Tadaaki Kirita
Ken Omura *Editors*

Oral Cancer

**Diagnosis
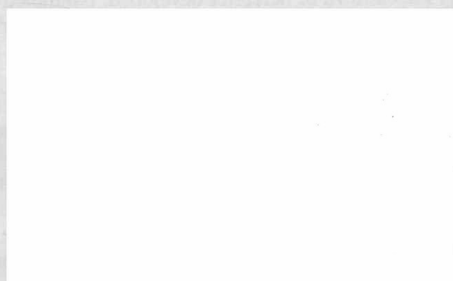and Therapy**

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Oral Cancer

Diagnosis and Therapy

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Preface

The oral and pharyngeal region represents the sixth leading site of cancer in the world, and oral cancer is widely accepted to have a higher incidence in people older than 50 years, primarily due to the relationship with chronic exposures to tobacco, alcohol, and other carcinogenic products. Particularly in India, Bangladesh, Pakistan, and Sri Lanka, oral cancer is the most common, accounting for about one third of all cancers. Recently, the incidence of this cancer in young adults (age <40 years) has appeared to be increasing in many Western countries.

Oral cancers can be treated curatively in the early stages by surgery or radiotherapy; however, locoregionally advanced disease continues to be a major clinical problem due to poor prognosis, poor appearance, and post-therapeutic functional impairment. It is not a tribute to professionals or public health authorities that an area of the body that is so easily accessible for examination and a lesion that is so easily diagnosed can still result in so many deaths. Early diagnosis of a lesion during the localized early stage, combined with adequate treatment, thus appears to be the most effective way to further improve oral cancer control. Prevention of oral cancer is also obviously important for the high-risk population of tobacco-smoking, alcohol-drinking males with poor oral hygiene and nutrition.

Therapy for oral cancer has improved significantly over the last 25 years. Chemotherapy has been added to surgical approaches and megavoltage radiation. Chimeric monoclonal antibody has also been applied in treatment with radiation and platinum-based chemotherapy. The increasing application of microvascular surgery for free tissue transfer has produced new dimensions in reconstructive techniques for oral cancer surgery. A combined therapeutic team approach is now the rule, with authoritative voices in all specialties joining their talents and experience for the benefit of the patient. Prompt implementation of multidisciplinary treatment based on the latest knowledge and clinical data will further contribute to the progression of oral cancer treatment.

The purpose of this publication is to present a wealth of information on oral cancers in one source. This book is composed of excellent contributions from well-established and distinguished specialists who have been working on topics related to the epidemiology, pathology, and treatment of oral cancer. The contributors have written their respective chapters based on their professional knowledge for target readers, including cancer researchers, oncologists, molecular biologists, pathologists, and clinicians in oral cancer. The editors are grateful to all the contributors for their excellent efforts in making their chapters accessible to these readers.

It is hoped that this book will allow a more intelligent understanding of oral cancer, resulting in skillful, excellent treatment to maximize the patient's chance of cure and preserve the highest quality of life.

Nara, Japan   Tadaaki Kirita
Tokyo, Japan   Ken Omura

Contents

Nobuharu Yamamoto and Takahiko Shibahara

Abstract

Oral cancer is a malignant neoplasm that occurs in the oral cavity. Squamous cell carcinoma accounts for over 90 % of the oral cancers in Japan, and others include adenocarcinoma derived from minor salivary gland, sarcoma, malignant lymphoma, and metastatic cancer. A number of cohort studies and case–control studies have been conducted as epidemiological technique to elucidate oral cancers. The number of oral cancer patients in Japan was 2,100 in 1975 and 6,900 in 2005 and further is estimated to be 10,000 patients by 2015, which is 1.6 times higher than the current number. Age-adjusted male-to-female ratio is 3:2, which is higher in males than in females, and the incidence of oral cancers decreases with the aging of the population in developed countries with the exception of Japan, in which the ratio is increasing. Of oral cancers, tongue carcinoma is the most common and accounts for 40 % of oral cancers. The oral cavity, an entrance of the digestive system, is exposed to chemical stimuli such as smoking, drinking, and food as well as to mechanical stimuli including caries and ill-fitting prosthetic appliance and characterized by the existence of multiple circumstances in particular and risk factors associated with carcinogenesis. Examination of oral cancers can be easily conducted because these cancers can be confirmed directly by visual observation and palpation. The significance of oral cancer examination is early diagnosis and early treatment of not only oral cancers but also premalignant lesions, including leukoplakia and erythroplakia, and precancerous conditions, including lichen planus. It is reported that the detection rate of oral cancers and premalignant lesions is 0.99 % in oral cancer screening and that the prevalence of precancerous lesions is 2.5 % in Japanese. Some patients with oral cancer may synchronously or metachronously develop double cancers. In patients with head and neck cancer including oral cancer, 60–70 % of double cancers are found in the upper gastrointestinal tract or lung.

