

Association between head-and-neck cancers and active and passive cigarette smoking

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ABSTRACT

Although there have been many reports on the toxicity of tobacco smoke, fewer studies have reported the relationship between the smoke and carcinogenesis of head-and-neck cancers. It is assumed that direct stimulations due to tobacco smoke, such as chemical and mechanical stimulations, strongly influence the epithelium of the nasal cavity, paranasal sinuses, pharynx, and larynx. We investigated the influence of active and passive cigarette smoking on head-and-neck cancers. The subjects were 283 head-and-neck cancer patients examined at the otolaryngology department of Showa University Northern Yokohama Hospital in a 9-year and 2-month period from April 2001 to June 2010, in whom the presence or absence of active and passive cigarette smoking could be confirmed in detail. The active and passive smoking rates and the Brinkman index were retrospectively investigated according to the primary cancer site, gender, and histopathological classification. The active and passive smoking rates were high (about 90%) in patients with hypopharyngeal, laryngeal, and cervical esophageal cancers, and the Brinkman index was high in all. Squamous cell carcinoma (SCC) patients accounted for a high ratio of the head-and-neck cancer patients, and the active and passive smoking rates were significantly higher in SCC than in non-squamous cell carcinoma (non-SCC) patients ($p < 0.0003$). The active and passive smoking rates and the Brinkman index were high in patients with head-and-neck cancers in regions receiving strong direct stimulation from tobacco smoke, and the Brinkman index was also high in these patients, suggesting that carcinogenesis of

head-and-neck cancers is strongly influenced by direct tobacco smoke stimulation.

Keywords: Head-and-Neck Cancers; Squamous Cell Carcinoma; Active Smoking Rate; Passive Smoking Rate; Brinkman Index

1. INTRODUCTION

It is widely known that active and passive cigarette smoking is toxic for the human body [1-3]. Tobacco smoke contains about 200 toxic substances, and 69 of these have been identified as carcinogens [4]. There is no doubt that the carcinogens contained in tobacco smoke are closely involved in the carcinogenesis mechanism, as demonstrated by many epidemiological studies [5,6]. Tobacco smoke includes many carcinogenic substances, but among them benzopyrene and nitrosoamine are particularly strong carcinogens. While benzopyrene exists in particulate form, nitrosoamine which mainly exists in gaseous form, can also be found in particulate form. The association between active and passive cigarette smoking and carcinogenesis has been clarified in cancers of the lung, oral cavity, pharynx, larynx, nasal cavity, paranasal sinuses, esophagus, stomach, large intestine, liver, kidney, pancreas, urinary bladder, and uterine cervix [7-10]. On the other hand, the relative risk of active and passive smoking-induced carcinogenesis varies among cancer types. A high relative risk of head-and-neck cancers, such as oral, pharyngeal, and laryngeal cancers, similar to that of lung cancer, has been reported [6]. Head-and-neck cancer generally refers to all cancers originating in the head-and-neck area excluding brain and eyeball cancers. In this study, however, the sites we are concerned with are only those that come into direct contact with tobacco smoke, namely nasal cavity/paranasal sinus cancer, tongue/oral cavity cancer, epipharyngeal cancer, mesopharyngeal cancer, hypopharyngeal cancer, laryn-

geal cancer, and esophageal cancer. Since the risk of carcinogenesis is higher in the lung, oral cavity, pharynx, and larynx directly exposed to tobacco smoke than in other regions, it is assumed that direct stimulations, such as chemical and mechanical stimulations, on the nasal, paranasal sinus, pharyngeal, and laryngeal epithelium by tobacco smoke strongly influence carcinogenesis [6, 11-13]. On that basis, regarding the fluid dynamics of tobacco smoke, when smoke passes through regions with a large volume, such as the nasal cavity/paranasal sinuses and oral cavity, the unit smoke passage area is large, smoke flow rate is slow, and concentration is low, whereas the unit smoke passage area narrows, smoke flow rate increases, and concentration rises in regions with a small volume, such as the pharynx and larynx. The airway anatomy is complex, and the strength and resistance as a lumen vary among the regions. Regarding the airway as a simple large lumen, we analyzed the fluid dynamics of cigarette smoke employing Bernoulli's principle (**Figure 1**). Briefly, Bernoulli's principle applies the law of the conservation of energy to fluid. Representing the flow rate as V , pressure as P , fluid density as ρ , height as h , and gravitational acceleration as g , the principle is presented as the equation below:

