REVIEW

Smoking as a risk factor for the development of breast cancer

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Abstract

Introduction: Smoking is considered a public health problem and in many cases is responsible for the development of lung diseases and cancer. One of the mechanisms by which tobacco can induce cancer is through the generation of free radicals, establishing an oxidative stress status in smokers. With increasing smoking among women, much evidence in the literature has shown a relation between smoking and breast cancer development. **Objective:** The aim of this review was to analyze the available studies in literature that demonstrate the association between smoking and the risk of breast cancer development. **Methods:** We performed a review from the literature based on the search results in PubMed and Scielo. The selected works were composed by current articles according to their relevance and human application. **Results:** The literature revealed several published studies linking smoking to oxidative stress through the action of free radicals that are generated by toxic compounds found in cigarettes. There are few studies relating smoking with breast cancer, which is a relatively more recent research line, where the vast majority of works includes epidemiological and controversial studies. **Conclusions:** The selected works show that, although controversial, smoking is considered a risk factor for developing breast cancer.

Keywords: breast cancer, oxidative stress, smoking.

INTRODUCTION

Smoking is a major cause of death worldwide, estimated to be responsible for the deaths of 1 in 10 adults[1]. Since 1986, federal legislation in force in Brazil has instituted several protective measures against the risks of exposure to environmental (secondhand) tobacco smoke, restricting access to tobacco products, implementing protective measures to reduce youth access to tobacco products and actions of public awareness, expanding the network of treatment and support to smokers and restricting advertising conveyed to tobacco products, among other legal measures[2].

Epidemiologic data show that in 2008 there were 25 million people who use tobacco-derived products in Brazil, with 10.5 million just in the Southeast. Socioeconomic data show that the vast majority of smokers in Brazil are between 45 and 64 years of age and live mainly in rural areas in low-income households[3].

The habit of smoking is associated with the development of several pathologies such as cancer and lung diseases. Cigarette smoking causes behavioral sensitivity mediated by acute actions in the mesolimbic dopamine system, due to long exposure to nicotine. In addition, it induces withdrawal symptoms, because nicotine exerts specific actions on other neurotransmitter systems. Thus, nicotine is directly or indirectly responsible for millions of deaths annually and a public health problem of great concern given that it is a lawfully marketed drug throughout the world[4].

Currently, an increase in smoking among women (or even a less pronounced decline) compared to the indices between men stands out[5]. Luo et al.[6] conducted a study over a period of 10.3 years with active and passive female smokers and found 3,500 cases of breast cancer by identifying a positive correlation between breast cancer and smoking. Breast cancer is one of the leading causes of death by cancer throughout the world in addition to being the most common malignancy among women, with smoking appearing as an important risk factor. Policies on the education and prevention of breast cancer and also the reduction of smoking have been constantly promoted to the female population, given the relevance and proportion that both problems pose to public health in Brazil.

Despite all the effort, smoking remains a major public health problem, due to both direct and indirect effects. Smoking appears as a risk factor for the development of several pathological conditions, including various types of cancer. The aim of this study was to analyze the literature that demonstrates the association between smoking and the risk of developing breast cancer.

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METHOD

This study employed a descriptive review methodology applied to the literature. For the theoretical scientific background, we used the electronic search engines PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) and Scielo (http://www.scielo.org/php/index.php). Using the keywords "smoking" and "oxidative stress", we found 1,789 articles published during the period of 1970 until March 2011. A search with keywords "oxidative stress" and "breast cancer" showed 661 results, with the first article published in 1987. Using a combination of the keywords "smoking", "oxidative stress" and "breast cancer," only 20 articles were found, the first being published in 1994. The articles found were published in English and Portuguese, including original articles and reviews. The articles selected to compose this systematic review were in accordance with their relevance and human application, using the most recent results.

RESULTS AND DISCUSSION

Smoking as a promoter of oxidative damage to biological structures

The cigarette has different toxic components and free radical generators responsible for causing damage to the body demonstrated by *in vitro* tests[7] through the generation of hydroxyl radicals by different concentrations of tar present in tobacco.

The correlation between oxidative stress and smoking is well established in the literature: decreased of antioxidants in the body or increased production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), elevated exposure to O_2 and the presence of toxins that are metabolized for the production and/or excessive activation of the natural systems of ROS/RNS characterized by stress[8].

Damage to cell structures such as proteins, lipids and DNA caused by oxidative stress is closely related with carcinogenesis. Such damage can be measured directly or indirectly through the use of various techniques[9]. Most of the articles found conducted their studies using the products of the action of reactive species on the biological system as markers.

Antioxidant parameters in smokers were analyzed by Chiu et al.[10], who observed that the levels of α-carotene, β-carotene, γ-tocopherol and lycopenes measured by high performance liquid chromatography were significantly decreased in smokers, with these levels inversely related with metabolites of nicotine. These results, obtained from a technique of high sensitivity, clearly indicate that oxidative stress in smokers is due in part to the performance of the products from the burning of the components of the cigarette that generate reactive species sufficient to alter the antioxidant balance and establish a systemic pro-oxidant status.

There is a well established correlation of cause and effect between oxidative stress, DNA damage and carcinogenesis. The agents capable of damaging DNA are highly active substances that react directly or indirectly with DNA to promote irreversible and cumulative oxidative damage[9]. Some experimental evidence has been demonstrated through comet assay of DNA damage induced by reactive species produced as a result of tobacco use[11]. There is a significant increase in single-strand breaks of DNA from circulating leukocytes in active smokers whose cigarette consumption is equivalent to half a pack per day (9-12 cigarettes). The damage to DNA was also evaluated by quantifying the marker 8-hydroxy-2'--deoxyguanosine present in the urine of smokers and nonsmokers[12] where the greatest damage was observed in active smokers who consumed more than 10 cigarettes per day.

