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Smoking and Its Relationship with Cancer

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ABSTRACT

Tobacco smoking is a popular pastime all over the world. It is the leading preventable cause of cancer. Tobacco smoke is loaded with carcinogens that harm literally every tissue in the human body. It is the main cause of cancers of the lung, esophagus, and urinary bladder. Besides its deleterious effect on the primary smokers, exhaled smoke and side-stream smoke from their cigarettes also increase the risk of cancer in non-smokers from passive inhalation. Almost one-half of the cancer sufferers continue to smoke after its diagnosis, and this interferes with treatment, increases the risk of recurrence, is associated with a poor quality of life, and markedly hikes mortality. Tobacco smoking is implicated in about a third of all cancer deaths. It also increases the risk of developing a second primary cancer. Smoking cessation not only reduces the risk of developing new cancer but also favorably alters the course of established cancer. It can also bestow an extra 20 years of life. This manuscript briefly reviews the noxious relationship between tobacco smoke and cancer.

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Introduction

Cancer is a major public health problem worldwide. It accounted for nearly 10 million deaths in 2020. It is now the second leading cause of death globally and is soon expected to become the leading cause. Cancer is also common in the world's most populous country, China has become its leading cause of death. According to data from Globocan 2020, Africa had 1,340,598,088 new cases of cancer in 2020. The World Health Organization estimates that one-quarter of the worldwide cancers occur in Europe, although it houses only one-eighth of the world population. Cancer is also pervasive in the US. It is estimated that an American male has a 40% lifetime risk while an American female has a 38% lifetime risk of developing cancer. Survival is poor, and about 40% of the US cancer sufferers die within 5 years. Tobacco smoking is a well-established preventable cause of cancer. Despite these facts, nearly 17% of U.S. adults continue to smoke. The total care of cancer in the US is estimated to be around $173 billion in 2020 [1-14].

Discussion

Percivall Pott in 1775 was the first to link environmental carcinogens with cancer, reporting that squamous cell carcinoma of the scrotal skin was prevalent among chimney sweeps. About 180 years later. Wynder and Graham in 1956 suggested that tobacco smoke inhalation is associated with lung cancer. This causal relationship is now widely accepted. Tobacco smoke has thousands of chemicals, with at least 250 known harmful chemicals and at least 69 that can cause cancer. These cancer-causing chemicals include toxic metals like nickel, cadmium and beryllium, toxic gases like ethylene oxide and 1,3-butadiene, poisonous substances like arsenic, radioactive elements like polonium-210, and toxic chemicals like polycyclic aromatic hydrocarbons, tobacco-specific nitrosamines, and vinyl chloride. Smoking tobacco exposes individuals to these noxious elements in several ways [15-21]. Most commonly, smoke enters the smoker's mouth directly from the cigarette being smoked. This is commonly known as first-hand smoke or mainstream smoke [19]. Side-stream cigarette smoke emanates from the burning ends of a cigarette and along with the exhaled main-steam smoke and is inhaled by non-smokers. This is called second-hand smoke or passive smoke [20]. Third-hand smoke is the residue from tobacco products, that cling to surfaces such as hair, clothing, and furniture. These pollutants may persist on these surfaces for several months. They may become airborne during regular cleaning, resulting in inhalation. Carcinogens are also inhaled during water pipe, e-cigarettes, and heat-not-burn tobacco smoking [21-24].

Tobacco smoking is known to be associated with an increased risk of several cancers, including those of the larynx, oropharynx, esophagus, lung, bladder, kidney, urinary tract, cervix, gastrointestinal tract, and blood [9,25]. A recent study estimated that smoking accounted for 81.7% of lung cancers, 73.8% of larynx cancers, 50% of esophageal cancers, and 46.9% of bladder cancers. It is estimated to be responsible for 28.8% of all cancer deaths. Unfortunately, smokers continue to smoke even after cancer diagnosis. Among current smokers with cancer, it is estimated that only 50% stop smoking after diagnosis. Continued smoking in these patients increases the risk of poor treatment response and treatment-related toxic effects. They tend to have a higher risk of cancer recurrence. They also face an increased risk of developing a primary second cancer. Smoking with cancer not only lowers the quality of life but also increases mortality. Smoking cessation

in these patients often has benefits that equal or exceed cancer treatments. Studies have estimated that smoking cessation after the diagnosis of cancer reduces the risk of dying by 30% to 40% [26-36].

Smokers also tend to lead other unhealthy lifestyles, such as high consumption of junk food, decreased levels of exercise, and greater alcohol use. This not only increases the cancer risk but also increases the risk of developing chronic ailments such as cardiovascular and respiratory diseases. They also tend to comply less with breast, cervical and colorectal screening guidelines than never-smokers. Tobacco deregulates many biological pathways, induces inflammation, impaired immune function, and DNA damage, leading to an increase in tumor proliferation, invasion, and angiogenesis [37-41].

