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REVIEW ARTICLE

Nicotine has implications in different tumors types. Expert's eye making a literature analysis

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Summary

In man, nicotine is commonly consumed via smoking cigarettes, cigars or pipes. The addictive liability and pharmacological effects of smoking are primarily mediated by the major tobacco alkaloid nicotine. There are elevated serum cadmium and lead levels in smokers resulting in glomerular dysfunction. There is a constant and direct attack of various cigarette smoke reagents on the oral epithelial cells, which gradually accumulate and may cause a stepwise malignant transformation. The association between cigarettes and lung cancer has been proven by large cohort studies. Tobacco use has been reported to be the main cause of 90% of male and 79% of female lung cancers.

Ninety percent of deaths from lung cancer are estimated to be due to smoking. This review describes the implication of nicotine, smoking, smoke extracts and other tobacco constituents on oral cancers, lung cancer and cancers of the urinary tract.

Key words: lung cancer, nicotine, oral cancer, smoke, tobacco, urinary tract cancer

Introduction

The extensive use of tobacco and its associated severe health issues have been a great concern to mankind. The World Health Organization (WHO) estimates that approximately one-third of the global population aged 15 years or older are smokers and each smoker consumes an average of 15 cigarettes daily. Cigarette smoking, the most common form of tobacco use, has been found to account for hundreds of thousands of premature deaths and chronic diseases annually [1]. It is well established that cigarette smoking can increase the risk of chronic obstructive pulmonary diseases (COPD), cardiovascular diseases, and several forms of cancer, in particular cancers of the lung, oropharynx, larynx, and esophagus [2]. Recent epidemiological evidence suggests that cigarette smoking is also deleterious to other parts of the gastrointestinal (GI) tract. Cigarette smoke, nevertheless, comprises thousands of chemicals, making it difficult to delineate the contribution of an individual compound to the toxicological and pharmacological properties of cigarette smoke as just described. Approximately 5 million people die from smoking-related disorders each year, and one-tenth of all adult deaths are related to tobacco use. It is estimated that deaths attributable to tobacco use will rise to 10 million by 2025, and one-third of all adult deaths are expected to be related to cigarette smoking [3]. Fifty percent of smokers die from smoking-related disorders. Smoking is known to be the cause of some 30 diseases, mainly cardiovascular and cerebrovascular disorders, COPD and cancers. Thirty percent of all cancer deaths, 75% of all COPD deaths and 25% of all atherosclerotic hearth diseases are attributed to smoking [4]. Life expectancy of people who smoke at least 20 cigarettes per day for 25 years is estimated to be 25% shorter compared with non-smokers.

In this article we attempted to make available the implications of nicotine to oral, lung and urinary tract carcinogenesis.

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Nicotine in cigarette smoking

Nicotine, a major component of cigarette, has been proposed to be responsible for many pharmacological effects of cigarette smoke. It has a bitter taste and is a mildly alkaline and volatile liquid alkaloid. Each cigarette contains 15-30 mg of nicotine. Nicotine is rapidly absorbed through mucous membranes, skin, alveoli, and the GI tract. Its half-life is 30-60 min. It is extensively metabolized in the liver to cotinine, and a considerable proportion is excreted unchanged in acidic urine. Venous nicotine levels in smokers range from 5 to 15 ng/mL and arterial nicotine levels peak as high as 80 ng/mL. Remarkably, nicotine levels in smokers are shown to be extremely high in saliva and gastric juice, reaching more than 1300 and 800 ng/ ml, respectively [5]. Nicotine plays a key role in smoking-related diseases by exerting a dual influence. On the one hand, nicotine produces reinforcing effects, tolerance and physical dependence, and the pharmacological effects that smokers enjoy such as modulation of mood, appetite, and task performance, resulting in perpetuation of the smoking habit. The mechanism for the development of nicotine dependence is complex but it is pertinent to the desensitization and the longer-lasting persistent inactivation of nicotinic receptors in the central nervous system together with dopaminergic modulation of the reward center [6]. On the other hand, nicotine is found to be actively involved in the pathogenesis of GI diseases including peptic ulcer formation and delayed wound healing [3], promotion of carcinogenesis [7], and disease progression of ulcerative colitis.