Keywords

Epidemiology • Japanese • Oral cancer • Prevention • Squamous cell carcinoma

1.1 Introduction: Oral Cancer in Japan

The number of death from cancer has been increasing to 340,000 yearly in Japan (30.3 % of the total deaths). This number corresponds to the number of deaths from car accidents of 60 years. It is estimated that half of the people of Japan are affected with cancer in their life regardless of sex. Cancer is a national disease, and it is no doubt that Japan is a

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Fig. 1.1 Number of deaths
due to oral and pharyngeal
cancers by developed
country (per 100,000
population). Increase is
observed only in Japan
among developed countries
and this is a disturbing fact
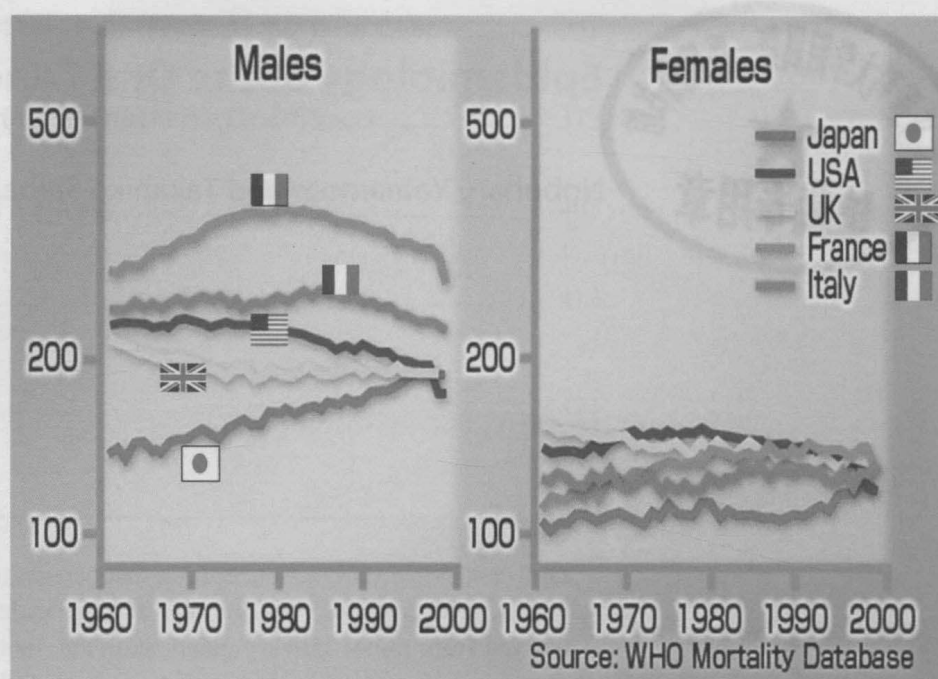
major cancer-affected country. According to the Revised
Policy Statement of the Federation Dentaire Internationale
(FDI) in 2000, the number of death from oral cancers includ-
ing pharyngeal cancer was 318,000 throughout the world
(2002). On the other hand, it is thought that the number of
death from breast cancers in the same year was 477,000.
When taking account of 1–2 % of incidence rate of oral can-
cers of the entire tumors, it is shown how high the incidence
of oral cancer rate is [1].

The number of death from oral cancers (6,000 patients/
year) and incidence of oral cancers as well as total cancers
demonstrate an upward trend [2]. The number of patients
with oral cancer was 2,100 in 1975 and increased to 6,900 in
2005 and is estimated to become 10,000 patients, which is
1.6 times higher than the present number, by 2015 in Japan
[2–4]. In addition, such increase is observed only in Japan
among developed countries and this is a disturbing fact.
Actual number of death from oral cancer and incidence rate
of oral cancer in the USA, the UK, and Italy are higher than
in Japan, but annual changes of the rate are obviously
decreasing in those countries. These decreases would reflect
the results of countermeasures against cancers (Fig. 1.1) [5].
It is known that the medical services in Japan provide the
latest equipment and maintain state-of-the-art standard;
however, these services seem to fail reducing the cancers.
This may reflects a tendency of the current medical system
emphasizing on treatment but not prevention.

Clinical statistics obtained in our department and mea-
sures for prevention of oral cancer that we addressed are pre-
sented, as well as epidemiology is discussed in this article.

1.2 Frequency of Oral Cancer

The number of cancer patients as well as patients with oral
cancers is increasing with the advent of a super-aging society
in Japan. The incidence rates of oral cancer are different by
ethnic, country, region, lifestyle, and practice.

Although an exact nationwide survey on oral cancers has
not been conducted yet, the numbers of death from oropha-
ryngeal cancers per 100,000 of population in males and
females were 2.4 and 1.3, 5.1 and 2.9 in 1975 and 1995,
respectively, and are estimated to increase to 8.6 and 5.2 by
2015 according to the Annual Report on Health and Welfare
[2]. Treatment performance has also been improved during
these years; however, the increase of death from cancers
largely exceeds the treatment performance. This means the
development of cancers also increases. The incidence of oral
cancers in Japan is as described in the above section [2–4],
and this number corresponds to about 1 % of the total cancer
number and 40 % of the total number of head and neck can-
cers. Therefore, it is considered that such steady increase
was caused by an increase of super-aging people [6–13].

Age-adjusted prevalence of oral cancer is highest in 60's
similar to other cancers, and the male-to-female ratio is 3:2,
which is higher in males than in females. According to
nationwide statistics of Japanese Society of Oral and
Maxillofacial Surgeons on oral cancers in 2002 [14], of 1777
patients, male patients were 1,051 (59.1 %) and female
patients were 726 (40.9 %). By age groups, 50s patients were
323 (18.1 %), 60s patients were 471 (26.5 %), and 70's

Table 1.1 Oral cancer patient characteristics in our department (2003/1–2012/12, n = 348)