$$\frac{V^2}{2g} + \frac{P}{\rho g} + h = \text{constant} \tag{1}$$

The fluid density, ρ , rises. The gravitational acceleration is constant, indicating that the flow rate increases. Considering that the potential energy, h , does not change in the supine position, (1) can be converted to the equation below:

$$\frac{1}{2}\rho V^2 + P = \text{constant} \tag{2}$$

The pressure, P , decreases when the density, ρ , and flow rate, V , increase, *i.e.*, when tobacco smoke passes through a region with a narrow passage area, the smoke concentration and flow rate increase, reducing the pressure, which causes traction of the surrounding tissue toward the lumen. Subsequently, the unit passage area is

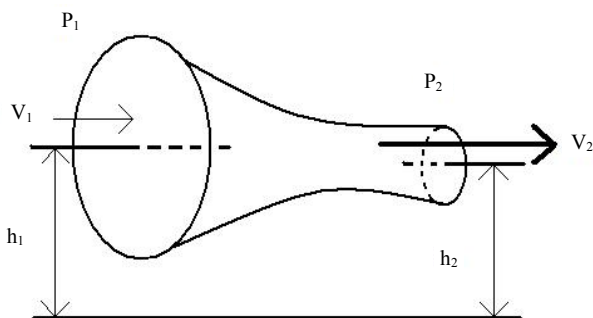


Figure 1. Model of fluid dynamics in lumen. V : Flow rate, P : pressure, h : height.

further narrowed. The stimulation level per unit area is higher when the energy of fluid is received by a narrow compared to wide area, *i.e.*, direct stimulations, such as mechanical and chemical stimulations, are stronger in regions with a narrow unit passage area, such as the pharynx and larynx, than in those with a wide passage area, such as nasal cavity/paranasal sinuses and tongue/oral cavity.

In this study, we calculated the active and passive smoking rates and the Brinkman index (number of cigarettes smoked per day x duration (years) of active cigarette smoking) in head-and-neck cancer patients according to the primary cancer site and histopathology, in order to investigate the influences of active and passive cigarette smoking on the development of head-and-neck cancers.

2. MATERIALS AND METHODS

The subjects were 283 head-and-neck cancer patients examined at the otolaryngology department of Showa University Northern Yokohama Hospital in a 9-year and 2-month period from April 2001 to June 2010, in whom the presence or absence of active and passive cigarette smoking could be confirmed. The diseases include: nasal cavity/paranasal sinus cancer in 27 patients, tongue/oral cavity cancer in 48 (tongue cancer: 22, oral cavity cancer: 26), pharyngeal cancer in 99 (epipharyngeal cancer: 11, mesopharyngeal cancer: 41, hypopharyngeal cancer: 47), laryngeal cancer in 79, and cervical esophageal cancer in 30 patients.

These patients were retrospectively surveyed using their electronic medical records with regard to the following items: 1) The active and passive smoking rates, the total of these (total smoking rate), and the Brinkman index according to the primary cancer site, 2) these rates and index by gender, and 3) these rates and index by histopathological classification.

Current and previous active cigarette smokers were combined as active cigarette smokers. Subjects who had smoked 100 cigarettes or more in total or for 6 months or longer and smoked every day or sometimes in the last one month were regarded as current active cigarette smokers, and those who had smoked 100 cigarettes or more in total or for 6 months or longer but did not smoke in the last one month as previous active smokers. Passive smokers were defined as those who were not included in the above active smokers but living with an active smoker or one of the subject's parents was an active smoker in childhood. The other subjects were handled as non-active cigarette smokers. In investigation item 3), all patients were divided into squamous cell carcinoma (SCC) and non-SCC groups, and the significance of differences was analyzed using Fisher's test. This study was

performed according to the rules of the ethical committee approved by the Showa University Northern Yokohama Hospital.

3. RESULTS

1) Active and passive smoking rates, the total of these (total smoking rate), and the Brinkman index according to the primary cancer site.