Smoking and cancer

Rottman first claimed that lung cancer might stem from tobacco use in 1898 [8]. Decades later this hypothesis was proved by Roffo, who produced skin cancer in mice, using cigarette tar, in 1931. The epidemiological relation between cigarette smoke and lung cancer was first reported by Muller in 1939 [8]. In the wake of Muller's report, large case control studies from the United States and Great Britain also proved the scientific basis for an association between cigarette smoking and lung cancer in the 1950s [9,10]. Consequently, the main cause of lung cancer in males was reported to be cigarette smoking in the Surgeon General's Report in 1964 [11]. Interestingly, a similar relation concerning females was only proved in 1980.

Over 4000 bioactive chemical compounds have been isolated from cigarette smoke, of which more than 60 are carcinogens [12]. Topical, intratracheal or subcutaneous administration of polyaromatic hydrocarbons, found in cigarette smoke, may produce cancer in animals. Tobacco chewing and snuff taking have also been reported to cause oral, esophageal, laryngeal and pharyngeal cancers [13].

Lung, larynx, pharynx, esophagus, oral cavity, pancreas, urinary bladder and renal pelvic cancers are strongly related to tobacco use. Tobacco is known to be the causative factor in the development of colorectal, sinonasal, adrenal, gastric, uterine, cervical and liver cancers, as well as of myeloid leukemia. However, it is not known whether there is a causative association between tobacco use and carcinomas such as prostate, brain, skin and breast carcinomas, testicular and endometrial cancers, soft tissue sarcomas, lymphomas and melanomas [14].

In developed countries, one-third of all cancer deaths (47% of male and 14% of female cancer deaths) are associated with cigarette smoking. Deaths from cancer are twice as high in smokers compared to non-smokers. Moreover, if the number of the cigarettes smoked per day exceeds 20, death rates are 4 times higher compared to non-smokers [15].

Smoking and lung cancer

Lung cancer accounts for 12.8% of all cancers worldwide and it is highly lethal among both males and females. More than 90% of patients with lung cancer die of it. Of cancer deaths, 17.8% are attributed to pulmonary carcinoma and 5-year survival rates are less than 10%. The number of lung cancer-related deaths was reported to be 1 million in 1990 [16]. In contrast to most cancers the incidence and mortality of lung cancer are gradually increasing. Death rates from pulmonary carcinoma have been reported to have risen by 400% between 1950 and 1990 [17]. Tobacco use has been reported to be the main cause of 90% of male and 79% of female lung cancers [18]. Ninety percent of lung cancer deaths are estimated to be due to smoking [19]. Compared to non-smokers, the risk of development of lung cancer in lifelong smokers is 20-40 times higher [20]. The synergy between cigarette smoking and exposure to asbestos, arsenic and radon has been shown to increase the risk of pulmonary carcinoma [21]. The association between cigarette smoking and lung cancer has been proven by large cohort studies [22]. Twenty percent of smokers develop pulmonary carcinoma and approximately 90% of patients with lung cancer are smokers. Capewell et al. showed that only 2% of patients with lung cancer were non-smokers [23]. The association between cigarette smoking and lung cancer is stronger for squamous cell (SCC) and small cell types

and large cell carcinoma (other than adenocarcinoma). The risk of pulmonary carcinoma in smokers increases with commencing smoking at an early age, the number of cigarettes consumed per day and the depth of cigarette smoke inhalation [23]. Geographical variations and gender differences in the incidence of lung cancer are also related to the frequency of tobacco use.

