Review Paper

Natural Radioactivity of Tobacco and Its Role in Cancer Development

Mohammad Haghparast1, Leili Darvish1*

1. Department of Radiology, Tobacco and Health Research Center, Faculty of Para Medicine, Hormozgan University of Medical Sciences, Bandar Abbas, Iran.

* Corresponding Author:
Leili Darvish, PhD.
Address: Department of Radiology, Faculty of Para Medicine, Hormozgan University of Medical Sciences, Bandar Abbas, Iran.
Tel: +98 (917) 0098053
E-mail: leilidarvish@gmail.com

ABSTRACT

Background: Tobacco use has remained a significant public health challenge worldwide due to its strong association with various cancers. One of the little-known factors contributing to tobacco-related cancers is the presence of naturally occurring radioactive substances in tobacco leaves. These naturally occurring radionuclides, such as radium-226, actinium-228, bismuth-214, and radium-228, originate from soil and fertilizers used in tobacco growing.

Materials and Methods: In this review study, articles were collected from Medline, PubMed, Scopus, and Google Scholar search engines using keywords: “natural radioactivity,” “tobacco,” “cancer development,” “cigarette,” “smoking,” “cancer,” “carcinogenesis,” “radioresistance,” and “radiotherapy.” Articles were searched without a time limit. The inclusion criteria were articles written in English and having full-text availability.

Results: The studies demonstrate a strong correlation between smoking and side effects of cancer treatment. These effects are not limited to specific cancer types but have been observed across various malignancies and therapies.

Conclusion: The carcinogenic mechanism of tobacco is very diverse and complex, involving both chemical and radiobiological factors. Understanding these mechanisms can help develop sensitive methods to identify signature carcinogens in tobacco, facilitating effective and targeted epidemiological studies.

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Introduction

The main mechanism of mixing radioactive elements with tobacco involves their absorption by soil roots and phosphate fertilizers. These radionuclides are an essential cause of lung cancer [1-5]. In 2023, 81% of the 127070 lung cancer deaths are due to tobacco smoking [6]. Tobacco use has remained a significant public health challenge worldwide due to its strong association with various forms of cancer. One of the little-known factors contributing to tobacco-related cancer is the presence of naturally occurring radioactive substances in tobacco leaves [7]. Tobacco smoking can decrease the effectiveness of radiotherapy by increasing the creation of cancer stem cells (CSCs), thereby promoting the occurrence and development of many types of cancer. Although the presence of radioactivity in tobacco has been proven, the specific mechanism that contributes to the development of cancer has remained unclear. Current research mainly focuses on the radioactivity components of tobacco smoke and their role in the development of cancer. The part of naturally occurring radionuclides and their decay products in cancer development is not fully understood. This study’s main objective was to investigate tobacco’s natural radioactivity and how these elements interact with the human body to contribute to cancer development.

Materials and Methods

In this review article, we used keywords including “natural radioactivity,” “tobacco,” “cancer development,” “cigarette,” “smoking,” “cancer,” “carcinogenesis,” “radioresistance,” and “radiotherapy” in the title and abstract. Articles were collected without a time limit from Medline, PubMed, Scopus, and Google Scholar search engines. The inclusion criteria included articles written in English and having full-text availability. Conference articles were excluded. After reviewing the titles and abstracts of 79 articles, 52 relevant articles were selected (Figure 1).

Radioactive elements in tobacco

Tobacco leaves used in cigarette production contain radioactive elements that cause global concern and contribute significantly to the prevention of illness and death. It is strongly associated with many different types of cancer, including lung, oral, esophageal, and pancreatic cancer [8]. These naturally occurring radionuclides, such as radon-226 (226Rn), actinium-228 (228Ac), bismuth-214 (214Bi), and radium-228 (228Ra), originate from the soil and fertilizers used in farming [9]. Tobacco smoking increases their absorption and radiation dose. Additionally, other radioactive elements such as lead-210 (210Pb) and polonium-210 (210Po) are found in tobacco due to their presence in phosphate-rich fertilizers and natural soils [10, 11]. As a result, these radioactive elements seep into the tobacco leaves and remain there even after tobacco processing.