The active and passive smoking rates and total of these (total smoking rate) according to the primary cancer site are shown in **Figure 2**. The active, passive, and total smoking rates were 44 and 19 for a total of 63% in nasal cavity/paranasal sinus cancer patients, respectively, 65, and 8, for 73% in tongue/oral cavity cancer patients, respectively, 64, and 0, for 64% in epipharyngeal cancer patients, respectively, 76, and 12, for 88% in mesopharyngeal cancer patients, respectively, 85, and 4, for 89% in hypopharyngeal cancer patients, respectively, 94, and 4, for 98% in laryngeal cancer patients, respectively, and 90, and 10, for 100% in cervical esophageal cancer patients, respectively.

The mean Brinkman index according to the primary cancer site is shown in **Figure 3**. The mean Brinkman index was 603 in nasal cavity/paranasal sinus cancer patients, 876 in tongue/oral cavity cancer patients, 542 in epipharyngeal cancer patients, 727 in mesopharyngeal cancer patients, 693 in hypopharyngeal cancer patients, 975 in laryngeal cancer patients, 892 in cervical esophageal cancer patients, and 785 in all patients.

2) Active, passive, and total smoking rates and the Brinkman index according to the primary cancer site in each gender.

In the nasal cavity/paranasal sinus cancer patients, the male: female ratio was 16:11. The active, passive, and total smoking rates were 75, and 6, for 81% in males, respectively, and 9, and 27, for 36% in females, respectively. In tongue/oral cavity cancer patients, the sex ratio was 30:18, and the rates were 81, and 3, for 84% in males and 34, and 22, for 56% in females, respectively. In the epipharyngeal cancer patients, the sex ratio was 10:1, and the rates were 70, and 0, for 70% in males and 0, and 0, for 0% in females, respectively. In the mesopharyngeal cancer patients, the sex ratio was 32:9, and the rates were 84, and 3, for 87% in males and 44, and 44, for 88% in females, respectively. In the hypopharyngeal cancer patients, the sex ratio was 44:3, and the rates were 91, and 2, for 93% in males and 0, and 33, for 33% in females, respectively. In the laryngeal cancer patients, the sex ratio was 75:4, and the rates were 95, and 3, for 98% in males and 75, and 25, for 100% in females, respectively. In the cervical esophageal cancer patients, the sex ratio was 27:1, and the rates were 93 and 0, for 93% in males and 0, and 0, for 0% in females, respectively.