Types of cigarette smoked

The risk of cancer development may vary according to the type of cigarette smoked. The risk decreases with the use of filter cigarettes. Engeland et al. reported a higher risk with handrolled cigarettes compared to factory-made cigarettes [24]. At the same time, Chinese cigarette brands were found to be less mutagenic than Western brands [25]. Cigar and pipe smoking increases the risk of lung cancer 7 times. The carcinogens found in cigars and pipes are reported to be the same as those in cigarettes [26]. However, those studies that have reported a reduced risk with cigars and pipes may be related to the limited use and shallow inhalation. In fact, the risk of lung cancer in cigar and pipe smokers in Denmark and Holland, where cigar and pipe smoking involves deeper inhalation, was found to be the same as that among cigarette smokers. Because of their higher tar content and carcinogen levels, mentholated cigarettes may increase the risk of lung cancer. Moreover, menthol facilitates carbon monoxide absorption and causes retention of cigarette smoke in the lung by restricting ventilation [27]. Light cigarettes, which were produced to enhance safety, do not lower the risk of cancer. During the last 30 years, the increasing trend of consuming cigarettes containing low tar and nicotine levels has caused a predominance of peripherally located adenocarcinomas, in contrast to centrally located SCCs [27]. Because real cigarette smoking may differ from smoking simulated by machine, light cigarette users smoke a greater number of cigarettes per day and make deep inhalations to restore their previous nicotine levels. Consequently, the smoke and carcinogens reach more distal areas and cause peripheral lung cancers [28].

Smoking and oral cancer

Oral SCC is the most common malignancy of the head and neck, with a worldwide incidence of over 300,000 new cases annually [29]. The disease is characterized by a high rate of morbidity and mortality (about 50%) [29]. The major inducer of oral SCC is exposure to tobacco, considered to be responsible for 50-90% of the cases worldwide [30]. The incidence of oral SCC in cigarette smokers is 4-7 times higher than in non-smokers; when alcohol is also consumed this incidence is even higher. Moreover, compared with non-smokers, the higher cigarette smoke-related risk for oral SCC is manifested by a reduction in the mean age of development of the disease by 15 years. The "field cancerization" concept is the currently accepted explanation for the carcinogenic effect of cigarette smoke on oral mucosa [31]. According to this theory, there is a constant and direct attack of various cigarette smoke reagents on the oral epithelial cells, which gradually accumulate and may cause a stepwise malignant transformation. It has been suggested that free radicals, reactive oxygen species and reactive nitrogen species in the inhaled cigarette smoke induce this gradually evolving process, initially expressed by dysplastic lesions of the mucosa, which then transform into *in situ* carcinoma lesions and eventually result in full-blown infiltrating and metastasizing oral SCC. Further credence for the suggested role of free radicals in the pathogenesis of evolving oral SCC is found in a recent study [32] demonstrating that reactive oxygen species, such as hydroxyl radical, are formed in the human oral cavity during areca quid chewing, and that the activity might cause oxidative DNA damage to the surrounding tissues. In this respect the salivary anticarcinogenic capacity, which has only recently been recognized, may be based on its antioxidant system.

The peroxidase found in the oral cavity is the most important salivary antioxidant enzyme. This oral peroxidase (OPO) is composed of two peroxidase enzymes, salivary peroxidase (SPO) and myeloperoxidase. SPO, secreted from the major salivary glands, mainly the parotid gland, contributes to 80% of OPO activity, while myeloperoxidase, produced by leukocytes in inflammatory regions of the oral cavity, contributes to the remaining 20% of OPO activity. OPO plays a dual role: a) it reduces the level of hydrogen peroxide (H_2O_2) excreted into the oral cavity from the salivary glands by bacteria and leukocytes, and b) it increases specific antibacterial activity by inhibiting the metabolism and proliferation of various bacteria in the oral cavity. In a very recent paper, the mechanism responsible for the inactivation of OPO by the cigarette smoke was described [33]. In order to understand and elucidate the factors in the cigarette smoke that are responsible for the cigarette smoke-associated inactivation of OPO, several oxidants and antioxidants were applied to saliva in the presence or absence of cigarette smoke. No protection for cigarette smoke-induced loss of OPO activity occurred in the presence of glutathione, N-acetylcystein, ascorbic acid or desferal. Exposure of saliva to purified aldehydes present in the cigarette smoke had no effect on OPO activity. In addi-