When a smoker lights a cigarette and inhales tobacco smoke, these toxic and radioactive substances enter the lungs, causing direct and immediate damage to cells and tissues. The radioactive elements 210Pb and 210Po found in tobacco emit alpha particles, a form of ionizing radiation. When inhaled tobacco smoking, these particles deposit energy in the alveolar epithelial cells of the lungs. This energy deposition can trigger anti-inflammatory and antithrombotic effects [12]. Fertilizers used by tobacco growers often contain radium, a naturally radioactive substance, and its decomposition products. As the tobacco plant grows, radon from fertilizers and natural radon in the surrounding soil and rocks will move into the tobacco plant. One of radon’s decay products, 210Po, poses a significant risk due to its radioactivity [13]. Smokers are exposed to radiation from these factors, leading to an increased risk of lung cancer. In addition to the cancer-causing chemicals found in tobacco smoke, radiation from these radioactive elements can also play a role in causing cancer.

Radiation dose from tobacco smoking

A study showed that the annual effective dose due to inhalation of 238U from tobacco smoking ranged from 49.35 to 139.40 μSv/y, while the quantity of 232Th ranged from 23.86 to 111.06 μSv/y. These doses are high and contribute to an increased risk of developing lung cancer [5]. Another study found that the radiation dose received by the bronchial epithelium from inhaled 210Po in tobacco smoke was at least 7 times greater than from background sources. In local areas, it can reach 10 Sv (1000 rem) or more within 25 years [4]. Although tobacco smoking is linked to several health problems, the presence of radioactive elements in tobacco smoke increases the level of risk. Ionizing radiation emitted from these elements can damage lung tissue, increasing the risk of lung cancer. Therefore, it seems important to understanding the role of radioactive elements in tobacco-induced diseases for public health initiatives as well as informing individuals about the risks involved in tobacco smoking. Notably, these harmful factors can also affect the lungs of people exposed to passive smoke.
Secondhand tobacco smoke

Secondhand smoke (SHS), also known as environmental tobacco smoke or unintentional tobacco smoke, poses significant health risks to nonsmokers [14]. It contains toxic and carcinogenic chemicals similar to those found in direct tobacco smoke, including nitrosamines. Exposure to SHS is associated with an increased risk of lung cancer in non-smoking adults and an increased risk of leukemia, lymphoma, and brain tumors in children [15]. Exposure to SHS has immediate adverse effects on the cardiovascular system and can cause heart disease and lung cancer [16]. Exposure to secondhand smoke during pregnancy can lead to reduced fertility, pregnancy complications, and poor birth outcomes, including impaired lung development, low birth weight, and premature birth [17]. Children exposed to SHS may be at risk of sudden infant death syndrome, ear infections, colds, pneumonia, bronchitis, and worsening asthma [18]. Exposure to secondhand smoke also slows the development of children's lungs and can cause children to cough, wheeze, and feel short of breath. There is no safe level of exposure to SHS. Even low levels of secondhand smoke can be harmful [19].

A study in Egypt also found that infants born to women exposed to SHS had a significantly lower average birth weight than those born to women who were not exposed to tobacco smoke. The mechanism behind birth weight loss in exposed infants may be due to the adverse effects of nicotine on placental development and function, leading to a decrease in the amount of oxygen supplied to the fetus. A recent study reported that exposure to SHS during pregnancy leads to an increase in inflammatory mediators, causing low birth weight, either directly or indirectly through reduced placental weight [20]. Eliminating tobacco use is the only way to protect people from exposure to SHS completely. Comprehensive laws and policies of banning smoking in all areas of the home are the only way to protect nonsmokers from SHS exposure fully. Most tobacco control laws and policies also prohibit the use of e-cigarettes [21]. The aerosol that e-cigarette users inhale and exhale may contain toxic and potentially harmful substances. E-cigarettes in smoke-free or tobacco-free policies could protect non-e-cigarette users from exposure to e-cigarette emissions. They could help change social norms and associations related to smoking. Despite these measures, confronting neighbors about passive smoking can be difficult due to a lack of regulation and fear of causing conflict with...
neighbors. In summary, the harmful effects of exposure to SHS during pregnancy are significant and require effective prevention measures. Pregnant women should be informed about the risks associated with exposure to SHS and encouraged to maintain a smoke-free environment, especially at home [22].

