

Is Smoking a Risk Factor of Breast Cancer?

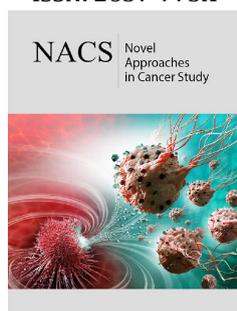
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Abstract

The incidence of breast cancer is increasing worldwide, making it the most common cancer among women. The etiology of breast cancer is multifactorial, including genetic risk factors, family history, age, gender, ethnicity, dense breast tissue and life-style related risk factors. Cigarette smoking is one of the risk factors in many cancers and recently been shown to be associated with breast cancer. The relationship between cigarette smoking and breast cancer has been explored in vitro and in vivo. One of the important components of cigarette smoke, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), a representative carcinogen of N-nitrosamines, has also gained focus in breast cancer carcinogenesis. Other than promoting tumor growth in cancer cells, NNK has also been proved to cause malignant transformation in normal breast cells. However, clinical association of NNK and breast cells is still limited, and there are controversies that warrant further explorations.

Keywords: Breast cancer; Risk factor; Smoking; 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)

Introduction

In 2013, World Health Organization estimates globally that 21% of adults were current smokers, which include 250 million women and 1 billion men [1]. Women account for 15.7% of all current smokers, and most of them live in mid- and low-income countries. World Health Organization has also estimated that smoking is causing death of about six million people in the world each year [2]. The current available knowledge about the relationship between some certain human cancers and smoking is based mainly on epidemiological studies. In recent years, many studies announced that consumption or exposure of smoking is associated with various types of cancers, including cancers of oral cavity, lung, nasal cavity and nasopharynx, paranasal sinuses, oropharynx, larynx, hypopharynx, stomach, esophagus, liver, myeloid leukemia, cervix, urinary bladder, pancreas, kidney, ureter and upper aerodigestive tract [3-6]. Except for lung cancer, the development of other cancers is due to systemic effect of cigarette smoke, thus, the possible association between smoking and breast cancer has gained attention in recent years.

Not until recently the association between cigarette smoke and breast cancer has received much attention. Many epidemiological and preclinical studies have implicated that cigarette smoke is one of risk factors of breast cancer [7]. Cigarette smoke contain more than 4000 components, in which over 70 of them have been classified as carcinogens by International Agency for Research on Cancer [6,8]. For example, N-nitrosamines, polycyclic aromatic hydrocarbons, aromatic amine, nicotine-derived nitrosamines, aldehydes and inorganic compounds can cause cancer or elevate the risk of some cancer types in animal experiments and human cells [4,5,9]. There are several tobacco carcinogens that have been detected in the circulation of smokers. These carcinogens include aromatic amines, N-nitrosamines and polycyclic aromatic hydrocarbons [10]. Breast epithelial cell activates and metabolizes these compounds into electrophilic intermediates which because DNA adduct formation and DNA damages [11,12]. Thus, much attention has been extended to breast cancers, other than lung cancer. 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) is a nitro sated derivative of nicotine and also has been considered as carcinogen in human by IARC [6]. NNK is one of the representative components of N-nitrosamines and has been extensively studied in other types of cancer including lung cancer and gastric cancer [13,14]. Some experiments explored the influence of NNK in breast cells from the receptor to downstream molecular pathway

and DNA adducts formation [15-20]. However, the exact effect and mechanism of NNK in breast cells still remain unclear.

Association of cigarette smoke and breast cancer risk

Many epidemiological studies have revealed the association between smoking and breast cancer risk among women. Reynolds and Cui have demonstrated that breast cancer incidence was associated with cigarette smoking [21,22]. Similarly, a positive correlation between breast cancer risk and active cigarette smoking was observed in a separate study. Current smokers have a higher risk of breast cancer than former smoker. Among them, those who smoked for more than 40 years showed significant association with increased breast cancer risk than those who have less smoking history [23]. Pierce JP et al. [24] found that current smokers have increased rate of breast cancer recurrence and mortality by 41% and 60% respectively. Former smokers who exposed to 20-34.9 pack-years of cigarette had a 22% increased risk of recurrence in breast cancer, and a 26% increased risk of mortality for all causes, when compared with non-smokers. For former smokers who exposed to 35 or more pack-years of cigarettes, the risk of breast cancer recurrence increased by 37%, breast cancer mortality increased by 54%, and mortality of all causes increased by 68% [24]. On the other hand, the exposure of cigarette smoke in different stages in life course is one of the aspects that have been widely studied. Dossus L et al. [25] studied the association between smoking and specific stages in life course, and found that a significant increase in breast cancer risk with pack-years of smoking occurred from menarche to first full-term pregnancy.