tion, nicotine as well as ascorbic acid in the presence of $FeCl_3$ also had no effect on OPO activity. Finally, the exposure of OPO in saliva to cyanate in levels present in the cigarette smoke caused a marked 65-70% loss of OPO activity, which could have been prevented by pre-incubation of the saliva with hydroxycobalamine, a known chelator of cyanate. These results indicate that hydrogen cyanide, known to be present in significant amounts in the cigarette smoke, is most probably the agent responsible for the cigarette smoke-associated loss of salivary OPO activity [33]. The oral and pharyngeal epithelium is constantly exposed to saliva, which contains advanced antioxidant/anticancer systems. Destruction of these salivary systems by the smoke may play a pivotal role in the pathogenesis of the disease.

Smoking and cancers of the urinary tract

Cigarette smoke and its metabolites cause cancers of the bladder and kidney [34], resulting in the death of over 40% of men in some countries of Eastern and Central Europe, and 17% of women in the USA. Risk factors for renal cell adenocarcinoma include cigarette smoking which presumably accelerates the risk in a patient whose first-degree relative is suffering with renal cell carcinoma, that is, an elevated odds ratio above 2.5 (95% CI 1.04-5.90) [35]. Tobacco and cigarette use especially on a Western diet (high total fat, fried or broiled meats, low in fibre, vegetables and fruits) poses a high risk for renal adenocarcinoma development [36]. Cigarette smoking is associated with elevated plasma carcinoembryonic antigen (CEA) levels among patients suffering from non-neoplastic diseases, including chronic renal failure [37]. Further studies have demonstrated that the prominent nicotine-related alkaloid ß-nicotyrine, present after smoking, strongly inhibits human CYP2A6 [38]. As CYP2A6 is involved in the metabolic activation of numerous carcinogens, reduction of this enzyme could potentially promote the development of renal adenocarcinoma.

Transitional bladder cancer (TBC) is estimated to be the 4th most common cancer among men and the 14th among women in the European Union (cumulative risk of 2.82 and 0.52%, respectively). Apart from age, sex and a small number of occupational groups (dye workers, rubber workers, leather workers, painters, truck drivers and aluminium workers), smoking is the only risk factor of TBC for which clear epidemiological evidence has been found [39,40]. Cigarette smoking has been proposed to account for more than 50% of TBCs in men and approximately 30% in women. This association between active (cigarette) smoking and TBC has been confirmed by more than 35 case-control studies and 10 cohort studies [41-43]. The European Prospective Investigation Into Cancer and Nutrition (EPIC), for instance, found an increased risk of TBC for both current (incidence rate ratio 3.96; 95% confidence interval [CI]: 3.07-5.09) and ex-smokers (incidence rate 2.25; 95% CI: 1.74-2.91) [41].

Conclusion

Current experimental evidence supports the notion that nicotine is actively involved in the initiation and promotion of cancer. Nicotine and its metabolite cotinine possess intrinsic mutagenic activity that may result in DNA damage. Nicotine also promotes cancer growth through the modulation of cell proliferation, apoptosis, and angiogenesis. Nevertheless, the effect of nicotine on other cellular processes relevant to carcinogenesis, that is, metastasis and cancer immunology, warrants further investigation. Furthermore, although no epidemiologic evidence exists to date, supporting the notion that the use of nicotine increases cancer risk, preclinical findings converge to suggest that nicotine may pose a safety issue to current nicotine users. Therefore, a close monitoring and survey on these issues dealing with a carcinogenic potential is justified.