Effects of tobacco smoking on health

Cumulative doses of alpha, beta, and gamma radiation from inhaled radionuclides deposited in small amounts of bronchial tissue may significantly trigger the onset of bronchial (lung) cancer in smokers [4]. In the following, some effects of tobacco smoking on health status are described.

Tobacco smoke and carcinogens

Tobacco smoke is a mixture of chemicals, with at least 7000 identified components, including known carcinogens [23]. These carcinogens include nitrosamines (such as N′-nitrosonornicotine [NNN] and 4-[(methyl)nitrosamino]-1-(3-pyridyl)-1-butanone [NNK]), polycyclic aromatic hydrocarbons (PAHs), aldehydes, phenols, aromatic amines, volatile hydrocarbons, nitro compounds, other organic, and inorganic compounds [23]. These substances can cause cancer in both animals and humans. Nicotine, the main addictive ingredient in cigarettes, is not a direct chemical carcinogen. However, it contributes to cancer progression by activating signaling pathways that facilitate cancer cell growth, angiogenesis, invasion, and metastasis. Additionally, nicotine can undergo chemical conversion to carcinogenic nitrosamines during smoking.

The role of nitrosamines in tobacco smoking in cancer

Nitrosamines, especially NNK and NNN, play specific roles in tobacco-induced carcinogenesis. These compounds induce harmful mutations in oncogenes and tumor suppressor genes by forming DNA adducts, which can be considered tumor-initiating [23]. They also promote tumor growth by enhancing and disrupting cell proliferation, survival, migration, and invasion, creating a microenvironment conducive to tumor growth. Tobacco products contain many chemical carcinogens, including tobacco-specific nitrosamines such as NNK and NNN. The nitrosation of nicotine and related tobacco alkaloids forms these nitrosamines. These nitrosamines contribute to cancer by causing oxidative stress [24]. Oxidative stress occurs when the production of oxidants exceeds the cell’s neutralizing capacity [25]. Tobacco smoke contains free radicals that can trigger redox cycling and cause oxidative damage in smokers. In particular, NNK and NNN can lead to oxidative stress, which can cause DNA damage and alter the microenvironment necessary for tumor growth [23].

Tobacco smoke and cancer stem cells

Cancer stem cells (CSCs) are believed to cause cancer [26, 27]. They are resistant to conventional chemotherapy and radiotherapy and can remain slumbering for many years before causing cancer [28]. Tobacco smoke has been shown to increase the creation of CSCs, thereby promoting the occurrence and development of many types of cancer, including liver cancer, kidney cancer, breast cancer, and especially lung cancer. Tobacco smoke is also known to enhance the properties of CSCs [29]. These cells are believed to cause cancer, development, and drug/radiation resistance [30]. Tobacco smoke can promote the acquisition of CSC characteristics, thus playing an essential role in the initiation, growth, and metastasis of lung cancer [29]. Furthermore, exposure to tobacco smoke induces epithelial-mesenchymal transition (EMT) in cells, allowing cell invasion and migration [31]. This process contributes to acquiring CSC-like properties, increasing the likelihood of cancer metastasis [28]. Long-term exposure to tobacco smoke increases the formation of CSCs in the liver, induces EMT, and increases interleukin (IL)-33 expression. It also enhances self-renewal, stemness, and generation of CSC-like cells, promoting the occurrence and growth of various cancers, including lung cancer (Figure 1) [29].

Tobacco smoke and radiotherapy outcomes

Tobacco smoking is a well-established causative factor for at least 13 malignancies, and more than 60% of cancer patients are current or former smokers. Many studies have demonstrated that continued smoking after a cancer diagnosis harms the survival and quality of life (QoL) while increasing treatment toxicity, the risk of morbidity, and the mortality of secondary malignancies. Radiation therapy (RT) is the leading cancer treatment, contributing to approximately 40% of cures. About half of all cancer patients will receive RT during their disease.