In 2005, the California Environmental Protection Agency (EPA) reviewed 52 studies and concluded that there is a positive correlation of breast cancer risk with active cigarette smoking [26]. In 2009, Canadian Expert Panel concluded that early age of smoking, longer duration and higher pack-years of smoking increased breast cancer risk from 15% to 40%. Noteworthy, secondhand cigarette smoke also increased the risk of breast cancer among women who were primarily premenopausal and younger, but never smoked [27]. These findings were consistent with IARC that cigarette smoking increased the risk of breast cancer in women [28]. Moreover, it has been suggested that cigarette smoking plays a role in contribution to DNA alteration in breast cancer patients. This will be discussed in the following section. Although increasing evidence revealed the potentiation of cigarette smoke in the development of breast cancer, there are still some controversies on the significance of cigarette smoking on breast cancer risk. In 2001 and 2004, the Surgeon General of United States reported that the breast cancer risk is not affected by active smoking [29,30]. Due to this controversies, there are recent increase in interest and there are more studies being conducted on the clinical association of smoking with breast cancer risk [24,25,31-33].

The active component in cigarette smoke ---- NNK

More than 60 known carcinogens have been identified in cigarette smoke, among which N-nitrosamines and nicotine have gained much attention in cancer initiation and promotion [10,34].

NNK has been classified as a Group 1 carcinogen by IARC in 2007 and is one of the important nitrosamines which has carcinogenic ability with considerable amount in cigarette smoke [6]. The level of NNK varies in different cigarette brands. The concentration of NNK range from 53.5-220.7ng/cigarette in mainstream and 50.7-96.7ng/cigarette in sidestream [6]. Among all tobacco-specific nitrosamines, NNK has been proved to cause lung cancer in human and animals [35,36]. Besides, NNK also causes other types of cancers including pancreatic, oral, gastric, and breast cancers [10,14,37-39]. In preclinical studies, NNK has been proven to induce lung cancer, gastric cancer, pancreatic cancer and liver cancer in animal models [13,14,40,41]. However, the effect of NNK in the development of breast cancer is still unclear.

NNK in breast cancer

The effect of NNK on breast cancer initiation has been studied in normal breast cells. Treatment with NNK on breast epithelial cell line MCF-10A showed malignant transformation with overexpression of $\alpha 7$ -, and $\alpha 9$ -nicotinic acetylcholine receptors (nAChRs). NNK up-regulated extracellular signal-regulated kinase (ERK)1/2 phosphorylation, stimulated expression of hepatocyte growth factor (HGF), and down-regulated expression of tumor suppressor gene CDKN2A [15]. MCF-10A cells treated with combination of NNK and B[a]P induced breast cancer carcinogenesis through DNA damage, Ras-ERK-Nox signaling activation and reactive oxygen species elevation [16]. Another study showed that repeated exposure to NNK resulted in progressive changes of cellular carcinogenic development, transformed from an immortalized non-cancer stage to pre-cancerous stage, that acquired anchorage-independent growth, reduced dependence on growth factors, and altered acinar [17]. By profiling gene expressions using cDNA microarray, NNK regulated several important breast cancer related genes including down regulation of PCSK2, TUBB2C, S100A2 and up-regulation of CRYAB, HSD11B2, FLJ20366 and TRIM29 [17]. In addition, NNK is competent to induce malignant transformation of noncancerous breast epithelial cells, accompanied by a loss of responsiveness to 17β -estradiol via ERK-dependent pathway [18]. On contrary, study on the effect of NNK on breast cancer cells are limited, hence the mechanism of how NNK enhances breast cancer carcinogenesis are still unclear. NNK, as a high affinity agonist for β -adrenergic receptors, has been proved to stimulate the activation of ERK1/2 pathway in breast cancer cells [19]. NNK increased cell proliferation through $\alpha 5$ - and $\alpha 9$ -nAChRs [20].