Patient characteristics	n = 348
Age, mean (range)	62.9 (21–94)
Sex, men/women	188/160
Performance status	0–2
Primary site (%)	
Tongue	183 (52.6)
Mandibular gingiva	68 (19.5)
Maxillary gingiva	38 (10.9)
Buccal mucosa	26 (7.5)
Oral floor	22 (6.3)
Palate	9 (2.6)
Others	2 (0.6)
Histology (%)	
Well	102 (29.3)
Moderate	36 (10.3)
Poor	8 (2.3)
Early	36 (10.3)
Unknown	166 (47.7)
Mean follow-up, month (range)	46.3 (4.4–123.2)
T-stage (%)	
1	113 (32.5)
2	151 (43.4)
3	36 (10.4)
4	48 (13.8)
N-stage (%)	
0	209 (60.1)
1	77 (22.1)
2a	8 (2.3)
2b	33 (9.4)
2c	21 (6.0)
Stage (%)	
I	103 (26.5)
II	94 (24.2)
III	74 (19.1)
IV	77 (19.8)

Fig. 1.2 The incidence according to the men and women with oral squamous cell carcinoma in our department. The male-to-female ratio is 3:2, which is higher in males than in females

to this tendency, and it is estimated that the incidence rate of oral cancer is 0.5–5 % and the number of patients with oral cancer reaches 2.5 million in India [16–19]. Mortality rate from oropharyngeal cancer in Japan is lower than France and Italy, and this is considered because this is largely affected by food and life habitat [5].

Cancer registry is increasingly becoming popular, but still inadequate. Establishment of nationwide cancer registry in consideration of the Private Information Protection Law would be required.

1.3 Favorite Site

Favorite site of oral cancer is different depending on the race and lifestyle. We describe about frequency of oral cancer occurrence by sites in Japan in this section. The frequency of oral cancer occurrence by sites is different depending on the ethnic, country, region, lifestyle, and practice. According to a tally by the Japanese Society of Oral and Maxillofacial Surgeons in 2002, the occurrence frequency of oral cancer (n = 1,784) by sites was highest in the tongue and accounted for 40 % of the entire oral cancers [14], followed by the mandibular gingiva (20.3 %), maxillary gingiva (12.0 %), buccal mucosa (10.3 %), oral floor (9.2 %), maxillary antrum, and palate in Japan [5]. In the USA, the frequencies were reported as the tongue (35.2 %), oral floor (28.0 %), mandibular and maxillary gingiva (10.4 %), hard palate (8.9 %), and buccal mucosa (2.9 %) [10]. Eighty percent of tongue cancer tends to occur at the lingual border, and it is exceptionally rare to occur at the apex or back of tongue. For gingiva, research has still not shown that the occurrence frequencies are different between the maxilla and mandible. The occurrence frequency in our department was also in the order of the tongue, mandibular gingiva, oral floor, buccal mucosa, maxillary gingiva, palate, and lips, in which percentages almost

patients were 517 (29.1 %), and patients of 50 years old and older account for 80 % of the total patients. In the present day seeing the super-aged society, it is estimated that the number of old–old patients would increase furthermore. Although it was previously considered that the development of oral cancer in 30's and younger is rare, increase in 20's patients is reported in these years. Effects of lifestyle, living environment, chemical factors, viruses, and bacteria are considered. Clinical characteristics with recently 10-year oral cancer patients in our department are shown in Table 1.1 and Figs. 1.2, 1.3, and 1.4.

The incidence of oral cancers is high in countries with a higher rate of both smoking and drinking habit [10, 15], especially high in south Asian countries. It is considered that a habit of chewing tobacco such as betel nut highly contributes

Men
Women

Men: 19-94 yrs, mean: 62.7 yrs
Women: 26-94 yrs, mean: 62.9 yrs

Fig. 1.3 The age distribution according to the men and women with oral squamous cell carcinoma in our department. Age-adjusted prevalence of oral cancer is highest in the 1960s similar to other cancers

Stage I   93.7 %
Stage II   86.4 %
Stage III 87.0 %
Stage IV   73.0 %

Maxillary gingiva   93.1 %
Tongue   86.3 %
Palate   82.4 %
Oral floor   85.7 %
Mandibular gingiva 78.5 %
Buccal mucosa   76.7 %