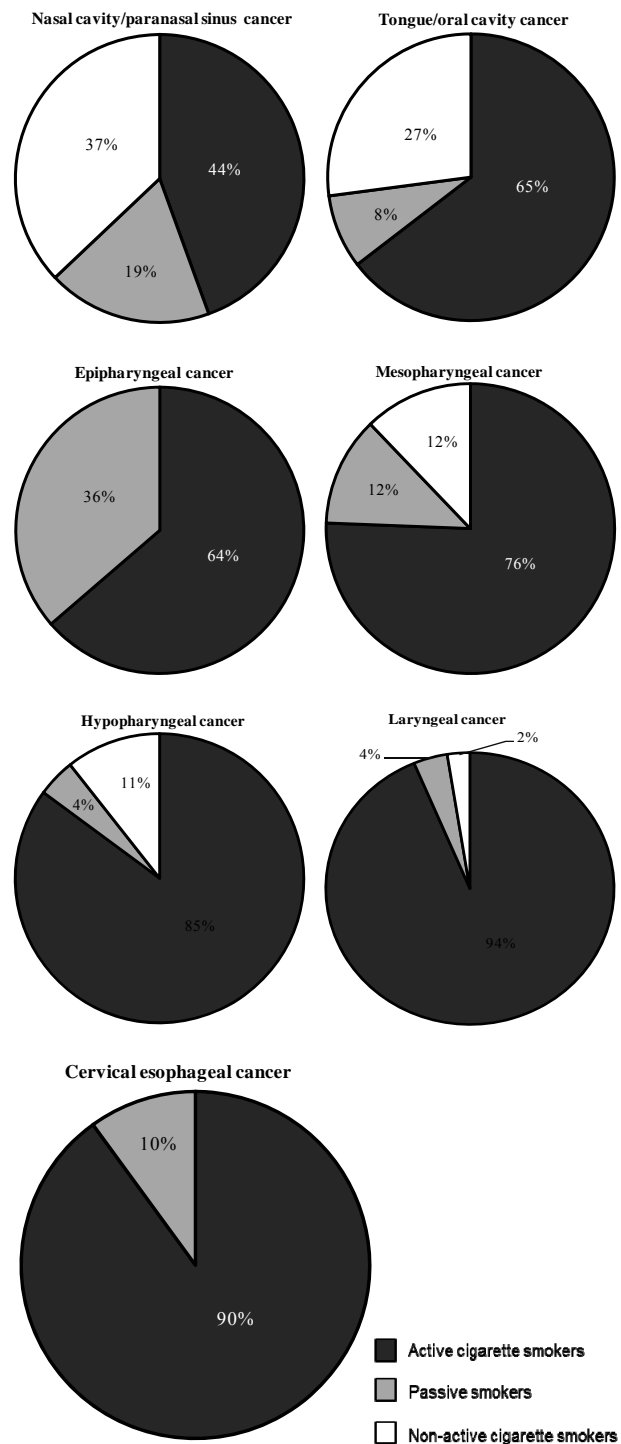


Figure 2. Active, passive, and total smoking rates according to the primary cancer site. The total smoking rate is the sum of the active and passive smoking rates.

The mean Brinkman index by gender was 643 in males and 135 in females in nasal cavity/paranasal sinus cancer patients, 886 and 825 in tongue/oral cavity cancer patients, respectively, 542 and 0 in epipharyngeal cancer patients, respectively, 961 and 494 in mesopharyngeal

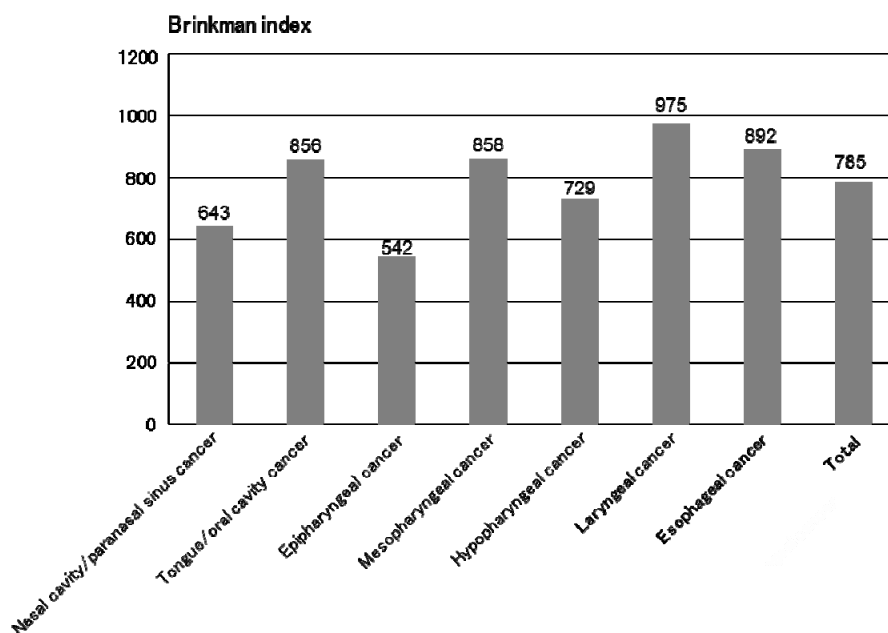


Figure 3. The mean Brinkman index according to the primary cancer site.

cancer patients, respectively, 693 and 0 in hypopharyngeal cancer patients, respectively, 955 and 583 in laryngeal cancer patients, respectively, and 892 and 0 in cervical esophageal cancer patients, respectively.

3) Active, passive, and total smoking rates and the Brinkman index according to the primary cancer site in each histopathologic type.