Formation of DNA adducts

Cigarette smoke is known to cause DNA adductions and mutations to induce tumor growth in human [42,43]. DNA adduct formation is considered as a critical step during tumor initiation. Among smokers who were passively exposed to second-hand smoke, electrophilic metabolic forms of tobacco components were detected in breast epithelial cells, which bound to DNA and formed DNA adducts [44]. These phenomena is shown in both cancerous and normal breast tissue. Evidence showed that mutagens including prochlorperazine from exogenous sources were detected in breast fluid from women [45]. Also, cigarette-induced DNA adducts were

identified in normal breast tissues in smokers with breast cancer [46]. Smokers had a higher prevalence of TP53 mutation than non-smokers [47]. The benzo(a)pyrene caused genomic alteration in breast epithelial cells after exposed to smoking showed similar level with those seen in familial breast cancer cells [23]. The action of cytochrome P450 plays an important role in NNK metabolism to form N'-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL). These metabolites induce pyridylhydroxybutylation, pyridyloxobutylation and methylation of nucleobases inside the nucleus [48]. Subsequently, NNK metabolites bind to DNA and change into the covalent binding forms named DNA-adducts. Nettekheim find that this NNK induced DNA adducts is exactly an attack form to DNA and can lead to DNA mutations [49].

NNK mediated signaling pathways

NNK induces the formation of DNA adducts, and subsequent gene mutations have been observed in several studies (Table 1). These gene mutations are believed to play an important role in carcinogenesis. These perhaps may be developed into potential therapeutic targets for breast cancer patients. However, limited studies have been carried out to explore this area. Conway et al. [47] found that tobacco consumption increased the TP53 gene mutation frequency in breast cancer patients, which showed similar levels as

those observed in lung cancer and implicated the carcinogenesis of smoking in breast. Olivier et al. [50] found that the tumor suppressor gene TP53 mutation has been detected among 15-30% of breast cancer patients. N-acetyltransferase 2 (NAT2), functions for activation and detoxification of carcinogens and drugs. The development of neoplasia in Brazil individuals with NAT2 slow acetylation type increased three times compared to controls [51]. Firozi et al. [44] reported that higher levels of DNA adduct in breast tissue had been detected in women who smoked and had slow NAT2 genotypes than those who never smoked and had rapid NAT2 genotype. Terry et al. [52] concluded that more significant increase of breast cancer risk was observed in postmenopausal women who were smokers and had NAT2 slow genotypes. NAT2 slow genotypes elevated breast cancer risk with 20 pack-years and was dose-dependently increased among NAT2 slow genotypes smokers [53]. Recent studies provide evidence on the relation of NAT2 with cigarette smoke. The harmful effects of cigarette may be relevant for breast cancer patients with NAT2 slow acetylation type [54]. It is well known that breast cancer susceptibility genes (BRCA1/2) are associated with increased risk of breast cancer [55]. Smoking increased the breast cancer risk before age 50 in BRCA1 and BRCA2 mutation carriers [56]. For smokers with five or more pack-years, breast cancer risk increased 7% per pack-year among BRCA1 and BRCA2 carriers [56].

Table 1: Impact of cigarette smoke on gene mutations in breast cancer patients.

Genes	Effects of Smoke	Subjects and Reference
TP53	Increase the TP53 gene mutation frequency.	456 archival invasive breast tumors (47)
		IARC TP53 mutation database (50)
		378 patients from a case-control study (62)
NAT2	Slow NAT2 genotype may elevate breast cancer risk by increasing formation of DNA adducts.	166 women with breast cancer (44)
		110 women with breast cancer (63)
		Meta-analysis of 9,215 breast cancer (64)
		70 patients with invasive ductal breast carcinoma (51)
		3340 postmenopausal patients with invasive breast tumors (54)
BRCA1/2	Smoking can increase the breast cancer risk in BRCA1 carriers.	195 BRCA1 mutation patients with breast cancer, 128 BRCA2 mutation patients with breast cancer (56)
		1,920 BRCA1 and 618 BRCA2 mutation patients with breast cancer (65)

