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A Review of the Relation of Cigarette Smoking and Breast Cancer

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Abstract:

Carcinogens are substances which could stimulate the development of cancer cells. Most carcinogens are found in tobacco products, such as cigarettes. These substances could lead to the production of a segment of DNA bound to a cancer-causing chemical, which invades the cellular repair mechanisms, and could also cause mutations. The detection of carcinogens activity in breast shows that there would be a higher possibility of developing breast cancer. However, females who both smoke and have breast cancer tend to have a family history of relatives having the breast cancer as well. This suggests that cigarettes alone may not cause breast cancer. This type of cancer is currently the second most frequent type of cancer being diagnosed in females. However, the rate of smoking in women has been gradually declining. The decrease in rate of smoking in females did not correlate to breast cancer, but cigarette smoking may have been linked with the development of cancer cells in the breast. By gathering much information from many research projects, studies, and laboratory experiments, this literature review provides clear content of carcinogens, breast cancer, and cigarette smoking. Furthermore, laboratory studies are a key factor in this review literature as they discovered that substances from cigarette smoking can reach the breast tissue. Breast, after and during puberty, consist of mainly undifferentiated terminal ductal and lobular structures, which animal research projects illustrate that these structures are more sensitive to carcinogens. Therefore, a higher chance of developing breast cancer comes with smoking during adolescence and high amount and duration of cigarette smoking.

Keywords **—Breast cancer, carcinogens, cigarette smoking**

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I. INTRODUCTION

Cancer, or malignant tumor, is a disease in which some of the body's cells grow uncontrollably (1). It is one of the biggest costs of death worldwide, whose death rate could be up to 158.3 over 100,000 women and men (1). Despite the equal rate of death between men and women, research shows that men are more prone to cancer than women (1). Apart from radiation and alcohol, smoking is the most obvious cause of cancer. In 2018, there were an estimated 34.1 million adults who smoked (2). About 10 to 15 percent of people who smoke developed cancer and an even higher ratio of deaths associated with lung cancer are linked to cigarette smoking (3, 4). There are about 17 or more cancers that could be caused solely by smoking . Lung and oral cancer might be obvious (5, 6). However, there are oesophagus, bladder, stomach, liver, cervix, bowel, acute myeloid leukemia, and breast cancers that can also potentially develop from smoking (5, 6). Heavy smokers do not usually reach the age of 65 due to cancer death and heart diseases (7-9). The substance in tobacco products includes more than 60 known carcinogens, which incorporates polycyclic aromatic hydrocarbons (PAHs), nitrosamines, and aromatic amines, and nicotine . Nicotine does not only make the product additive, but also cause pathogenesis of cancer to be genotoxic (10). However, the most damaging substances inside tobacco are hydrogen cyanide, carbon monoxide, and ammonia (11, 12). When

these harmful substances enter a human's lung, the chemicals damage the DNA, including the part which protects cancer, and make it harder for DNA to get repaired (13-15). The mutated and damaged cell is how a typical cancer is formed (13, 16, 17). Therefore, this review aims to explore the correlation between breast cancer and smoking cigarettes and the carcinogenic pathway involved.

II. CIGARETTE SMOKING AND RISK OF BREST CANCER

The second highest tumour occurrence diagnosed in females, and the second highest cancer related death rate cannot be anything but breast cancer. The National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results Program (SEER) estimated 246,660 recent breast tumours diagnosed in 2016, accounting for 14% of all recent cancer cases (18). Thus, it is unsurprising that women have a life span potential of breast cancer development at 12.4% (19, 20). Some factors that have been found to raise the potential development of breast cancer include older age, genetic inheritance, obesity, drinking alcohol, and specific mutations, such as the *BRCA1/2*, dense breast tissue, and the use of birth control pills (21, 22). Ductal carcinoma in situ is the highest occurring type of histopathological type of breast cancer (23). It is possible that invasive ductal carcinoma will spread beyond the primary site, highly likely to the bone, lung, or liver (23). Rather than primary tumour formation, metastatic cancers are responsible for the high rate of death caused by cancer (23). According to the National Cancer Institute's SEER programme, of all the patients, 6% are found to develop metastatic disease during the initial diagnosis, causing the hospitalisation to be more complex, and clinical management of metastasis critical (24, 25).