Smoking and Lung Cancer

Lung cancer is strongly related to smoking and is extremely deadly [9,42]. Although rare at the beginning of the 20th century, an increase in smoking has resulted in a dramatic rise in its incidence [43,44]. Today, 85-90% of lung cancers can be attributed to smoking [45]. The association is dose-dependent and higher levels of smoking are associated with a higher lung cancer risk, in both men and women. Although gender differences have been reported by several studies, a recent systemic review and meta-analysis found no difference in risks of smoking-induced lung cancer between men and women. It is the leading cause of cancer-related death, accounting for nearly 25% of all cancer deaths in the US. Smoking cessation is beneficial in reducing the risk of lung cancer. The Framingham Heart Study showed that heavy former smokers see a drop in lung cancer risk within five years of quitting compared to continuing smokers. However, the risk remains threefold higher than never smokers even after 25 years since quitting. It is estimated that 37%–63.9% of patients with lung cancer continue to smoke after diagnosis. Continued smoking after lung cancer diagnosis increases the symptom burden, decreases the quality of life, and is associated with a shorter survival time. It also increases the risk of developing a second, primary cancer [46-57].

Smoking and Breast Cancer

Smoking as a risk factor for the development of breast cancer has been studied extensively. Several earlier studies have provided contradictory results regarding the role of smoking in breast cancer [58-61]. While some studies showed a causal association between smoking and breast cancer, others have not corroborated this connection [59-61]. Recent studies, using advanced techniques, have however validated the deleterious causal relationship between smoking and breast cancer. Xu et al, in an MR analysis, found that smoking was associated with a higher risk of overall and ER-positive breast cancer. In a case-controlled study of 1000 women with breast cancer and 1000 healthy controls, probabilistic bias analysis found that smoking increased the risk for breast cancer, with an odds ratio (OR) of 1.7 - 2.8. Smokers with a diagnosis of breast cancer also suffer from more post-operative complications. They have more radiation-induced toxicities and a worse quality of life. They are also more susceptible to a second primary cancer. Radiation therapy increases their risk of developing ipsilateral lung cancer. They demonstrate a higher all-cause and breast cancer-related mortality. The latter is almost 50% greater in smokers than never smokers among breast cancer survivors. Active smokers are also less likely to use breast cancer screening services, thereby increasing their risk of not detecting early stage breast cancer [62-72].

Smoking and Colorectal Cancer

Several studies have noticed that ever-smokers are at an increased risk for incident colorectal cancer compared with never-smokers [73-75]. In a study involving a total of 925 colorectal cancer cases and 2775 controls, Lee and his group found that colorectal cancer risk was significantly increased by smoking, in both men and women. This risk, especially for cancer of the distal colon, increased with a higher amount (>40 cig/day in men and >20 cig/day in women) or duration (>40 years in men and >20 years in women) of smoking. Some studies have suggested that smoking is more likely to cause left-sided colorectal cancers. Yang and colleagues in a recent study confirmed this increased tendency for left-sided lesions, especially rectal cancer, in smokers. In an evaluation of 4,879 incident cases of invasive colorectal adenocarcinoma in 188,052 individuals aged 45-75 years, with a follow-up of 16.7 years, Gram et al noted that rectal cancer was more common in female smokers. Gram et al also reported that male smokers had a higher risk of the left colon while female smokers had a 20% higher risk of cancer of the right colon. In a meta-analytic study, former and current smokers experienced a worse colorectal cancer prognosis compared with never smokers. Smoking cessation also improved survival when compared with current smokers [76-81].

Smoking and Prostate Cancer

Cigarette smoking is associated with the development of several genitourinary cancers. However, an association with prostate cancer appears to be only linked with prostate cancer progression. Smokers tend to have higher tumor volumes with prostate cancer, have more recurrences after surgery, and develop more metastasis. Heavy smokers also have higher mortality, and this may be 24% to 30% higher when compared with nonsmokers. The number of cigarettes smoked per day also has a dose-related association with prostate cancer mortality. Smoking cessation for at least 10 years in men reduces the risk of prostate cancer mortality like those who have never smoked [82-91].

