Tobacco products which are used in a way other than smoking are known as smokeless tobacco. The most common smokeless tobaccos are chewing tobacco, naswar, snuff, snus, gutka, and topical tobacco paste. Any product which contains tobacco is not safe for human health. There are more than twenty-five compounds in smokeless tobacco which have cancer causing activity. Use of smokeless tobacco has been linked with risk of oral cancer. Smokeless tobacco contains tobacco-specific nitrosamines (TSNAs), polonium, formaldehyde, cadmium, lead, and benzo[a]pyrene, which are carcinogenic agents. Although there is presence of some compounds, carotenoids and phenolic compounds, that have cancer inhibiting properties, they are in low concentrations. Dry snuff use is linked with higher relative risks, while the use of other smokeless tobacco is of intermediate risk. Moist snuff and chewing tobacco have a very low risk for oral cancer. Therefore, from this review article, it was concluded that smokeless tobacco has risk for oral cancer – either low, medium or high depending on the balance between cancer causing agents and cancer inhibiting agents.

Key words: smokeless tobacco, oral cancer, TSNAs.

Introduction

Tobacco products which are used in a way other than smoking are called smokeless tobacco. The most common smokeless tobacco products are chewing tobacco, naswar, snuff, snus, gutka, and topical tobacco paste. Any product which contains tobacco is not safe for human health. There are more than twenty-five compounds in smokeless tobacco which have cancer causing activity. The most harmful compounds in smokeless tobacco are tobacco-specific nitrosamines (TSNAs) and their levels are directly related to the risk of cancer. Smokeless tobacco has nicotine as an important constituent that causes addiction [1, 2]. Smokeless tobacco-induced carcinogenesis is entirely negative in animal models. In fact, the description of smokeless tobacco as a carcinogen is based exclusively on epidemiologic studies in humans [3]. There is insufficient evidence available for the carcinogenicity of smokeless tobacco in animals [4]. This evaluation is restricted to smokeless tobacco as used in Western societies, largely within the United States and Sweden. Smokeless tobacco is certainly used by numerous cultures in many parts of the world, including the Middle East as well as the Indian continent. On the other hand, smokeless tobacco goods inside these countries are significantly dissimilar from the products used within the West. For instance, within India, smokeless tobacco making is performed by individual farmers plus small companies with modest control in excess of fermentation in addition to curing, which increases the levels of TSNAs [5]. In India, smokeless tobacco is not all the same, given that the tobacco is frequently adulterated [6]. Three different types of smokeless tobaccos – chewing tobacco, wet snuff, and dried out snuff – are used within the US, while in Sweden wet snuff is almost the only type of smokeless tobacco product used. All of these goods are detained inside the lips, more often than not among the buccal mucosa as well as gingiva. These products are distinctly different from each other with respect to the tobacco used, the procedures for their production, and the populations that use them. Smokeless tobacco type is a precondition towards an understanding of smokeless tobacco-linked oral cancer [7, 8].

Smokeless tobacco types include loose-leaf chewing tobacco, moist snuff, and dry snuff [9]. Loose-leaf chewing tobacco is made from plants grown in Pennsylvania and Wisconsin; the leaves are air-cured, crushed into pieces and sweet flavoring agents are added. The use was originated by men in the US, mainly in combination with outdoor activities, the tobacco juices being spat out. There is decreased popularity of this product; use of it has slowly decreased by about 35% over the past 15 years [10]. Fire- and air-cured dark tobaccos are used for moist snuff. The most well-liked type of smokeless tobacco in the US is moist snuff; it has become more popular by about 77% in the last 15 years [10]. Moist snuff is also called ‘snus’. Conventional users of moist snuff put a ‘pinch’ of very crushed tobacco between the gingival and buccal mucosa. It is difficult to keep in place for a person, due to esthetically displeasing resultant movement.
Small, pre-portioned pouches similar to tea-bags are now used for sale of the modern moist snuff products. In the mouth these products remain fixed and produce very little juice. There is no need to spit them out and they can be used carefully. American and Swedish moist snuff products are manufactured in different ways. The fermentation process is used in traditional American products, providing specific flavors but leading to high concentrations of unnecessary by-products that are bacterially mediated, particularly TSNAs and nitrite. In Sweden during manufacturing heat is provided to moist snuff to pasteurize it and make a sterile product. Fermented, fire-cured tobacco is used for dry snuff that is subjected to powder, and originally was used through nasal inhalation. Dry snuff as an oral form of tobacco has been used by women in the southern US since the early 1800s [11, 12]. There is a decline in this type of use and sales have decreased by about 60% in the past 15 years [10].