SCC accounted for 52%, 91%, 78%, and 97% of the nasal cavity/paranasal sinus, tongue/oral cavity, epipharyngeal, and mesopharyngeal cancer patients, respectively, and 100% of the hypopharyngeal, laryngeal, and cervical esophageal cancer patients. SCC accounted for 92% of all head-and-neck cancer patients. The active, passive, and total smoking rates were 84%, and 5%, for 89% in SCC patients, respectively, and 26%, and 21%, for 47% in non-SCC patients, respectively. The rates were compared between the SCC and non-SCC groups employing Fisher's test. A significant difference was noted in the active smoking rate ($p < 0.001$). The passive smoking rate was also significantly different ($p = 0.0338$), but it could not be definitely concluded because the number of patients was small. A significant difference was also noted in the total smoking rate ($p < 0.001$). The active and total smoking rates were significantly higher in the SCC group.

Regarding the rate of SCC patients in each gender, SCC accounted for 63% and 36% of male and female nasal cavity/paranasal sinus cancer patients, respectively, and the active, passive, and total smoking rates in these males and females with SCC were 90% and 0%, 0% and 50%, and 90% and 50%, respectively. In the tongue/oral cavity cancer patients, SCC accounted for 100% of males

and 78% of females, and the rates in these males and females were 90% and 46%, 5% and 8%, and 95% and 54%, respectively. In the epipharyngeal cancer patients, SCC accounted for 78% and 0% of males and females, respectively, and the rates in these males were 75%, and 0%, for 75%, respectively. In the mesopharyngeal cancer patients, SCC accounted for 100% of males and 89% of females, and the rates were 81% and 50%, 6% and 38%, and 88% and 88%, respectively. In the hypopharyngeal, laryngeal, and cervical esophageal cancer patients, SCC accounted for 100% in both genders. Accordingly, the rates were the same as those described in 2): 91%, and 2%, for 93% in males and 0, and 33, for 33% in females with hypopharyngeal cancer, respectively, and 95%, and 3%, for 98% in males and 75%, and 25%, for 100% in females with laryngeal cancer, respectively. In the cervical esophageal cancer patients, SCC accounted for 93%, and 0%, for 93% in males, respectively, and all rates were 0% in females.

The Brinkman indices of SCC and non-SCC patients were 733 and 314 in the nasal cavity/paranasal sinus cancer patients, respectively, 880 and 880 in the tongue/oral cavity cancer patients, and 566 and 400 in the epipharyngeal cancer patients, respectively. The histologic type was SCC in all mesopharyngeal, hypopharyngeal, laryngeal, and cervical esophageal cancer patients, and the Brinkman indices were 727, 693, 955, and 892, respectively.

4. DISCUSSION

Although there have been many reports on the toxicity of tobacco smoke, cigarette smoke-induced carcinogene-

sis of head-and-neck cancers has been investigated in only a few reports. It is known that chronic mechanical stimulations loaded by active cigarette smoking and mal-fitting dentures induce carcinogenesis of SCC in the tongue [12,13]. This tongue cancer development mechanism is considered to be multistep carcinogenesis [14,15], in which gene aberration occurs in onco- and antioncogenes when mucoepithelium is exposed to chronic stimulation (cell injury) in the proliferation/differentiation process, which causes oncogene activation and inactivation of an antioncogene, *p53*, resulting in the appearance of immortalized cells with dividing potential (initiated cells), and then aberration of other onco- and antioncogenes occurs, expanding the cell population (clonal expansion). These gene aberrations accumulate in a multistep-manner, and normal cells alter to precancerous and then cancer cells (**Figure 4**). It is assumed that chronic stimulation induces the development of SCC, the same type as tongue cancer, through the above carcinogenesis mechanism in not only the tongue but also other regions.