Smoking and Stomach Cancer

Several studies have established a firm causal role of smoking in gastric cancer [92-94]. In a study of 23 epidemiological studies that included 10,290 cases and 26,145 controls, compared with never smokers, smokers demonstrated a higher risk of developing stomach cancer, with increased ORs of 1.12 for former, and 1.25 for current cigarette smokers. The risk was higher in heavy smokers (>20 cigarettes per day) and with those smoking for more than 40 years, with ORs of 1.32 and 1.35, respectively. These risks decreased to that of never smokers 10 years after smoking cessation. Helicobacter pylori infection is a major risk factor for gastric cancer. Smoking in those infected tends to further increase their risk of gastric cancer [95-98].

Smoking and Liver Cancer

Tobacco smoking was recognized, based on published reports, as a causal factor in the development of liver cancer by the International Agency for Research on Cancer in 2004. Several subsequent studies have confirmed this causal relationship [99-102]. Lee and colleagues found that current cigarette smokers had an increased meta-relative risk of hepatic cancer of 1.51 (and 1.12 in former smokers) after adjusting for hepatitis B infection (HBV), hepatitis C infection (HBC), and alcohol consumption [101]. A recent study of 14 US prospective cohort studies found that current smokers had an increased hazard ratio of both hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma of 1.86 and 1.47, respectively. However, quitting smoking for more than 30 years

reduced the HCC risk to that seen in never smokers. Chronic infection with HBV and HBC are major causative factors for primary HCC. Chuang et al, found in a meta-analysis of 9 studies, that the presence of HBV infection increases the risk of HCC in current and past smokers. This increased risk with smoking has also been noted with chronic HCV infections [102-105].

Smoking and Esophageal Cancer

Several studies have documented an increased risk of esophageal cancer in smokers. Cook et al. reported that the risk for esophageal adenocarcinoma, in current smokers as compared to nonsmokers was associated with an OR of 2.08. Smoking cessation for 10 years or more reduces the risk of esophageal adenocarcinoma when compared to current smokers, decreasing the OR to 0.71. A meta-analysis of 12 studies by Oze and group indicated that the summary increased risk for esophageal carcinoma in ever smokers relative to never smokers was 3.01. This risk was higher in current smokers (3.73) than former smokers (2.21) compared to never smokers. Barrett's esophagus is related to long-standing gastroesophageal reflux and is often associated with the conversion of the normal lower esophageal squamous epithelium into a metaplastic columnar epithelium. It is a premalignant condition. Smoking enhances the risk of Barrett's esophagus progressing to cancer. Smoking is associated with higher rates of short-term perioperative morbidity in patients with esophageal cancer. Wang and his group found that in an analysis of 52 studies, using nonsmokers as a reference, the risk of esophageal squamous cell carcinoma was lower among former smokers (risk ratio or RR = 2.05) than among current smokers (RR = 4.18) [106-112]. Compared with current smokers, a strong risk reduction was evident after five or more years (RR = 0.59) and became stronger after 10 or more years (RR = 0.42) and even greater after 20 or more years (RR = 0.34) following smoking cessation.

Smoking and Cervical Cancer

Tobacco smoking plays an important causal role in the genesis and progression of cervical cancer [113-117]. Winkelstein Jr., in 1977, first suggested that smoking was a risk factor for cervical cancer [113]. Since then, several studies have confirmed this deleterious connection, prompting the International Agency for Research on Cancer to list smoking as a risk factor for cervical cancer. A major meta-analysis (involving 8,097 women with squamous cell carcinoma, 1,374 women with adenocarcinoma, and 26,445 women without carcinoma of the cervix), confirmed that tobacco smoking increased the risk of squamous cell carcinoma of the cervix in smokers, but not that of the less common, adenocarcinoma of the cervix. A Berrington de González et al. also found that the risk for squamous cell carcinoma with current smoking had an OR of 1.47, indicating increased risk, with no increased risk noted with adenocarcinoma. Several subsequent studies, including many meta-analyses, have confirmed this smoking-cervical cancer relationship, and pointed out the increased cervical cancer mortality in smokers. Waggoner et al, in a study of 2661 women diagnosed with invasive cervical cancer, reported that, after adjustment for many confounding factors, smokers were 21% more likely to die of cervical cancer compared with nonsmokers with cervical cancer. Mayadev and colleagues found that following radiation therapy, smokers with cervical cancer had a decreased disease-free period, and died early. Smoking cessation or smoking decrease in patients with cervical cancer during treatment is still not common. Human papillomavirus (HPV) infection plays an important causal role in cervical cancer. Studies have shown a potential link between smoking and incidence of cervical cancer, in the setting of concurrent HPV infection [114-128]. Smoking increases the risk of HPV infection and smokers often have delayed clearance of HPV infection from the cervix or regression of HPV-related squamous cell lesions. Many patients with persistent HPV infection tend to proceed to high-grade cervical lesions. Cervical cancer screening is a powerful diagnostic tool to diagnose pre-malignant lesions or early malignancy. However, many smokers have negative attitudes towards cervical screening than nonsmokers and tend to be less compliant with these screening procedures and any recommended treatment [126-131].

