EXPOSURE OF TABACCO LEAVES INDUCES MUTATION IN BRCA GENE CAUSING RISK OF BREAST CANCER

Neeraja Tatipakala, Research Fellow, Royal Life Sciences Pvt Ltd., Hyderabad, India.
Email-neerajavelisala.au@gmail.com

ABSTRACT

Animal research and in vitro tests have shown that compounds present in cigarette smoke, such as polycyclic carbohydrates, aromatic amines, and N-nitrosamines, may cause mammary tumours. The results in smokers' breast tissue with smoking related DNA adducts and p53 gene mutations still endorse the biological plausibility of a causal relationship between cigarette smoking and breast cancer, as does the discovery of carcinogenic activity in breast fluid. This study discusses worldwide tobacco use trends and the processes by which tobacco use is involved in carcinogenesis. A second section will address the association between the consumption of nicotine and the risk of different forms of cancer. Tobacco use has historically been a norm in high-income countries but it has been taken up lately in low-income countries and is especially popular in people. There is a wide range of tobacco items, the cigarettes being used more commonly. Tobacco products contain more than 50 known or proven carcinogens, which may raise the risk of cancer by inducing mutations that interrupt the function of the cell cycle or by affecting the immune or endocrine systems. Many factors such as genes, diet, and exposures to the environment can alter the susceptibility of tobacco users to cancer. Smoking was linked to a modest but significantly increased risk of breast cancer, particularly among women who began smoking at teenage or peri-menarcheal ages. Among people with a family history of the condition, the increased risk of smoking-related breast cancer was higher.

1. INTRODUCTION

Its average prevalence rates ranging from 11.8 per 100,000 in Eastern China to 86.3 per 100,000 in North America, breast cancer is the most frequently diagnosed neoplasm by women worldwide. Breast cancer prevalence rates have been steadily increasing in the United States for the last two decades. The numerous variations in incidence rates between regions with high incidence and low incidence and changes in incidence rates over time and among
migrants indicate that environmental factors that affect the risk of breast cancer. Of the environmental factors associated with possible significance to breast cancer, cigarette smoking has been among the most widely researched. Cigarette smoking is among the leading preventable cancer risk factors in general, including many cancers that develop at places not in direct contact with tobacco smoke, such as prostate cancers and pancreas.

Tobacco use, particularly tobacco smoking, is so strongly rooted in the public conscience as a source of cancer that it acts as a template of a risk factor for disease in many respects. Smoking is the leading cause of cancer mortality and smoking is believed to be due to at least 15 per cent of all cancers. Although this proportion is higher in men (25%) than in women (4%) and higher in high-income countries (16%) than low-income countries (10%) [1], smoking by women and citizens in low-income countries will gradually reduce these differences [2]. Moreover, the risk of death associated with cigarette smoking has increased over time, as the average smoking period has increased. Nonetheless, it isn't doom and gloom; avoiding smoking substantially decreases mortality threats even for long-term smokers and increasing numbers of smokers, mostly people from developed countries, have quit their habit in recent decades [2]. Epidemiological tobacco studies were important not only because they showed the destructive impact of tobacco use on the environment, but also because they paved the way and went hand in hand with the growth of scientific epidemiology from the middle of the last century. Tobacco smoke's carcinogenic potential is unarguable [1,2], and there are possible biological explanations why smoking could affect the risk of breast cancer [2–5]. In this review article we present tobacco exposure induces BARC gene mutation which causes breast cancer risk.

2. Reported work strategies

Michael E. Jones et al., 2017 [14] Recorded a longitudinal questionnaire details dataset of Generations research in the UK to predict Hours for breast cancer in relation to smoking corrected for possibly misleading factors, like alcohol consumption. We studied in 102,927 women, 1,815 having developed advanced breast cancer with an average of 7.7 years of follow-up. The HR (reference category was never smokers) was 1.14 (95% CI 1.03–1.25; P = 0.010) for ever cigarettes, 1.24 (95% CI 1.08–1.43; P = 0.002) for beginning smoking ages < 17 years, and 1.23 (1.07–1.41; P = 0.004) for beginning smoking 1–4 years after menarche. The probability of breast cancer was not statistically associated with the time from smoking initiation before first birth (P-trend = 0.97). People with a family history of breast cancer (ever smoker vs. never smoker HR 1.35; 95 per cent CI 1.12–1.62; P = 0.002)
have slightly higher HR than women without (ever smoker vs. never smoker HR 1.07; 95 per cent CI 0.96–1.20; P = 0.22) compared to those without. The association was dominant for age before initiating smoking (P = 0.003) and beginning smoking at menarche compared to age (P = 0.0001). They concluded in this study that smoking was associated with a modest but significantly increased risk of breast cancer, particularly among women who started smoking in teenage or peri-menarcheal ages. The increased risk of smoking-related breast cancer for people with a family history of the disease was higher.