To date, smoke components have been proved to cause DNA alteration and various signaling pathways (Figure 1). As NNK is an agonist of nAChRs, most of the effects are mediated by the binding to nAChRs, such as $\alpha 9$ - or $\alpha 7$ -nAChRs, to cause proliferation, apoptosis, migration, invasion, angiogenesis and chemoresistance. NNK activates PKC, ERK1/2, PKA or AKT pathways, or activates Bcl2, Mcl-1, cMyc, or suppresses Bad and Bax, to induce proliferation

and apoptosis [13,35,57]. On the other hand, activation of ERK activates calpains and suppresses E-cadherin, β -catenin or ZO-1 to promote migration [58,59]. NNK increases the influx of Ca^{2+} to activate PKA, VEGF and FGF2 for angiogenesis [60,61]. Although drug chemoresistance is commonly seen in smokers, the study of underlying mechanism between NNK and chemoresistance is still limited, which warrants further investigation.

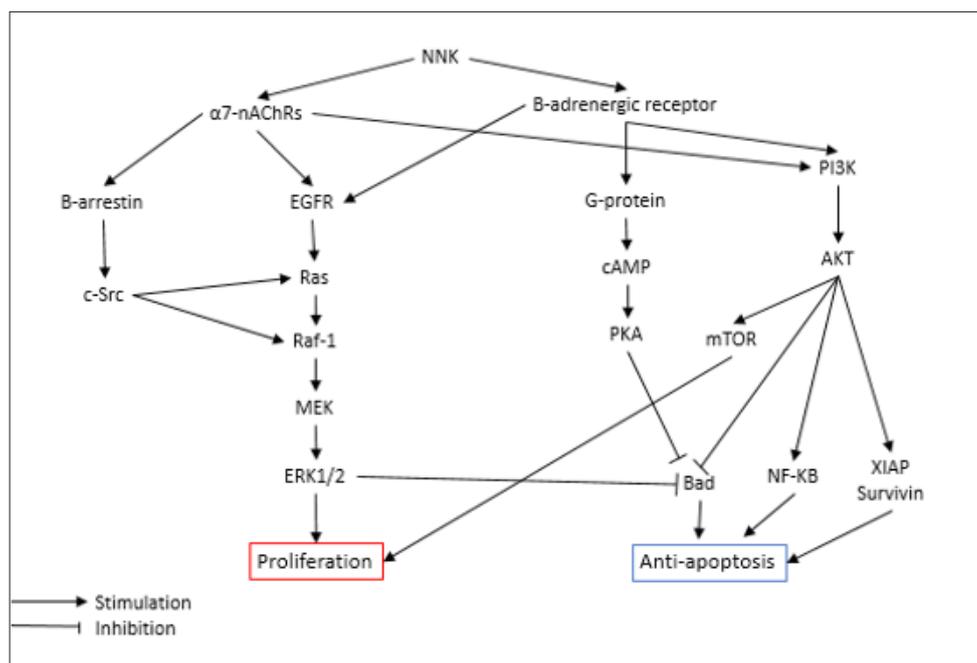


Figure 1: An overview of NNK-induced signaling pathways.

Conclusion

In the past, breast cancer is not considered as a tobacco related cancer. Until recently, increasing evidence showed that smoking increased the risk of breast cancer. However, results of some studies are lack of agreement or sometimes controversial. The methodological differences could easily obscure the real risks caused by smoking, for examples, the timing of smoke exposure, the average cigarette dose, the exact disease endpoint, the detection and diagnosis of breast cancer and smoking cessation. There are also some confounding factors, like the alcohol consumption, use of post-menopausal hormones, mammography screening frequency, physical activity, which may also contribute to the discrepancies between studies. NNK as an important component in cigarette smoke has been proved to cause carcinogenic transformation in normal breast epithelial cells. Recent epidemiological studies showed that smoking affect the survival and prognosis of breast cancer patients, as well as its influence in incidence rates. Preclinical studies on the effect of NNK in breast cancer may provide more knowledge to understand breast cancer progression. Correlation studies could serve as a strong and convincing evidence to arouse awareness of smoking banning for the public health. Moreover, potential therapeutic targets may be developed to improve prognosis for breast cancer patients who smoked.

Conflict of Interest Statement

None declared.

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