Effect of tobacco smoking on treatment outcomes

Studies have shown that smoking during RT is associated with worse outcomes. For example, in a study of non-small cell lung cancer, smoking during radiotherapy was associated with worse 2-year local control rates (34% for smokers vs 59% for nonsmokers) [32]. In cervical can-
cer, excessive smoking was found to be the most potent inducer of complications. Two-year pelvic control and disease-free survival were lower in women with cervical cancer who smoked heavily and received concurrent chemotherapy than in female nonsmokers. Additionally, tobacco smoking was associated with a higher symptom burden during treatment. Higher symptom burden may lead to treatment interruptions, dose reductions, and treatment delays, reducing treatment effectiveness and lowering survival rates [33, 34]. Continued smoking during cancer treatment, including RT, is associated with adverse effects on overall survival, tumor control, quality of life, treatment toxicity, and incidence of primary or secondary malignancies.

Studies demonstrate a strong correlation between smoking and side effects of cancer treatment. These effects are not limited to specific cancer types but have been observed across various malignancies and therapies [35, 36]. Healthcare professionals should view the diagnosis and treatment of cancer as a learning moment and advise their patients to stop smoking immediately. If possible, cancer patients should undergo an intensive smoking cessation program, including both behavioral and pharmacological therapy [15]. Tobacco smoking during radiotherapy treatment is associated with an increase in radiation-induced side effects, both during and after treatment. These side effects depend on the treatment site, including fatigue, skin reactions, and diarrhea. Some of these side effects may last up to 6 months after treatment. Tobacco smokers reported significantly higher levels of concentration problems, skin problems, sleep problems, weight loss, and depression. Furthermore, the reduction in symptom burden from the end of treatment to the 6-month follow-up was significantly less in smokers than in nonsmokers [37]. Tobacco smoking is perhaps the most important modifiable factor affecting the outcome of cancer treatment. A complete smoking history should be recorded in routine clinical practice and prospective clinical studies to characterize its effect on RT outcomes better.

Patients need to be aware of the dangers of tobacco smoking and informed when they and their families receive counseling. Healthcare professionals should use the diagnosis and treatment of cancer as a teachable moment and recommend that patients stop smoking immediately [38, 39]. Tobacco smoking may also affect the effectiveness of radiotherapy by reducing tumor oxygenation, an essential factor in the efficacy of radiotherapy. This effect could be due to smoking-induced respiratory insufficiency before RT, exacerbated by increased carboxyhemoglobin levels in patients who continued tobacco smoking during RT. However, it is worth noting that the impact of smoking on overall survival in non-small cell lung cancer (NSCLC) was inconsistent. This

<table>
<thead>
<tr>
<th>Author (y)</th>
<th>Cancer</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
<td>Menoux, et al. (2020) [43]</td>
<td>NSCLC</td>
<td>Lower radiation-induced pulmonary (RP) incidence in smokers vs nonsmokers (P=0.02)</td>
</tr>
<tr>
<td>Fisher-Valuck, et al. (2013) [44]</td>
<td>NSCLC</td>
<td>Treatment-related toxicity is 14.5% in smokers and 0% in nonsmokers</td>
</tr>
<tr>
<td>Sarihan, et al. (2005) [45]</td>
<td>NSCLC</td>
<td>Risk of infections during treatment associated with tobacco exposure (P=0.001)</td>
</tr>
<tr>
<td>EgestadH, et al. (2014) [46]</td>
<td>HNC</td>
<td>Increased fatigue (P=0.027) pain (P=0.009), affected mouth opening (P=0.049), more speech disturbances (P=0.017), and poorer cognitive function (P=0.041) in smokers vs non-smokers</td>
</tr>
<tr>
<td>Al-Mamagani, et al. (2013) [47]</td>
<td>HNC</td>
<td>Smoking quitters showed better voice quality during two-year follow-up (P=0.001 for all time points)</td>
</tr>
<tr>
<td>Silveira, et al. (2015) [48]</td>
<td>HNC</td>
<td>Mental health (P=0.03), worse burden (P=0.003), and fatigue (P=0.028) in smokers vs non-smokers</td>
</tr>
<tr>
<td>Jensen, et al. (2007) [49]</td>
<td>HNC</td>
<td>Increased nausea/vomiting, decreased cognitive function, dyspnea, diarrhea, and weight loss in smokers vs nonsmokers (P=0.05)</td>
</tr>
<tr>
<td>Al-Mamagani, et al. (2013) [47]</td>
<td>HNC</td>
<td>Smoking quitters indicated better voice quality during two-year follow-up (P=0.001 for all time points)</td>
</tr>
<tr>
<td>Wong, et al. (2020) [50]</td>
<td>BC</td>
<td>Increased failure rate of capsular contracture reconstruction prevalence and other major complications in smokers vs nonsmokers</td>
</tr>
<tr>
<td>Sharp, et al. (2013) [51]</td>
<td>BC</td>
<td>HR for severe acute radiation skin reactions in current smokers vs nonsmokers HR 2.5 (P=0.031)</td>
</tr>
<tr>
<td>Hooning, et al. (2007) [52]</td>
<td>BC</td>
<td>HR for myocardial infarction in smokers during RT vs nonsmokers 3.04 (P=0.039)</td>
</tr>
</tbody>
</table>