Fig. 1.4 The 5-year survival rate according to stage and site of the oral squamous cell carcinoma in our department
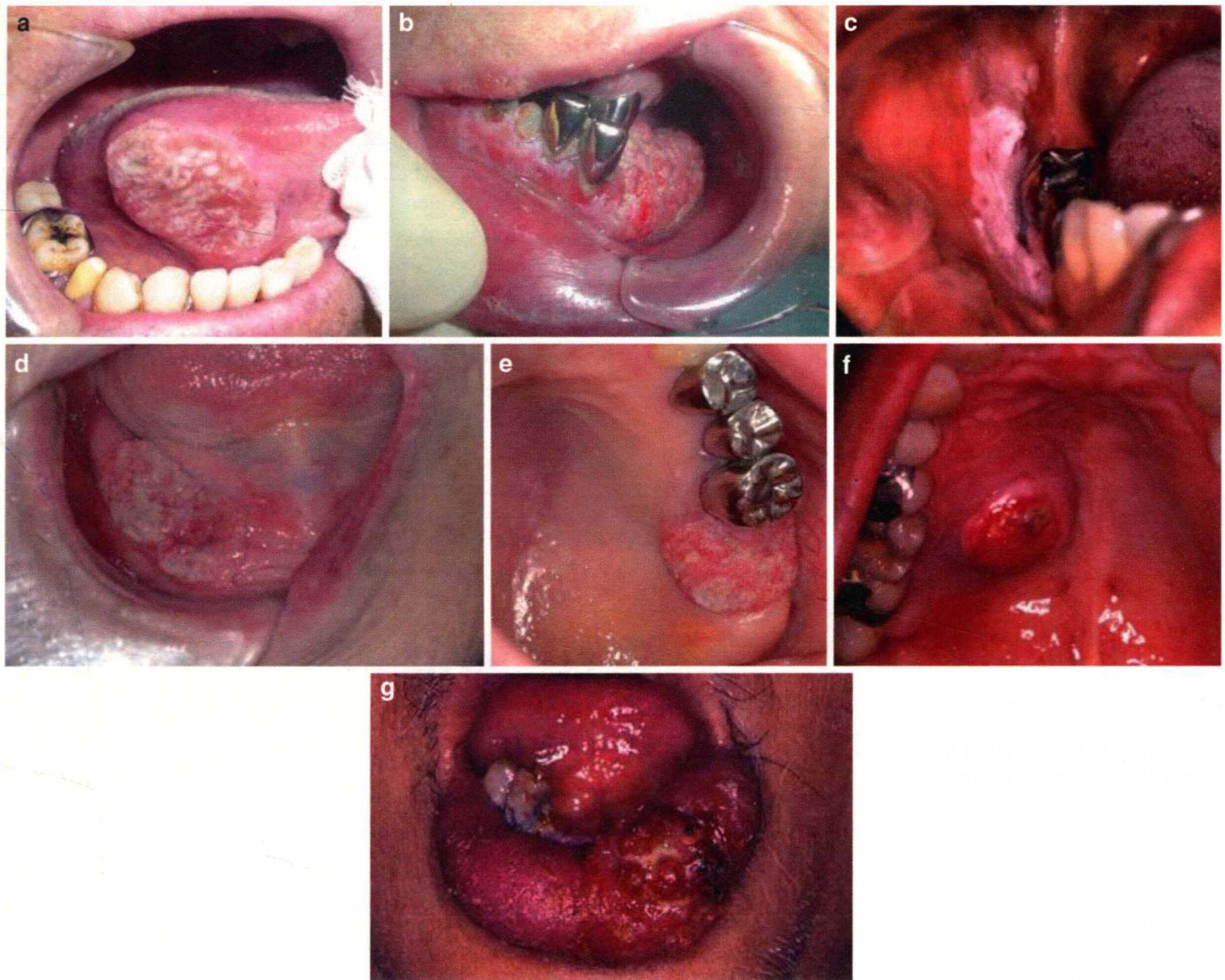
Fig. 1.5 Favorite site of oral cancer. (**a**) Tongue cancer. (**b**) Mandibular gingival cancer. (**c**) Buccal mucosa cancer. (**d**) Oral floor cancer. (**e**) Maxillary gingival cancer. (**f**) Palate cancer. (**g**) Lower lip cancer

corresponded to the statistics published from other facilities (Table 1.1). Characteristics by sites of occurrence are summarized as below:

1. Tongue cancer (Fig. 1.5a)
   (a) Tongue cancer accounts for 40 % of the entire oral cancers and makes up the majority of the oral cancers.
   (b) Tongue cancer occurs more commonly at the lingual border or inferior surface of tongue and occurs only infrequently at the apex or back of tongue.
   (c) Advanced tongue cancer spreads over the oral floor and tongue base and causes adhesion, lingual movement disorder, dysmasesis, dysphagia, dysarthria, and trismus, and it results in respiratory distress when it progresses to the pharyngeal region.

2. Mandibular gingival cancer (Fig. 1.5b)
   (a) Mandibular gingival cancer accounts for 20 % of the oral cancers and occurs in the next highest number after tongue cancer.

(b) It is often detected through symptoms such as inadaptation of denture, swelling or ulcer formation of gingiva, or tooth movement.
   (c) It is often treated with misdirected therapy including tooth extraction, anti-inflammation treatment, and adjustments to denture without aim based on the diagnosis of periodontal diseases and stomatitis.
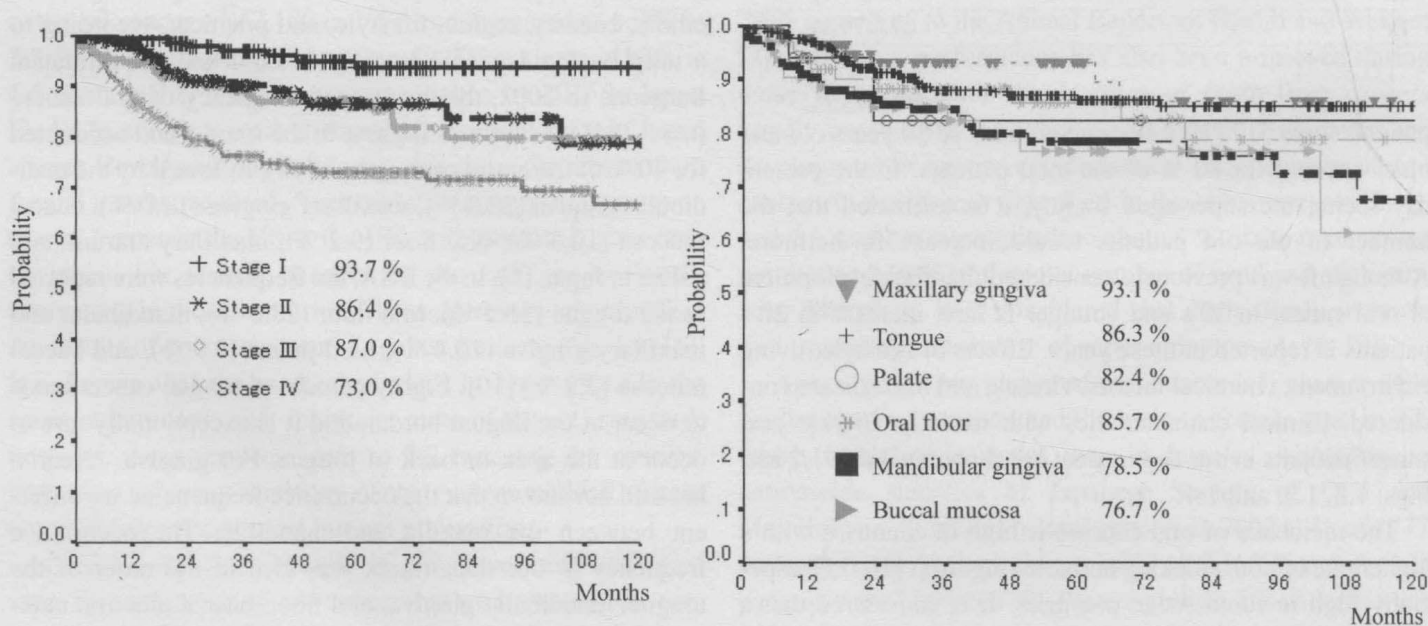   (d) Mandibular gingival cancer is likely to cause destruction and absorption of the mandibular bone in relatively early stage because the tumor becomes infiltrated along the periosteum. Infiltration is categorized into three types, pressure type, invasive type, and moth-eaten type based on its characteristics.