In addition to acting on DNA, the reactive species can act on other cell structures such as lipids and proteins. When acting on lipids, free radicals trigger the process known as lipid peroxidation, generating intermediate products such as hydroperoxides, malondialdehyde (MDA), isoprostanes and 4-hydroxynonenal[13]. Some studies have been conducted in an attempt to evaluate the products derived from lipid peroxidation induced by oxidative stress in smokers, comparing the results with healthy nonsmokers.

In a study using mass spectrometry of the exhaled breath of smokers and nonsmokers, Puri et al.[14] recently evaluated differences between the levels of ethane as a marker of lipid peroxidation levels. That study revealed high lipid peroxidation among smokers, consistent with recent results reported by Chiu et al.[10]. The association found of those results indicates a possible consumption of non-enzymatic antioxidant defenses of low molecular weight in an attempt to contain the advancement of the process of lipid peroxidation and damage to biological structures provoked by tobacco.

Additionally, urinary levels of 8-isoprostane-F2α were measured as a marker of lipid peroxidation by Frost--Pineda et al.[15]. The results showed levels 42% higher among the group of smokers compared to nonsmokers, and when associated with other studies in the literature, suggests a direct relationship between lipid peroxidation and smoking. The results available at present show that there is the formation of products resulting from the action of oxidative stress on the body exposed to tobacco, showing the close molecular relationship between smoking and the risk of developing cancer. However, further studies are needed to confirm this correlation in humans and allow some type of intervention on oxidative stress in an attempt to prevent the advancement of the process of breast cancer in female smokers.

Epidemiologic evidence on smoking and incidence of female breast cancer

The participation of smoking as a risk for developing breast cancer reveals controversial results, although there are more than 100 epidemiological studies conducted in the last three decades[16].

Some environmental factors have been suggested as risk factors for developing breast cancer, including smoking, due to the potential carcinogenic and mutagenic components of cigarettes. Evidence shows that about 100 substances present in tobacco and cigarette smoke are proven mutagenic and carcinogenic to mammary cells[17] and that this association with risk should take into account several individual genetic factors[18].

Experimental studies show that nicotine is able to activate several signaling pathways related to cell multiplication, in addition to stimulate angiogenesis and tumor growth. In human mammary cell lines, both normal and tumor, exposure to nicotine promotes migration and cell proliferation[19], suggesting the involvement of this substance in the onset of breast cancer.

Additionally, exposure to cigarette smoke has also been described as capable of inducing the transformation of human breast epithelium cells through increased expression of anti-apoptotic gene Bcl-xL, thereby preventing apoptosis and allowing the accumulation of DNA damage, with consequent cell transformation and carcinogenesis[20]. The fact that some women are more likely to develop breast cancer when exposed to cigarettes due to several genetic polymorphisms of susceptibility should also be considered[16,18].

Some studies have been conducted in an attempt to identify whether there is any association between the experimental evidence and human exposure to tobacco. Controversial results have been demonstrated in some important studies discussed below and summarized in Table 1.

Major epidemiological studies conducted in the global population relating to smoking and the risk of breast cancer reveal controversial results regarding the type of correlation between these factors, mainly due to population and genetic factors.

Among the main studies, Pirie et al.[21], in a prospective study of 224,917 women who are passive smokers in the UK (of the Million Women Study), found no association between tobacco exposure and the onset of breast cancer, although follow-up had been done for a shorter period (average of 3.5 years).

Conversely, in a study of 57,523 American women, Reynolds et al.[22] found that 1,754 were diagnosed with invasive breast cancer after a decade, suggesting that there is a greater risk of developing breast cancer in postmenopausal women who were passive smokers throughout life, although the mechanism by which this occurs remains unknown. Nagata et al.[23], in a review of epidemiological studies conducted in Japan between 1966 and 2005, observed a positive association between smoking and the risk of developing breast cancer in the female Japanese population attributed to a long period of smoking, number of cigarettes smoked per day and metabolic genotype. In Canada, a study conducted by Young et al.[24] in 2009 showed that the risk of developing breast cancer in a population of 12,768 women showed a positive association with increased age.

A cohort study of more than 10 years in postmenopausal women showed a high probability of 16% among current smokers and 9% among ex-smokers, whose high risk persisted for over 20 years. The risk of developing breast cancer was positively related with the intensity, duration and amount of smoking, and inversely associated with age at which these women began smoking. Among the passive smokers, only those with high exposure to smoke throughout their lives also had a greater risk of developing breast cancer[6].

Table 1. Summary of major epidemiological studies on the association between smoking and risk of developing breast cancer published in the last five years.

Author	Association between breast cancer and tobacco use	Comments
Luo et al. 2011[6]	Positive	Consideration of exposure time to tobacco as a main factor
Terry and Goodman. 2006[16]	Positive according to standard acetylation	Meta-analysis of 14 epidemiological studies with different results
Yang et al. 2007[18]	Positive for polymorphisms of endothelial nitric oxide synthase (eNOS)	Follow-up study
Pirie et al. 2008[21]	None	Follow-up study
Reynolds et al. 2009[22]	Positive	Prospective study of American women exposed to secondhand smoke
Nagata et al. 2006[23]	Positive	Review of epidemiological studies in Japan
Young et al. 2009[24]	Positive with the advance of age	Case-control study of Canadian women
Brown et al. 2010[25]	None	Specific focus on women of Asian descent

CONCLUSION

Although presenting some controversial data among themselves, the epidemiological studies mentioned in this review clearly indicate that smoking (directly or indirectly) is an important risk factor for developing breast cancer among women in the world, mainly taking into account the genetic diversity among the populations studied and the role of oxidative stress in breast carcinogenesis.

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