Chisato Nagata et al., 2006 [15] Conducted a MEDLINE review finds epidemiological findings related to the prevalence or mortality of smoking and breast cancer by Japanese women of 1966 and 2005. Correlation assessment was based on the quality of proof and correlation size, along with biological plausibility as previously determined by the International Organization for Cancer Research. In their tests they find relative risk (RR) or odds ratio (OR) of breast cancer ranging from 0.71 to 6.26 for active smokers. In one of the three cohort studies, a significantly increased risk among current smokers compared to none smokers (RR = 1.7) has been found. Across four of the eight case-control trials, mild to large correlations have been identified between smoking and breast cancer risk (OR > 2.0). The biological plausibility of a causal relationship between cigarette smoking and the occurrence of breast cancer has been demonstrated by laboratory trials. They believe that the risk of breast cancer in the Japanese population can increase with tobacco smoking.

Hadar Goldvaser et al., 2017 [16] Assessed the effect smoking has on the symptoms and result of breast cancer. It was a single-centre observational analysis. All women diagnosed and treated in our institute from 4/2005 to 3/2012 with early, positive oestrogen receptor, human epidermal growth factor receptor 2 (HER2) negative breast cancer, the tumors of which were included for Oncotype DX review. Health reports for ethnicity, clinico-pathologic criteria, diagnosis, and outcome were reviewed. Statistics on smoking is gathered during the first visit to the oncology clinic due to the experience of patients. Patients were grouped and compared by smoking history (ever smokers vs. never smokers), smoking status (current vs. former and never smokers) and smoking intensity (pack years ≥30 vs. rest of the cohort). Results were modified in multivariate analyzes, including age, menopause status, race, tumor size, nodal status and ranking. It has involved a total of 662 people. 28.2% have a smoking background, 16.6% were active smokers and 11.3% were moderate smokers. Smoking did not affect tumor size, nodal activity and recurrence level of Oncotype DX. In current smokers, angiolymphatic and perineural levels of invasion were higher than in the rest of the population (10.4% vs. 5.1%, p = 0.045, 8.3% vs. 3.5%, p = 0.031, respectively).
Smoking had no further impact on histological characteristics. Five-year disease-free survival and overall survival rates were 95.7% and 98.5% respectively. Smoking did not have an impact on outcomes. Adjusted disease-free survival and overall survival did not affect outcomes. They conclude that smoking did not have a clinically significant effect on tumor characteristics and outcomes among women with positive, HER2-negative, early breast cancer receptors. Because the analysis was restricted to a small subgroup of the breast cancer population in this heterogeneous community, and because smoking is a modifiable risk factor for the community, more work is needed to explain the potential effect of smoking on breast cancer.

Wael K. Al-Delaimy et al., 2014 [17] Investigate in a broad retrospective study primarily in premenopausal women the link between smoking and invasive breast cancers distinguished by their estrogen-receptor status. In 1989, this study was carried out on 112,844 women aged 25–42 years, followed by 10 years; questionnaire information on medical diseases and risk factors was collected biennially, and diet information was collected in 1991 and 1995. In this follow-up period (1,077,536 person-years), it recorded 1009 cases of breast cancer incidents. Across the multivariate-adjusted models, smoking status was not substantially related to the overall risk of breast cancer: relative risks (RRs) for former smokers were 1.18 [95 per cent confidence interval (CI) 1.02–1.36] and 1.12 (95 per cent CI 0.92–1.37) for current smokers compared to never smokers. Growing smoking period before the first pregnancy was associated with a higher risk of breast cancer, although there was no increase in the highest category: RRs were 1.42 (95 percent CI 1.10–1.83) for 15–19 years of smoking relative to never smokers, and 1.10 (95 percent CI 0.80–1.52) for ≥20 years of smoking (P for trend = 0.01). Smoking was most closely linked to the occurrence of receptor-positive estrogen breast cancers. The RR for estrogen receptor-positive cancer was 1.37 (95 percent CI 1.07–1.74) for women who had smoked for ≥20 years, and the RR for estrogen receptor-negative cancer was 1.04 (95 percent CI 0.71–1.53). For smoking before age 15, RRs were 1.49 (95 percent CI 1.03–2.17) for receptor-positive estrogen cancer, and 1.19 (95 percent CI 0.69–2.08) for receptor-negative estrogen cancer. They conclude in their study that longer smoking duration may be related to the risk of estrogen receptor-positive breast cancer but possibly less so for estrogen-negative breast cancer.