3. Buccal mucosa cancer (Fig. 1.5c)
   (a) The frequency of buccal mucosa cancer is only about 10 % in Japan, but is highest, about 50 %, in India. It is believed that the reason of such a high rate in India is caused by betel nut and chewing tobacco, which are key carcinogenic factors.

(b) Buccal mucosa cancer occurs more commonly in buccal mucosal surface facing to the molar tooth region and in the distomolar region.

(c) Most of the cancers are well-differentiated type and often associated with leukoplakia.

4. Oral floor cancer (Fig. 1.5d)

(a) The frequency of oral floor cancer is about 10 % and relatively low. Patients become aware of mass formation associated with ulcer and induration of the oral floor in many cases.

(b) Oral floor cancer infiltrates into the opening or duct of the submandibular gland and may be associated with excretory disturbance of saliva or swelling of the submandibular gland.

(c) Oral floor cancer can spread to the tongue and gingiva or adhere to periosteum of the jawbone or infiltrate into suprahyoid muscles, which form the oral floor, relatively early in the course because the oral floor is close to the tongue, gingiva, and mandible.

(d) Patients have marked pain and a feeling of strangeness during eating and talking and also easily develop inadaptation of denture.

5. Maxillary gingival cancer (Fig. 1.5e) and maxillary sinus cancer

(a) Maxillary cancer consists of maxillary gingival cancer, which develops from the gingiva, and maxillary sinus cancer, which occurs primarily in the maxillary sinus mucosa. The frequency of oral floor cancer is about 10 % and relatively low.

(b) Subjective symptoms of maxillary gingival cancer include swelling, ulcer, and pain, but few tooth pain occurs. When advanced, the cancer infiltrates and destroys the buccal and palatine mucosa, as well as the nasal cavity and maxillary sinus floor.

(c) Subjective symptoms of maxillary sinus cancer are mainly nasal symptoms, such as nasal congestion,

rhinorrhea, and nasal bleeding; oral symptoms, such as tooth pain, tooth movement, and swelling of the palate; and swelling of the cheek. If the cancer spreads into the orbit, exophthalmos, double vision, and visual impairment occur.

6. Palate cancer (Fig. 1.5f)

(1) The frequency of palate cancer is about 2 % and low. The site of onset is the hard palate by gingiva in general; however, the cancer crosses over the midline or results in absorption and destruction of the soft palate, gingiva, or palatal bone in advanced cases.

(b) Subjective symptoms are mainly swelling of the palate region and followed by ulcer and pain.

7. Lip cancer (Fig. 1.5g)

(a) The frequency of lip cancer is about 1 % and lowest.

(b) Lip cancer occurs more commonly in the lower lip and develops ulcers and swelling relatively early in the course.

1.4 Risk Factors and Prevention of Oral Cancer

1. Risk factors of oral cancer

A number of risk factors of oral cancer have been reported [21, 22]. Risk factors of oral cancer reported up to the present are summarized in Fig. 1.6. Surprisingly, however, only few factors have been epidemiologically or experimentally established. In addition, it is widely recognized as an underlying concept that oral cancer is very unlikely to develop with single factor and is caused by overlapping several factors in multistages. Especially smoking and drinking are representative risk factors of oral cancer, which are epidemiologically and experimentally established.

1 Smoking
2 Drinking
3 Physical stimuli (tilted tooth, caries, poor fillings, poorly-fitting denture)
4 Chemical stimuli (spices, high-salt food etc.)
5 Mucosal damage due to inflammation (periodontitis, maxillary sinusitis)
6 Virus infection (hepatitis viruses, HPV etc.)
7 Age

Fig. 1.6 Risk factors of oral cancer

Fig. 1.7 Chewing tobacco and betel nut in Taiwan. Betel nut and chewing tobacco, which are key carcinogenic factors in buccal mucosa cancer

2. Smoking and oral cancer

   There are no other risk factors like smoking in which causal association with cancer has been clearly established. Now, tobacco could be said to be an enemy of every disease to put it in extreme terms. Smoking is a luxury item, which also has the highest causal relation with carcinogenesis in oral cancer.