Cancer causing agents

Tobacco-specific N-nitrosamines

Long-term use of some products having smokeless tobacco show increased risk of oral cancer and mainly this elevated risk is due to the presence of tobacco-specific N-nitrosamines (TSNAs). N-nitrosonornicotine (NNN), 4-methyl-N-nitrosamino-1-(3-pyridyl)-1-butanone (NNK), N-nitrosoanatabine (NAT), and N-nitrosoanabasine (NAB) are the four principal compounds. Green tobacco has low levels of TSNAs, but during curing has high levels [13, 14]. N-nitrosoanatabine, NAB, and NNN are synthesized from nor-nicotine, anabasine, and anatabine, respectively. N-nitrosonornicotine can also be produced from nicotine, whereas NNN is produced only from one precursor, nicotine.

Over the past decade the factors favoring the synthesis of TSNAs have been observed [13]. To reduce TSNAs, manufacturers and leaf growers use numerous strategies. Research includes the formation of tobacco cultivars having low levels of alkaloids, with special importance to stop the development of NNN and nor-nicotine [13, 14]. The removal of nitrate-reducing microbial activity inhibits the development of TSNAs, whereas the action of other microbes gives an attractive essence. Careful temperature and humidity control conditions during curing also cause a reduction in TSNAs concentration. For traditional cured tobacco, the replacement of heat exchange methods also causes a lower level of nitrosamine [15].

4-methyl-N-nitrosamino-1-(3-pyridyl)-1-butanone and NNN are the two TSNAs which are major cancer causing agents in smokeless tobacco. The International Agency for Research on Cancer (IARC) classified them as carcinogenic to humans [16, 17]. Carcinogenicity is not related to NAB and NAT, according to IARC [18, 19].

Cadmium

In most soils, cadmium has a low concentration [20, 21], and in food it causes extensive spread of heavy metals [22]. The International Agency for Research on Cancer considered cadmium as a cancer causing agent due to increased cancer of lungs in industrial workers through inhalation of high concentrations of it or animal research [21]. A routine diet contains cadmium. Maximum percentage of total intake is provided by cereals and grains. Shellfish and some vegetables, such as spinach, also contain cadmium [22]. About 25 g of cadmium daily is supplied by a routine diet. 52 g daily cadmium intake is recommended by the Codex Alimentarius Commission of the WHO [23, 24].

Polonium

Polonium-210 is a radioactive decay product of radium-226 [25]. It is present in the environment from rain or other weather events. Polonium-210 is not properly classified by IARC [26]. It is deposited in plants through surface absorption and then moves into edible parts such
as seeds and fruits. The major source of polonium-210 is food ingestion. One to 10 picocuries (pCi) daily is supplied by the diet. In tobacco it originates from fertilizers [24, 27].

**Formaldehyde**

Formaldehyde is used widely in industry as a chemical and in manufacturing [28]. The International Agency for Research on Cancer classified it as a cancer causing agent in humans, basically in workers who work in industry and are continuously exposed to it or in animal research. Two to 3 mg/l concentration of formaldehyde is present endogenously in human blood and when exposed to the substance present in air its concentration changes [29]. Up to 6 ng/g is present in meat and poultry, 6 to 14 ng/g in fish, 2 to 26 ng/g in fruits and vegetables [30, 31].

**Polycyclic aromatic hydrocarbons**

Incomplete combustion of organic compounds produces polycyclic aromatic hydrocarbons (PAHs). Since the advent of fire they have been present in the environment and human diet, especially in meat [32]. Benz[a]pyrene (BaP) is the most common and intensively studied PAH; IARC classified it in Group 2A as a cancer causing agent [33]. Sources of BaP are plants due to surface contamination and charcoal cooked meat [34, 35]. Low levels of about 0.1 to 4 ng/g of BaP were present in some brands of moist snuff, while some contained up to 63 ng/g. Smokeless tobacco contains BaP mainly from fire-curing [24], and thus its concentration depends on the amount of tobacco used that is fire cured.