References

1. WHO. Tobacco or health: a global status report. Geneva: World Health Organization, 1997, pp 1-48.
2. Mannino DM. Chronic obstructive pulmonary disease: definition and epidemiology. Respir Care 2003; 48: 1185-1191; discussion 1191-1193.
3. Available from http://www.who.int/tobacco/about/en/
4. Available from http://www.emro.who.int/Publications/HealthEdReligion/Smoking/QA.htm
5. Lindell G, Farnebo LO, Chen D et al. Acute effects of smoking during modified sham feeding in duodenal ulcer patients. An analysis of nicotine, acid secretion, gastrin, catecholamines, epidermal growth factor, prostaglandin E2, and bile acids. Scand J Gastroenterol 1993; 28: 487-494.
6. Mansvelder HD, De Rover M, McGehee DS, Brussaard AB. Cholinergic modulation of dopaminergic reward areas: upstream and downstream targets of nicotine addiction. Eur J Pharmacol 2003; 480: 117-123.
7. Ye YN, Liu ES, Shin VY, Wu WK, Luo JC, Cho CH. Nicotine promoted colon cancer growth via epidermal growth factor receptor, c-Src, and 5-lipoxygenase-mediated signal pathway. J Pharmacol Exp Ther 2004; 308: 66-72.
8. Christiani DC. Smoking and the molecular epidemiology of lung cancer. Clin Chest Med 2000; 21: 87-93.
9. Doll R, Hill AB. Smoking and carcinoma of the lung; preliminary report. Br Med J 1950; 2: 739-748.
10. Wynder EL, Graham EA. Tobacco smoking as a possible eti-