Kim E. Innes et al., 2001 [18] Assess the relationship of smoking during a woman's first pregnancy, time of marked growth and mammary tissue differentiation, and subsequent risk of breast cancer. They used related birth certificate and tumor registry data from the New York State Health Department in this matched case–control study. Cases included 319
women aged 26–45 who had been diagnosed with breast cancer in New York State between 1989 and 1995 and who had completed a first pregnancy in New York State at least one year before cancer was diagnosed in 1987. Controls were 768 primiparous women on county of residence and delivery date compared to events. Data on prenatal smoking and other factors that influence the woman's first pregnancy was collected from each subject's pregnancy record, and the correlation of these factors with the risk of breast cancer was assessed using conditional logistic regression. They found that Smoking was associated with increased risk of breast cancer during pregnancy (crude OR = 2.7, 95 per cent confidence interval (CI): 1.1–6.3). This correlation was reinforced by the adjustment for maternal age, subject age, race and education (OR = 4.8, CI 1.6–14.6). These findings suggest that smoking cigarettes during a woman's first pregnancy may increase her risk of breast cancer from early onset.

Fei Xue, MD et al., 2011[19] Did Prospective longitudinal study of 111 140 Nurses ' Health Survey participants from 1976 to 2006 on active smoking and 36 017 people on passive smoking from 1982 to 2006. 8772 incident cases of invasive BC were recorded within 3 005 863 person-years of follow-up. BC's hazard ratio (HR) was 1.06 percent (95 percent confidence interval [CI], 1.01 percent -1.10 percent) for ever smokers relative to never smokers, after adjustment for potential confounders. The prevalence of breast cancer was correlated with higher rates of current (P for trend = 0.02) and past (P for trend = 0.003) smoking, younger age at smoking initiation (P for trend = 0.01), longer smoking period (P for trend = 0.01), and more smoking pack-years (P for trend = 0.005). Premenopausal smoking was associated with a marginally higher incidence of BC (HR, 1.11; 95 per cent CI, 1.07-1.15 for each 20 pack-year increase), especially before birth (1.18; 1.10-1.27 for each 20 pack-year increase). In comparison, the direction of the relationship between postmenopausal smoking and BC was the reverse (0.93; 0.85-1.02 for every 20 pack-year increase). During childhood or adulthood passive smoking was not associated with risk of BC. They indicated that active smoking, particularly before the first child, may be associated with a modest rise in BC risk.

3. **BRCA GENE**

BRCA1 and BRCA2 are human genes producing proteins for the treatment of tumours. These proteins help to repair degraded DNA, and thus play a role in maintaining the integrity of the genetic material of each cell. When one of these genes is damaged or changed in such a manner that their protein product is not produced or does not function correctly,
damage to the DNA can not be adequately restored. Cells are also more likely to experience additional genetic mutations which may lead to cancer.

Different hereditary mutations in BRCA1 and BRCA2 raise the risk of female breast and ovarian cancers most significantly, but they were also linked with elevated rates of many other cancer types. People who inherited BRCA1 and BRCA2 mutations continue to develop breast and ovarian cancers at a later age than people who do not have such mutations. Mother or father of a child may inherit a dangerous BRCA1 or BRCA2 mutation – offspring of a parent carrying a mutation in one of those genes has a 50 percent probability of inheriting the mutation (or 1 probability in 2). The results of BRCA1 and BRCA2 mutations are seen only though the second copy of the gene is common for a human.

**Presence of Carcinogen in Tobacco And Its Relevance To Breast Cancer**

More than 2000 chemical compounds were found in tobacco leaves, some of which are emitted by smoking, and 55 of these were classified by the International Agency for Research on Cancer (IARC) as providing 'good evidence of carcinogenicity' in either laboratory animals or humans[6]. These include polycyclic aromatic hydrocarbons (PAHs), aza-arenes and heterocycles, N-nitrosamines, aromatic amines, heterocyclic aromatic amines, aldehydes, and inorganic compounds.