Smoking and Thyroid Cancer

Smoking and thyroid cancer studies have either showed no or an inverse association [132,133]. A meta-analysis of 25 case-control studies, published in 2014, concluded that smoking was associated with a lower risk of thyroid cancer in current smokers. In a recent study of 96,855 individuals, current smoking at baseline was significantly associated with a decreased risk of incident thyroid cancer, especially in men. A similar, although non-statistically significant, an inverse association was also noted in women in this study. Smoking may reduce the incidence of thyroid cancer by lowering the body mass index and lowering the levels of thyroid-stimulating hormone (TSH). Studies have shown that higher TSH values are associated with a higher frequency and more advanced stages of thyroid cancer [134-138].

Smoking and Urinary Bladder Cancer

Tobacco smoking is a major risk factor for bladder cancer. It is estimated that nearly 50% of bladder cancer cases are related to smoking. A current or past smoking history results in a threefold higher chance of developing urinary bladder cancer when compared to non-smokers. Further, high-dose smokers or those with a long smoking history, are more likely to have a more aggressive form of cancer. Smokers also do not respond well to chemotherapy for bladder cancer. Smoking cessation is associated with a reduced risk of tumor recurrence and progression. Unfortunately, a significant number of bladder cancer patients continue to smoke following its diagnosis [139-145].

Smoking and Skin Cancer

Published data on tobacco smoking and its relationship to skin cancer is sparse. The major risk factors for skin cancer are sun exposure, pigmentary traits, and family history of skin cancer [146-148]. Some studies have suggested that smoking may increase the risk of squamous cell carcinoma of the skin [149]. Cigarette smoking appears to not affect cutaneous malignant melanoma and may even decrease its risk. A recent study has suggested that smoking may increase the risk of melanoma lymph node metastasis [149-152].

Smoking and Kidney Cancer

Smoking increases the risk of development and progression of renal cell cancer. The International Agency for Research on Cancer and the United States Department of Health and Human Services classifies tobacco smoking as a kidney carcinogen. In a meta-analysis of 114 papers, Cumberbatch and his group reported that the pooled relative risk of renal cell carcinoma incidence was 1.27 for all smokers, 1.29 for current smokers, and 1.14 for former smokers. The cancer risk is higher when the quantity of tobacco smoked per day is higher. In developed countries, 6% of kidney cancer deaths are a result of tobacco smoking. Smoking cessation reduces the risks of developing and dying from this cancer. The longer the period of cessation, the lower the risk [153-160].

Smoking and Pancreatic Cancer

Tobacco smoking is an important risk factor for pancreatic cancer. Smokers have a 74% greater risk of developing pancreatic cancer

compared with nonsmokers. Ordóñez-Mena and colleagues estimated that current smoking will prepone the overall risk of developing and dying from cancer by eight years and ten years, respectively, when compared with never smokers. Smoking cessation for 10 or more years reduces the relative risk of pancreatic cancer to levels seen in non-smokers [161-164].

Smoking and Rare Cancers

Rare cancer affects fewer than 6 - 15 per 100,000 people per year [165]. Rare cancers account for nearly 13% (1 in 8) of all cancers diagnosed in adults over the age of 20 years. Rare cancers of the digestive system include cancers of the small intestine, anus, anal canal, rectum, and gall bladder. The most common rare cancers of the respiratory system occur in the larynx, nasopharynx, nose, and nasal cavity. Rare cancers of the genitourinary system include cancers of the vulva, vagina, penis, and testis. Rare bone and joint cancers in adults include chondrosarcoma and osteosarcoma. Soft tissue sarcomas include cancers of the adipose tissue (liposarcoma), skeletal muscle (rhabdomyosarcoma), smooth muscle (leiomyosarcoma), and blood and lymph vessels (angiosarcoma). Other rare cancers include ocular melanomas, male breast cancer, mesothelioma, and Kaposi's sarcoma. Many of these cancers also demonstrate an increased risk with smoking and smoking cessation helps reduce this risk [166-167].

Conclusion

Smoking is a leading preventable cause of cancer. Tobacco smoke is loaded with carcinogens. These attack almost every organ in the body. The result is that smokers are at an increased risk of development and progression of most cancers when compared to never smokers. Further, continued smoking at cancer diagnosis may negatively interfere with treatment, is associated with a worse quality of life, and often increases mortality. Overall, smokers face a 10-20 years reduction in life expectancy, partly from premature cancer related death. Efforts directed at smoking cessation should be an integral part of every cancer treatment.

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