ologic factor in bronchogenic carcinoma. A study of six hundred and eighty-four proved cases. JAMA 1950; 143: 319-326.
11. US Department of Health, Education, and Welfare. Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public health service. Public Health Service Publication no. 1103, 1964.
12. Hoffmann D, Hoffmann I, El-Bayoumy K. The less harmful cigarette: a controversial issue. A tribute to Ernst L. Wynder. Chem Res Toxicol 2001; 14: 767-790.
13. Montesano R, Hall J. Environmental causes of human cancers. Eur J Cancer 2001; 37: 67-87.
14. Kuper H, Boffetta P, Adami HO. Tobacco use and cancer causation: association by tumour type. J Intern Med 2002; 252: 206-224.
15. Newcomb PA, Carbone PP. The health consequences of smoking. Cancer Med Clin North Am 1992; 76: 305-331.
16. Pisani P, Parkin DM, Bray F, Ferlay J. Estimates of the worldwide mortality from 25 cancers in 1990. Int J Cancer 1999; 83: 18-29.
17. Bilello KS, Murin S, Matthay RA. Epidemiology, etiology, and prevention of lung cancer. Clin Chest Med 2002; 23: 1-25.
18. La Vecchia C, Franceschi S, Levi F. Epidemiological research on cancer with a focus on Europe. Eur J Cancer Prev 2003; 12: 5-14.
19. Wingo PA, Ries LA, Giovino GA et al. Annual report to the nation on the status of cancer, 1973-1996, with a special section on lung cancer and tobacco smoking. J Natl Cancer Inst 1999; 91: 675-690.
20. Peto R, Darby S, Deo H et al. Smoking, smoking cessation, and lung cancer in the UK since 1950: combination of national statistics with two case-control studies. BMJ 2000; 321: 323-329.
21. Erren TC, Jacobsen M, Piekarski C. Synergy between asbestos and smoking on lung cancer risks. Epidemiology 1999; 10: 405-411.
22. Doll R, Peto R. Mortality in relation to smoking: 20 years' observations on male British doctors. Br Med J 1976; 2: 1525-1536.
23. Capewell S, Sankaran R, Lamb D et al. Lung cancer in lifelong non-smokers. Edinburgh Lung Cancer Group. Thorax 1991; 46: 565-568.
24. Engeland A, Haldorsen T, Andersen A, Tretli S. The impact of smoking habits on lung cancer risk: 28 years' observation of 26,000 Norwegian men and women. Cancer Control 1996; 7: 366-376.
25. Camoirano A, Bagnasco M, Bennicelli C et al. Oltipraz chemoprevention trial in Qidong, People's Republic of China: results of urine genotoxicity assays as related to smoking habits. Cancer Epidemiol Biomarkers Prev 2001; 10: 775-783.
26. Boffetta P, Pershagen G, Jockel KH et al. Cigar and pipe smoking and lung cancer risk: a multicenter study from Europe. J Natl Cancer Inst 1999; 91: 697-701.
27. Richardson TL. African-American smokers and cancers of the lung and of the upper respiratory and digestive tracts. Is menthol part of the puzzle? West J Med 1997; 166: 189-194.
28. Thun MJ, Lally CA, Flannery JT et al. Cigarette smoking and changes in the histopathology of lung cancer. J Natl Cancer Inst 1997; 89: 1580-1586.
29. Lippman SM, Hong WK. Molecular markers of the risk of oral cancer. N Engl J Med 2001; 344: 1323-1326.
30. Jordan RC, Daley T. Oral squamous cell carcinoma: new insight. Can Dent Assoc 1997; 63: 517-518, 521-525.
31. Holleb AI, Fink DJ, Murphy GP. Textbook of Clinical Oncology. American Cancer Society, 1991.
32. Chen CL, Chi CW, Liu TY. Hydroxyl radical formation and oxidative DNA damage induced by areca quid in vivo. J Toxicol Environ Health 2002; 65: 327-336.
33. Klein I, Nagler RM, Tofler R, Van der Vliet A, Reznick AZ. Effect of cigarette smoke on oral peroxidase activity in human saliva: role of hydrogen cyanide. Free Radic Biol Med 2003; 35: 1448-1452.
34. Dautzenberg, B. Tobacco related disease. Rev Prat 2004; 54: 1877-1882.
35. Gago-Dominguez M, Yuan JM, Castelao JE, Ross RK, Yu MC. Family history and risk of renal cell carcinoma. Cancer Epidemiol Biomarkers Prev 2001; 10: 1001-1004.
36. Weisburger JH. Worldwide prevention of cancer and other chronic diseases based on knowledge of mechanisms. Mutat Res 1998; 402: 331-337.
37. Frost MA, Coates AS. Plasma carcinoembryonic antigen in an Australian hospital population. Med J Aust 1976; 1: 950-953.
38. Denton TT, Zhang X, Cashman JR. Nicotine-related alkaloids and metabolites as inhibitors of human cytochrome P-450 2A6. Biochem Pharmacol 2004; 67: 751-756.
39. Silverman D, Devesa S, Moore L et al. Bladder cancer. In: Schottenfeld D, Fraumeni J (Eds): Cancer epidemiology and prevention. Oxford University Press, 2006.
40. Murta-Nascimento C, Schmitz-Drager BJ, Zeegers MP et al. Epidemiology of urinary bladder cancer: from tumor development to patient's death. World J Urol 2007; 25: 285-295.
41. Bjerregaard BK, Raaschou-Nielsen O, Sorensen M et al. Tobacco smoke and bladder cancer-in the European Prospective Investigation Into Cancer and Nutrition. Int J Cancer 2006; 119: 2412-2416.
42. Pitard A, Brennan P, Clavel J et al. Cigar, pipe, and cigarette smoking and bladder cancer risk in European men. Cancer Causes Control 2001; 12: 551-556.
43. Samanic C, Kogevinas M, Dosemeci M et al. Smoking and bladder cancer in Spain: effects of tobacco type, timing, environmental tobacco smoke, and gender. Cancer Epidemiol Biomarkers Prev 2006; 15: 1348-1354.