Substances in tobacco products, such as polycyclic aromatic hydrocarbons, N-nitrosamines, and aromatic amines stimulate the development of breast tumour in animal models and *in vitro* studies (26-29). Cigarette smoking is linked to a higher potential development of breast cancer because the existence of segments of DNA bound to carcinogens and genetic mutations (*p53* gene) and the detection of carcinogenic activity in breast fluid supports this hypothesis (30-32). Despite this, studies have demonstrated inconsistent results along the recent decades, sometimes showing positive, inverse, or null relationships (33). As the results of the epidemiological studies diverged, epidemiologists paid greater attention to possible modifiers of the correlation between breast cancer risk and possible differences in breast tumour types and cigarette smoking (34, 35).

III. SMOKING CIGARETTE AND BREAST CANCER SUBTYPES

Significantly increased breast cancer risks (ER-positive and ductal) (the highest frequent types) were reported, though, not a single notable heterogeneity by ER status or morphological type of breast cancer was reported concerning cigarette smoking (36). ER-negative tumours and non-ductal-type tumours were relatively uncommon in our cohort, limiting the statistical power to investigate differences based on these characteristics (33, 36-39). Although some studies have tended to illustrate increased potential development for ER-positive breast cancer, none have demonstrated important correlation, and the literature is inconclusive (40). Premenopausal breast cancer was associated with higher hazard ratios than post-menopausal breast cancer (40). Nevertheless, important statistics were not attained. Even though the research is, sometimes, unreliable, it generally suggests that women at the age before menopausal are more likely to get breast cancer the age after menopausal (39, 40). However, similar to other studies, we found no evidence or suggestion of a notable correlation between menopausal status and the study results (34, 37, 41).

IV. CONNECTION BETWEEN GENETIC ASPECTS BETWEEN SMOKING AND BREAST CANCER

According to various research projects, the correlation of cigarette smoking and breast cancer was notably higher among females who have at least a relative with the disease than those without (42). However, there are two studies which had suggested no correlation between breast tumour and cigarette smoking, but many results presented by

the researchers were not stratified, which means that we could not conclude the direction these studies support (33, 35). Despite this, three studies had shown significant interactions, in which the potential development of breast cancer rose among female smokers who had family history of positive in this disease (43). However, two illustrated that the potential risk was raised only for people without at least a relative with this disease (44-46). An increase of breast tumour development due to smoking has been shown in most studies of *BRCA1/2* carriers (47-49). Few reports also show important associations between smoking and the occurrence of multiple alleles at a locus in genes with cancer stimulation substances, *NAT2* and *CYP1A1*, along with breast cancer susceptibility single-nucleotide polymorphisms (50-56). Furthermore, repairing damaged DNA corporates using *BRCA1* and *BRCA2* proteins, and it is, then, potentially probable that *BRCA1/2* carriers may have a higher sensitivity to the consequences of cancer causing substances in cigarette smoke (49, 57-59). Moreover, ignoring both inadequate plus uncertain research, there might be gene-smoking interactions in association to potential development of breast cancer, with bladder cancer, and research projects might gain advantages from concerning more on the duration and increase accurate measures rather than just never smoking (60-62).

