natl Cancer Inst*, **96**, 29-37.

Scanlon EF, Suh O, Murthy SM, et al (1995). Influence of smoking on the development of lung metastases from breast cancer. *Cancer*, **75**, 2693-99.

Siegel R, Ma J, Zou Z, et al (2014). Cancer statistics, 2014. CA: *A Cancer J Clin*, **64**, 9-29.

Sundram FX(1995). Clinical studies of alveolar-capillary permeability using technetium-99m DTPA aerosol. *Ann Nucl Med*, **9**, 171-8.

Terry PD, Goodman M (2006). Is the association between cigarette smoking and breast cancer modified by genotype? A review of epidemiologic studies and meta-analysis. *Cancer Epidemiol Biomarkers Prev*, **15**, 602-11.

Wafa M, Bilal A, Ijaz J, et al (2014). Breast cancer: major risk factors and recent developments in treatment. *Asian Pac J Cancer Prev*, **15**, 3353-8.

Young E, Leatherdale S, Sloan M, Kreiger N, Barisic A (2009). Age of smoking initiation and risk of breast cancer in sample of Ontario women. *Tob Induc Dis*, **5**, 4.