**Absorption and metabolism of Breast Carcinogens**

Numerous studies have examined the absorption and metabolic activation of possible breast cancers in smokers and non-smokers, although the presence of these carcinogens or their metabolites or adducts in human breast tissue has not been reported. 1-Hydroxypyrene and its glucuronide are urinary derivatives of PAH pyrene, a noncarcinogen. For mammals, the urinary level of 1-hydroxypyrene is easily quantified. A variety of studies have found that urinary 1-hydroxypyrene in smokers is elevated compared with that in non-smokers, consistent with the involvement of pyrene in tobacco smoke [7, 8, 9].

Many causes of pyrene take-up include broiled beef, contamination of the atmosphere and workplace exposures. Thus 1-hydroxypyrene presence in urine is not due to exposure to tobacco smoke. However, the elevated levels of 1-hydroxypyrene found in the urine of smokers confirm increased absorption of PAHs compared to that of non-smokers. Several experiments have investigated human levels of B[a]P – DNA adducts and B[a]P – protein adducts. Such adducts were quantified using structure-specific approaches such as fluorescence of the HPLC, gas chromatography / mass spectrometry and similar techniques.
It was shown that it can not be concluded that adducts from B[a]P would be observable, except in conditions where sensitivity to B[a]P is fairly small. No single contact condition had resulted in an excessive concentration of detectable adducts. For eg. B[a]P DNA adducts have been found in 50% of smokers, 46% of former smokers, 52% of non-smokers, 39% of occupationally exposed individuals and 33% of environmentally exposed people. B[a]P – DNA adducts in the blood were typically higher in people exposed to cigarette smoke than those in non-smokers, but tissue tests B[a]P – DNA adducts and B[a]P – protein adducts provided contradictory findings.

This has found metallic amines in human urine. This quantified the 2-toluidine in human urine. This was observed to excrete 6.3 3.7 g/24 hr of 2-toluidine in smokers, while in non-smokers the rates were 4.1 3.2 g/24 hr, not substantially different from those of smokers[10]. Apart from cigarette smoke, there are obviously significant sources of human uptake of 2-toluidine. Nor did 4-aminobiphenyl levels vary greatly between smokers (78.6 85.2 ng/24 hr) and non-smokers (68.1 91.5 ng/24 hr)[11]. In comparison, adducts of 4 aminobiphenyl-hemoglobin are typically higher in smokers than in non-smokers [12]. Variants of carcinogen-metabolizing enzymes also change the levels of such adducts. For reference, in non-smokers and light smokers phenotyped for rapid cytochrome P450 1A2 and slow N-acetyltransferase-2 activities, Landi et al. [1996][13] showed that 4-aminobiphenyl hemoglobin adducts were higher compared with those in individuals with slow P450 1A2 and rapid N-acetyltransferase-2 activities.

This is consistent with the involvement of cytochrome P450 1A2 in 4-aminobiphenyl N-hydroxylation, the necessary step for the formation of hemoglobin adduct, while N-acetyltransferase-2 is involved in 4-aminobiphenyl acetylation which distracts the carcinogen from the formation of hemoglobin adduct. There is compelling proof that cigarette smoke pollutants such as nicotine penetrate breast tissue, and that tobacco smoke consumes and metabolizes mammary carcinogens in smokers. Tobacco smoke carcinogens are also likely to reach the breast tissue, and although each individual dose will be relatively small, the cumulative dose resulting from years of chronic exposure may be significant. Furthermore, there is actually no proof that particular carcinogens from the cigarette smoke enter human mammary tissue. Genetic polymorphisms that alter the dose of carcinogen to the breast in smoking, as already seen in studies of 4-aminobiphenyl hemoglobin adducts.
CONCLUSION

In this article we describes the exposure of tobacco induces mutation in BRCA gene causing risk of breast cancer. From numerous study and review article reported it was found that smoking was associated with a modest but significantly increased risk of breast cancer, particularly among those who began at adolescent or perimenarcheal ages, and that the relative risk of smoking-related breast cancer was significantly higher for women with a family history of the disease.

REFERENCES


16. Hadar Goldvaser et al., The association between smoking and breast cancer characteristics and outcome. BMC Cancer (2017) 17:624


19. Fei Xue, MD, ScD; Walter C. Willett, MD, DrPH; Bernard A. Rosner, PhD; et al Cigarette Smoking and the Incidence of Breast Cancer. Arch Intern Med. 2011;171(2):125-133