   The occurrence frequency of oral cancer is extremely high in Sri Lanka, India, or Taiwan as compared with Japan, and about 30 % of the entire cancer is oral cancer. It has been epidemiologically shown that such high occurrence of oral cancer is caused by a habit of chewing tobacco and betel nut (Fig. 1.7) [21]. The Declaration of Opposition to Smoking is adopted by about 40 academic societies including the Japanese Society of Oral and Maxillofacial Surgeons at the present day and supports promotion of the antismoking movement in Japan. It is indisputable that smoking is the largest factor for the prevention of oral cancer. A number of studies on carcinogenicity of smoking have been conducted since the mid-1900s, and it has been demonstrated that there are a number of substances that act as initiators or promoters in the carcinogenic process in about 4,000 kinds of chemical substances contained in cigarette smoke [23]. About 40 substances including benzopyrene and nitrosamines have been identified as carcinogenesis-related substances to date [23]. In addition, it is considered that oral cancer, pharyngeal cancer, laryngeal cancer, esophageal cancer, gastric cancer, pancreatic cancer, liver cancer, kidney cancer, bladder cancer, and uterine cancer are associated with smoking. Recently, smoking rate of Japanese is on a declining trend. However, it is pointed out that an increasing tendency is observed in only young females.

3. Drinking and oral cancer

   Drinking is a factor, which causation with oral cancer has been demonstrated similar to smoking. Different from tobacco, alcohol (= ethanol) itself has no carcinogenicity. However, it has been clarified in many studies that alcohol is indirectly associated with carcinogenesis. Moreover, a synergistic effect due to concomitant exposure to drinking and smoking often becomes a problem. Drinking and smoking cause exposure of carcinogenic factors to all pharynx, larynx, esophagus, and stomach in addition to the oral cavity at the same time (field cancerization); therefore, this is also related to the development of double cancer. According to our department, double cancers with upper digestive tract cancer were observed in 10.4 % of the entire oral cancer patients [24].
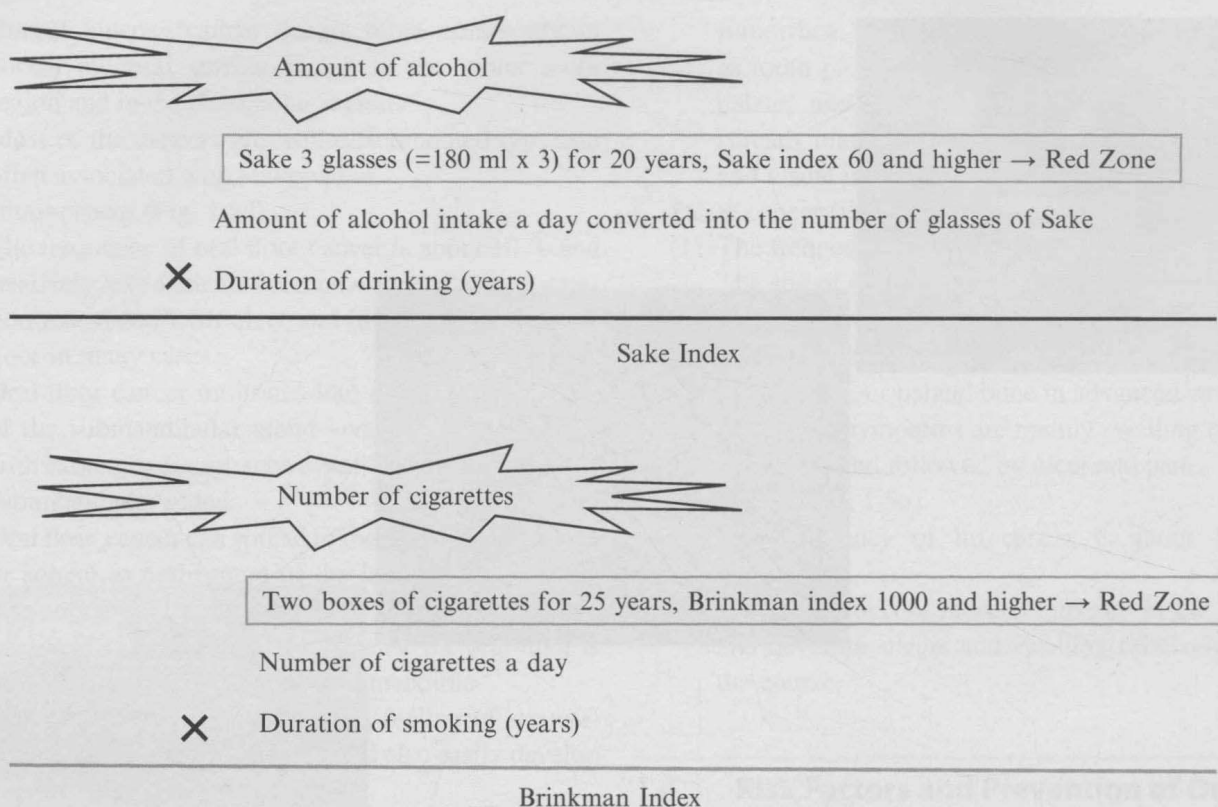
Amount of alcohol

Sake 3 glasses (=180 ml x 3) for 20 years, Sake index 60 and higher → Red Zone

Amount of alcohol intake a day converted into the number of glasses of Sake

✕ Duration of drinking (years)

Sake Index

Number of cigarettes

Two boxes of cigarettes for 25 years, Brinkman index 1000 and higher → Red Zone

Number of cigarettes a day

✕ Duration of smoking (years)