**Abbreviations:** NSCLC: Non-small cell lung cancer; HNC: Head and neck cancer; BC: Breast cancer; HR: Hazard ratio; RP: Radiation pneumonitis; RT: Radiotherapy.
outcome may be due to the high prevalence of tobacco smoking in this group, making comparisons with less numerous groups of nonsmokers challenging [36, 40]. Tobacco smoking is perhaps the most important modifiable factor affecting the outcome of cancer treatment (Table 1) [41, 42]. To better characterize its effect on RT outcomes, complete tobacco smoking history should be recorded in routine clinical practice and prospective clinical studies [33, 35].

The study findings suggest that patients who continue to smoke throughout cancer treatment are more likely to report a greater symptom burden, interfering with their ability to complete prescribed treatments. Clinicians should, therefore, consider recommending that patients quit smoking before the beginning of treatment and continue to target patients who have not quit after treatment initiation. Clinicians can make use of the multiple resources and services available, such as state-sponsored quit lines that often offer free or discounted nicotine replacement therapy to help patients quit smoking.

Despite these findings, there are limitations to the study. Most of the presented analyses are observational and retrospective, and the self-reported smoking status was not validated biochemically in many studies. Furthermore, many studies did not provide information on the number of patients who quit or continued smoking during treatment, as well as quantitative tobacco exposure. Patients need to be aware of the dangers of smoking and informed when they and their families are counseled. Healthcare professionals should use the diagnosis and treatment of cancer as a teachable moment and recommend that patients stop smoking immediately. If possible, cancer patients should undergo an intensive smoking cessation program, including behavioral and pharmacological therapy. In conclusion, tobacco smoking during radiotherapy is associated with poorer treatment outcomes and increased side effects. Therefore, it is important to encourage and support cancer patients to quit tobacco smoking as part of their treatment plan.

Conclusion

The presence of radioactive elements in tobacco and exposure during smoking contribute significantly to the development of tobacco-related cancers. This condition highlights the urgent need for effective tobacco control measures to reduce the cancer burden. The risk is increased due to the presence of radioactive elements in tobacco leaves inhaled by smokers. This risk is exacerbated by the concentration of these elements, which is influenced by factors such as soil composition and the use of phosphate fertilizers in tobacco growing. The carcinogenic mechanism of tobacco is diverse and complex, involving both chemical and radiobiological factors. Understanding these mechanisms can help develop sensitive methods to identify signature carcinogens in tobacco, facilitating effective and targeted epidemiological studies. Public health policy tries better approaches to preventing tobacco-related cancers. The study’s limitations were the lack of research in this field and the unavailability of scintillator dosimeters in some countries. Further research is needed to understand better the complex interactions between components of tobacco smoke, including radioactive elements and their role in the development of cancer.

Ethical Considerations

There were no ethical considerations to be considered in this research.

Compliance with ethical guidelines

The authors declared no competing interests.

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Authors' contributions

Project administration and supervision: Mohammad Haghparast; Writing the manuscript: Leili Darvish.

Conflict of interest

The authors declared no conflict of interest.

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