The nasal cavity, paranasal sinuses, and a part of the larynx are covered with pseudostratified ciliated epithelium, and the epipharynx is partially covered with columnar epithelium, but the mucoepithelium of the tongue/oral cavity, pharynx, laryngeal vocal cord, epiglottis, and cervical esophagus is comprised of stratified squamous epithelial cells. It is assumed that chronic stimulation by active/passive cigarette smoking loaded

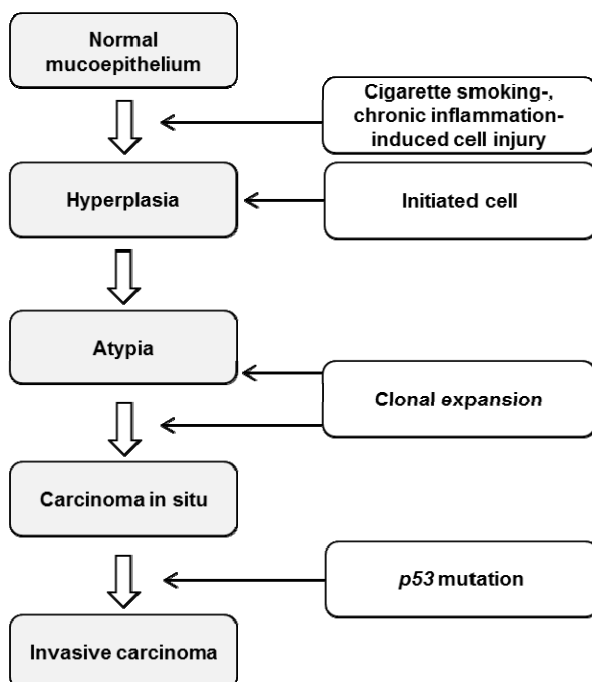


Figure 4. Multistep carcinogenesis mechanism. Multistep carcinogenesis involves oncogene activation and antioncogene inactivation.

on stratified squamous epithelial cells in these regions induces multistep carcinogenesis. The total smoking rates according to the primary cancer site were 63%, 73%, 64%, 88%, 98%, 89%, and 100% in the nasal cavity/paranasal sinus, tongue/oral cavity, epipharyngeal, mesopharyngeal, hypopharyngeal, laryngeal, and cervical esophageal cancer patients, respectively, showing that the rate rose as the region descends toward the central airway. Particularly, the total smoking rates were high: 88%, 89%, 98%, and 100%, in the mesopharyngeal, hypopharyngeal, laryngeal, and cervical esophageal cancer patients, respectively.

The mean Brinkman index was high at all primary cancer sites: 603, 876, 542, 727, 693, 975, and 892 in the nasal cavity/paranasal sinus, tongue/oral cavity, epipharyngeal, mesopharyngeal, hypopharyngeal, laryngeal, and cervical esophageal cancer patients, respectively, showing that cigarette smoking stimulation was chronically loaded. The Brinkman index exceeded 500 in all cancers, suggesting that a 500 or higher Brinkman index is a risk of developing head-and-neck cancers. Many head-and-neck cancers were SCC, and the total smoking rate was significantly higher in the SCC than in the non-SCC group, suggesting that chronic direct stimulation, such as mechanical and chemical stimulations of active/passive cigarette smoking, was loaded on squamous epithelial cells and induced carcinogenesis of SCC.

In the investigation by gender, the male ratio was higher than the female ratio at all primary cancer sites of head-and-neck cancers. In addition, the total smoking rate in males exceeded 80% in all cancers excluding epipharyngeal cancer (70%). These findings suggested that the risk of SCC in the head-and-neck region is high in males with a 500 or higher Brinkman index. The carcinogenesis risk is particularly high in the regions near the airway center strongly affected by mechanical and chemical stimulations, such as the pharynx, larynx, and cervical esophagus. Laryngoscopic examination by otolaryngologists and head-and-neck surgeons is necessary.

5. CONCLUSION

The carcinogenesis mechanism is complex, and it is not induced by a single cause, but direct stimulation by active/passive cigarette smoking may be a major cause of carcinogenesis of SCC in the head-and-neck region. Otolaryngologists and head-and-neck surgeons should promote smoking cessation as primary prevention, in addition to the treatment of head-and-neck cancers. Japan signed the Framework Convention on Tobacco Control (FCTC) with many other countries. FCTC is a treaty to continuously and practically reduce active and passive cigarette smoking effectuated in February 2005. However, there is a contradictory law, the “Tobacco Business Act”, in Japan, and the country promotes cigarette sales

to increase the tax revenue. This situation is problematic. Promotion of smoking cessation led by the government following FCTC is necessary, and the prevention of tobacco-induced social and environmental damage should be considered, in addition to health damage.

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