Brinkman Index

Fig. 1.8 Oral cancer risk and Sake and Brinkman indices. Sake index that is 60 or higher and Brinkman index that is 1,000 or higher are defined as the risk zones

The carcinogenic mechanism of alcohol was poorly understood until recently in contrast to tobacco. There is no report of carcinogenesis induced by only alcohol administration in animal experiments. However, International Agency for Research on Cancer (IARC) recognized alcohol as a carcinogen because acetaldehyde, which is a metabolic product of alcohol, has carcinogenicity [25]. In other words, the carcinogenic mechanism may directly or indirectly interact with biological reactions. As direct interaction, metabolic enzymes localizing in the oral mucosa degrade alcohol, and it causes exposure of the mucosa to acetaldehyde. Homann et al. [26] reported that bacteria existing inside the oral cavity increase carcinogenic risk of oral cancer by degradation of alcohol to acetaldehyde. As indirect interaction, it is considered that effects of alcohol include effect of acetaldehyde metabolized in the liver on local mucosa, effect as a solvent of carcinogens derived from tobacco and others, decrease of metabolic function of the liver, decrease of immunological capacity due to alcohol ingestion, and lowering of nutritional status.

4. Epidemiology of smoking and drinking

As the results of a meta-analysis of reports on a large-scale epidemiological studies, IARC concluded that smoking and drinking are distinct risk factors of oral cancer [25]. Of course, the more daily consumption of as well as longer exposure time to smoking and drinking

result in increase of carcinogenic risk. Accordingly, an index that takes account of them has an important implication. Brinkman index and Sake index shown in Fig. 1.8 are widely used to express relationship between the amount and duration of smoking and drinking with oral cancer. Sake index that is 60 or higher and Brinkman index that is 1,000 or higher are defined as the risk zones (Fig. 1.8). However, pack-years is used as a new smoking index instead of Brinkman index in recent years. This index is calculated by dividing Brinkman index by 20.

Based on the above findings, we conducted a case–control study in 191 patients with oral cancer and 121 healthy subjects with no oral mucosal diseases who visited our department [27]. The results of multiple logistic analysis on risk for the development of oral cancer are shown in Table 1.4. Risk of developing oral cancer (odds ratio) by smoking alone was 2.5, but it elevated to 4.3 in heavy smokers with Brinkman index 1,000 or higher. In addition, odds ratio of drinking alone was 4.5; however, it elevated to 10.4 in heavy drinker with Sake index 60 or higher. When subjects have a habit of smoking and drinking, the risk of developing oral cancer resulted in 4.8, which was higher than smoking or drinking alone. In other words, it is considered that the risk of oral cancer is high in people with Brinkman index 1,000 or higher and Sake index 60 or higher and especially high in people who have both smoking and drinking habits.

Table 1.2 Oral cancer risk in smoking and drinking-related metabolic genes

	Odds ratio (95 % confidence interval)
Patients with GSTM1 defect	2.5 (1.6–5.4)
Patients with ALDH2 hetero defect	2.9 (1.1–7.8)

Table 1.3 The risk of developing oral cancer in smoking and drinking

	Odds ratio (95 % confidence interval)
Smoking	2.5 (1.1–5.6)
B.I. 1,000~	4.3 (1.6–11.5)
Drinking	4.5 (2.5–8.1)
S.I. 60~	10.4 (3.6–29.4)
Smoking + drinking	4.8 (1.8–13.0)

B.I. Brinkman index, *S.I.* Sake index

5. Genotypic analysis of metabolic enzymes related to smoking and drinking

   Carcinogens accumulate in the body through tobacco use or alcohol ingestion and then are metabolized and detoxified. Recently, it is revealed that there are differences in individual's metabolic capability due to genetic variant of metabolic enzymes. In other words, it is speculated that the same loading from smoking and/or drinking may cause different degrees of carcinogenic risk in individuals because metabolic and detoxification capabilities against carcinogens vary considerably from individual to individual. Accordingly, we conducted an analysis of genes related to smoking and drinking in 127 patients with oral cancer and 33 healthy subjects with smoking and drinking habits, who preliminarily gave informed consent (Table 1.2) [27]. As a smoking-related enzyme, gene polymorphism of glutathione S-transferase M1 (GSTM1), which is an enzyme degrading benzopyrene in tobacco, was identified and analyzed with a multiple logistic analysis (Table 1.3) [27]. As a result, the risk of developing oral cancer in smokers with GSTM1 gene mutation was 2.5 times higher. Then aldehyde dehydrogenase 2 (ALDH2), which is an enzyme that degrades acetaldehyde, was identified and analyzed with a multiple logistic analysis. As a result, the risk of developing oral cancer in individuals with drinking habit with ALDH2 gene mutation (hetero deletion) was 2.9 times higher. Furthermore, an Italian research team recently conducted a meta-analysis of papers on ALDH2 gene polymorphism, including our report, and concluded that carcinogenic factor of drinking-related head and neck cancers is acetaldehyde [28]. Moreover, they also reported that higher alcohol consumption causes higher carcinogenic risk in ALDH2-deleted individuals [28].

   As mentioned above, the polymorphism pattern of metabolism-related genes may contribute to the identification of risk factors of oral cancer because the polymorphism pattern varies from individual to individual. New biomarkers would be discovered in the future, and the development of tailor-made prevention may be expected in this area.