V. EVIDENCE FOR A DIRECT LINK OF BREAST CANCER AND SMOKING

Although the link between breast malignant tumour and cigarette smoking has been highly debated, smoking does increase the risk of the disease (63). A cohort study published in 2015 by Luo et al. discovered that people who had never smoked had a higher probability (9%) of developing breast cancer than people who gave up smoking (64). This level of possibilities was significantly higher for current smokers, who were at a 48% increased risk. 33 One additional consideration is to look at studies that consider smoking alone, but also consider other habits, such as the length of time a person has smoked, the number of cigarettes they smoke, when they started smoking, and how long they have since quit (64). Researchers Xue et al. discovered that correlated to nonsmoker women, women who had previously smoked were 1.07 times more feasible to be diagnosed with breast cancer (64). However, the study found HRs of 1.09 (95% confidence interval [CI]: 1.06, 1.12) when comparing current and former smokers, suggesting that quitting after years of smoking had little effect on one's risk of heart disease (64). Each time there was an increase of 20 pack-years, an increase in HR was found and an increase in HR for the length, amount, and age of smoking (65). Additionally, women who smoked over 25 cigarettes daily, smoked for 2 decades or longer, and started smoking during their teens (before 17) had an elevated HR (CI 1.14). (HR 1.07, 95%CI) (65). Even new studies show that heavy smoking increases the possibility of getting breast cancer (HR 1.17, 95%CI) (34). When the Surgeon General released a summary on the results of 22 longitudinal and individual studies, he found that a meta-analysis of these studies was unable to determine whether smoking earlier in life has higher possibilities than gaining the habit later in life (40). Despite this, a new pooled analysis (which included over one million participants) showed that females who had smoked for over ten years before giving birth had an 18% greater chance of developing breast cancer (34). Several scientific studies have looked into the potential factors of development of breast cancer in those who have already developed it. In a study developed by Pierce et al., breast cancer patients who had smoked at least 30 packs of cigarettes every year and had over 3 decades history of smoking were found to have a 37% higher risk of redevelopment and a 54% higher risk of overall mortality compared to non-smoking patients (66). For these heavy smokers, overall mortality rose by 60% (66).

VI. LABORATORY STUDIES OF SMOKING-RELATED BREAST CANCER

Laboratory studies provide a crucial role in cigarette smoking and breast cancer development. The most important and notable study from the laboratory discovered whether the components from the burning of cigarettes could reach the breast tissue. The result supports the hypothesis, as the

fluid in the breast of women who smoke has shown to contain the components (67). Furthermore, another study shows the existence of smoking-related segments of DNA in epithelial cells of breast milk, which suggests that substances in cigarettes contacts breast tissue (67, 68). Understanding of the mechanisms can also reveal how cigarette smoking is linked to breast cancer. Carcinogens found in cigarettes, incorporating Benzo[a]pyrene, isoprene, and ethylene oxide, can cause mammary tumors in rodents (69). The cause of the widespread mechanism for tumor development as a consequence of cigarette smoking has been a proven possibility from the formation of DNA adducts (70-72).

Tobacco smoking is associated with tumour progression and metastasis as well. Previous studies have shown that exposure to cigarette smoke increases breast tumour cell spreading and epithelial-mesenchymal transition (EMT) (73-75). When treated with cigarette smoke, both normal mammary cells and breast cancer cells adopt fibroblastoid morphology. As normal mammary epithelial cells exposed to CSE were given to mice, they demonstrated increased survival and an improved ability to colonise the ducts. The injection of 44 CSE-treated MCF-7 breast tumour cells into the mammary pad of mice resulted in the development of lung metastases in all of the mice who received the injection compared to the lack of metastases in the mice who were injected with untreated MCF-7 cells, advocating that cigarette smoke stimulates tumour invasion (76, 77). Tumor cell adhesion from the basement membrane is lost in the EMT process, and tumour cells' invasive and migratory capabilities are increased (73-75). Several EMT markers were altered when MCF-7 and MDB-468 breast cancer cells were incubated with nicotine. As reported by Dasgupta et al. E-cadherin and B-catenin, the epithelial markers were declined in nicotine-exposed samples, although fibronectin and vimentin, the mesenchymal markers, were increased (78). In MDA-MB-231 breast cancer cells, exposure to CSE resulted in increased cell motility, which could be suppressed by inhibiting a precursor of platelet-activating factor, a protein known as iPLA2 (PAF). An increase in PAF and PAF receptor (PAF-R) expression was also observed with 15 CSE treatments (78). Cell adhesion in CSE-treated MDA-MB-231 cells was higher when compared to untreated cells, meaning that they bound to HMVEC-L endothelial cells better (79).

CONCLUSIONS

With the knowledge that smoking cigarette was correlated with a notable and significantly increased in the potential development of breast cancer, especially for people who started in their adolescence.Therefore, in conclusion, it is valid to summarise that high amount and duration of cigarette smoking leads to a clear potential risk of breast malignant tumors, or even worst disease. A few cohort studies also suggest that the high duration of cigarette smoking will increase the risk of getting breast cancer. Furthermore, laboratory studies found the consequences of cigarette smoking substances on normal mammary epithelial cells (rise up movement, survival, colonisation, and transition to mesenchymal phenotype).

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