**Lead**

Based on animal research, IARC classified lead as a cancer causing agent to humans [36]. It appears in the environment through combustion of lead-containing fuels [37]. Absorption from dietary sources is limited, because lead in the soil is not readily taken up by most plants. In addition, lead in livestock is largely deposited in bone tissue, which limits its transfer to meat consumers. The main sources of dietary lead are fruits and vegetables; about 50 g per day is supplied by the diet, and a 150 g daily intake is set by the Codex Alimentarius Commission [23, 24].

**Cancer inhibiting agents**

There are two classes of agents that have the property to inhibit cancer among all the chemical components in smokeless tobacco leaf.

**Carotenoids**

The first class is the carotenoids, which include neoxanthin, violaxanthin, lutein, and carotene, present in tobacco in higher concentrations [38]. Experimental evidence shows that carotene has the properties to inhibit the production of cancerous lesions [39, 40].

**Phenolic compounds**

Phenolic compounds are the second class which contains the greater anti-oxidant constituents in tobacco [9]. Fascinatingly, at both the initiation and the promotion stage of the lung tumor genesis by NNK, polyphenols exert an inhibitory effect [41–43]. As shown earlier, NNK is one of the important TSNAs.

**Risk for oral cancer**

Earlier epidemiological studies showed that the risk of oral cancer from smokeless tobacco was minimal. However, evidence from the experiment is controversial. For example, tumor formation is a result of chronic application of purified TSNAs to the oral mucous membrane [44]. Among tobacco products, there is significant variation in their cancer-producing activity. The characteristics of products are changed by the methods of processing (temperature variations, fermentation), and curing (flue curing, smoke curing or air curing) plays an important role [39, 45, 46]. Finally, the addition of preservatives and flavoring agents influences the anti-oxidant activity of tobacco products. Combustion of the smokeless tobacco causes the synthesis of a chemical mixture containing a highly reactive oxygen and smokers show low plasma levels of antioxidant vitamins, e.g. tocopherols, and ascorbic acid [47].

Regarding the management for oral cancer, the problem of resistance and tolerance to the existing drugs has led to decreased efficacy of these drugs. There have been attempts to overcome this problem by increasing the drug delivery to the target site by the use of polymers [48, 49] or through nanotechnology [50, 51], and synthesis of new drugs, either by the use of proteomics [52] or synthesis from lactic acid bacteria [53] or marine microorganisms [54]. Large numbers of drugs are constantly being invented for their possible pharmacological value, particularly for their anti-inflammatory [55], hypotensive [56], hepatoprotective [57], hypoglycemic [58, 59], amebicidal, anti-fertility, cytotoxic, antibiotic [60], spasmylytic [61], anti-musculoskeletal pain [62], bronchodilator, antioxidant, anti-diarrheal, anti-epileptic [63], anti-Parkinsonism [64] and anti-Alzheimer [65] properties. Similarly, as cancer is the major cause of death in humans, new drugs and methods [66–85] are being investigated for management of cancers.

In conclusion, tobacco-specific N-nitrosamines are the major cancer causing agents in smokeless tobacco. Others cancer causing agents that are present in smokeless tobacco include cadmium, polonium-210, formaldehyde, benzo(a)pyrene and lead. Although there is presence of some compounds, carotenoids and phenolic compounds, that have cancer inhibiting properties, they are in low concentrations. Therefore, it is concluded that smokeless tobacco has risk for oral cancer – either low, medium or high depending on the balance between cancer causing agents and cancer inhibiting agents.

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**Table 1. Relative risk of oral cancer by using smokeless tobacco**

| Tobacco                        | Relative risk          |
|--------------------------------|------------------------|
| moist snuff and chewing tobacco| very low risk          |
| dry snuff                      | higher risk            |
| other smokeless tobacco        | intermediate risk      |
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