6. Virus infection and oral cancer

   Several types of carcinogenesis caused by virus infection have been reported. For example, it is famous that hepatitis B virus and hepatitis C virus cause liver cancer and is also well known that adult T-cell leukemia (ATL) is caused by RNA virus (retrovirus). In the head and neck region, EB virus belonging to herpesvirus group causes Burkitt's lymphoma. In addition, it is reported that human papillomavirus (HPV) is associated with the development of oral cancer [29]. Recently HPV is watched with interest as the cause of oral cancer especially in young individuals with no risk factors of smoking and drinking.

7. Age and oral cancer

   Japan is becoming an unprecedented aging society with a falling birthrate in the world with progress of super-aging society and lowering of birthrate in these years. It is reported that oral cancer appears most frequently at 50 years old and older. However, it is considered that recent increasing tendency is due to the increasing number of the elderly.

8. Oral cancers in high-risk females (Figs. 1.9, 1.10, and 1.11)

   In general, it is believed that oral cancers are often found in middle-aged males and less frequent in females. It is presumed that this is greatly associated with having much stress from work in addition to lifestyle habits such as smoking and drinking. However, increase of female patients is recently being seen as a problem. There are more than a small number of female patients with no smoking/drinking history and no clear carcinogenic cause. There is a report that HPV, which is a cause of cervical cancer, is associated with carcinogenesis; however, concrete conclusion is still not obtained. Especially female patients need attention to aesthetic recovery in addition to functional aspect sufficiently taking into account the social background and living environment.

   We compared treatment results of males and females with oral cancer in recent two decades (the first 10 years and later 10 years were analyzed separately) in our department (Fig. 1.9). As a result, 5-year survival rate was lower in females (Fig. 1.10) than males (Fig. 1.11), and it was noted that the number of recurrence and metastasis was increased in females diagnosed with early cancer.

9. Young patients and oral cancer

   It has been known that oral cancer often occurs in males of 60 years and older; however, recently it is pointed out that the rate of oral cancer in young individuals and females is increasing [30–32]. There is no

Fig. 1.9 Five-year survival rate (whole men and women). The first 10 years and later 10 years were analyzed separately
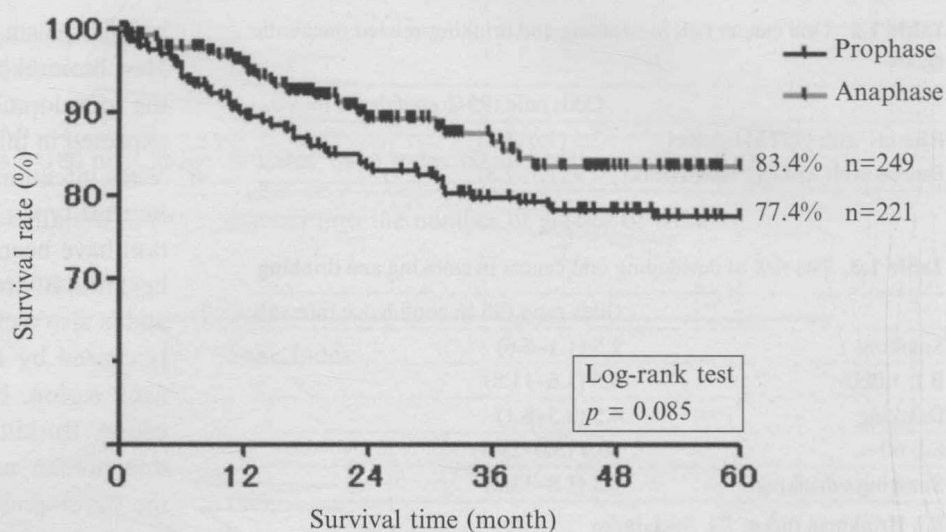

Log-rank test
$p = 0.085$

83.4% n=249
77.4% n=221

Fig. 1.10 Five-year survival rate (women). Five-year survival rate was lower in females than males

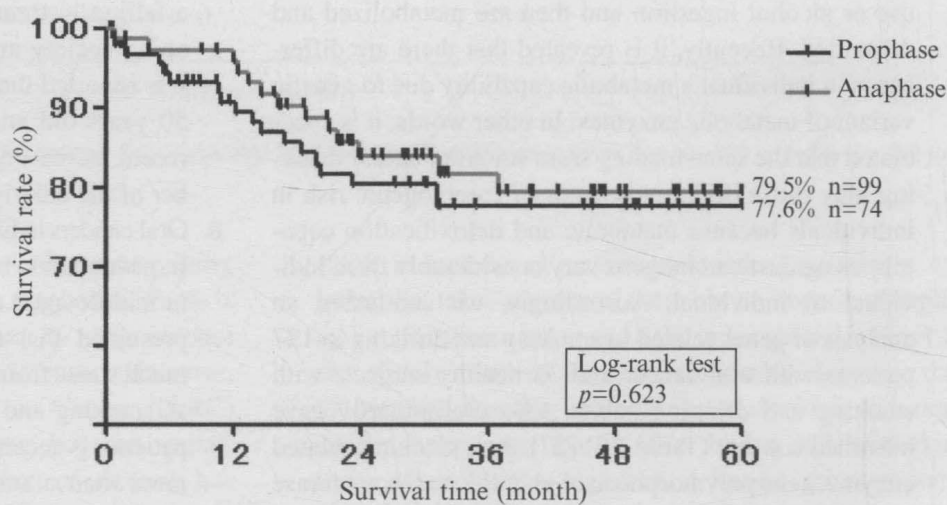Log-rank test
$p=0.623$

79.5% n=99
77.6% n=74

Fig. 1.11 Five-year survival rate (men). Five-year survival rate was lower in females than males

Log-rank test
$p = 0.063$

86.1% n=150
77.4% n=147