

Epidemiology of Hypopharyngeal and Oropharyngeal Cancers in Japan

Motoi Nishi

Motoi Nishi, Department of Fundamental Health Sciences, Health Sciences University of Hokkaido, Tobetsu, Hokkaido, Japan

Conflict-of-interest statement: The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Motoi Nishi, Department of Fundamental Health Sciences, Health Sciences University of Hokkaido, 1757 Tobetsu, Hokkaido, 061-0293 Japan.

Email: motoi@hoku-iryu-u.ac.jp

Telephone: +81-(0)133-23-1211

Fax: +81-(0)133-23-1669

Received: December 21, 2017

Revised: February 3, 2018

Accepted: February 6, 2018

Published online: March 23, 2018

ABSTRACT

BACKGROUND: Both hypopharyngeal cancer and oropharyngeal cancer are rare malignancies. However, it is reported that the incidences of these cancers have increased in Japan. It is known that smoking and drinking are risk factors for both cancers. Recently, human papillomavirus (HPV) is regarded as a risk factor for oropharyngeal cancer. In this article the changes in the mortality rates of these cancers are described from the viewpoint of descriptive epidemiology.

METHODS: The numbers of deaths due to the 2 cancers from 1979 to 2016 were obtained from the vital statistics of Japan. The numbers of persons in each of the years were obtained from the census and vital statistics of Japan.

RESULTS: For males, the ratio of the numbers of deaths from hypopharyngeal cancer/oropharyngeal cancer has been almost constant, at about 2. The crude mortality rate of hypopharyngeal cancer for males has been increasing. The rate in 2016 was about 9 times that in 1979. The male/female ratio has been increasing as well, which is due to the large increase for males and the small increase for females. The crude mortality rate of oropharyngeal cancer for males has been increasing. The rate in 2016 was more than 10 times that in 1979. In the group 50-59 years of age, the crude mortality rate of hypopharyngeal cancer for males has been almost constant. However, in the groups aged 70 years and older, it has been rapidly increasing. The changes in the crude mortality rates of oropharyngeal cancer were similar to those of hypopharyngeal cancer. In the group aged 50-59 years, the crude mortality rate remained stable. However, in the groups 70 years of age and older, it has been rapidly increasing. The age-adjusted mortality rate of hypopharyngeal cancer for males has been increasing, and there has been no clear sign of a decrease. The age-adjusted mortality rate of oropharyngeal cancer for males has been increasing as well, and there has been no sign of a decrease. While the smoking rate has been decreasing since 1966, the number of cigarettes per smoker per day was increasing during the period from 1960 to 2000. The percentage of heavy drinkers among the population remained almost stable.

CONCLUSIONS: For males, since the age-adjusted mortality rates of the 2 cancers have been increasing, it is certain that their incidences have been increasing. Their incidences may largely increase in older age groups. The contribution of the number of cigarettes per smoker to the pathogenesis of these 2 cancers may be larger than that of the smoking rate. The influence of HPV on oropharyngeal cancer was not apparent in the data for mortality rates.

Key words: Descriptive epidemiology; Hypopharyngeal cancer; Mortality; Oropharyngeal cancer, Vital statistics

© 2018 The Author(s). Published by ACT Publishing Group Ltd. All rights reserved.

Nishi M. Epidemiology of Hypopharyngeal and Oropharyngeal Cancers in Japan. *Journal of Tumor* 2018; 6(1): 504-509 Available from: URL: <http://www.ghrnet.org/index.php/jt/article/view/2233>

INTRODUCTION

Both hypopharyngeal cancer and oropharyngeal cancer are rare malignancies. In Japan in 2015, the former accounted for 0.41% of the total deaths due to cancer, and the latter 0.25%. Though their precise etiologies remain unknown, it is almost certain that tobacco and alcohol raise their risks^[1] and there is interaction between the cumulative exposures to smoking and alcohol and the risk of cancers of the upper aerodigestive tract^[2]. In the Netherlands, the incidence of oropharyngeal cancer increased between 1989 and 2006^[3]. In Scotland, its incidence continues to rise^[4]. Recently, based on the data of the cancer registry in Osaka, Japan, it is reported that the incidences of both hypopharyngeal and oropharyngeal cancers increased^[5], especially for males^[6]. In this article, the changes in the mortality rates of these cancers and related matters are described from the viewpoint of descriptive epidemiology.

MATERIALS AND METHODS

In Japan, the ICD9 was used from 1979 to 1994, and the ICD10 has been used since 1995. The codes for hypopharyngeal cancer are 148 in the ICD 9 and C13 in the ICD10. Those for oropharyngeal cancer are 146 and C10, respectively. The numbers of deaths due to the 2 cancers in 5-year age categories were obtained from the vital statistics of Japan for the period from 1979 through 2016. The numbers of persons in 5-year age categories in each of the years were obtained from the census and the vital statistics of Japan. To calculate the age-adjusted mortality rates from 1979 to 2016, the model population in Japan in 1985 (0-4, 5-9, 10-14, etc. to 80-84 and 85 years of age or older) was employed. For the statistical test of the correlation coefficient (Pearson), t-distribution was employed.

RESULTS

1. Numbers of deaths due to hypopharyngeal and oropharyngeal cancers (Table 1)

(1) **Hypopharyngeal cancer.** The numbers of deaths from hypopharyngeal cancer have been increasing for both sexes. That for males in 2016 was about 10 times that in 1979. That for females increased as well, but not so drastically.

(2) **Oropharyngeal cancer.** The numbers of deaths of oropharyngeal cancer have been increasing for both sexes. That for males in 2016 was more than 11 times that in 1979, whereas that for females increased modestly.

(3) **Ratio of hypopharyngeal cancer/oropharyngeal cancer.** For males, the ratio of the numbers of deaths from hypopharyngeal cancer/oropharyngeal cancer has been almost constant, at about 2.

2. Crude mortality rates of hypopharyngeal and oropharyngeal cancers (Table 2)

(1) **Hypopharyngeal cancer.** The crude mortality rate of hypopharyngeal cancer for males has been increasing. The rate in 2016 was about 9 times that in 1979. The male/female ratio has been increasing as well, which is due to the large increase for males and the small increase for females.

(2) **Oropharyngeal cancer.** The crude mortality rate of oropharyngeal cancer for males has been increasing. The rate in 2016 was more than 10 times that in 1979. The male/female ratio was around 5-6.

3. Crude mortality rates of hypopharyngeal and oropharyngeal cancers in 5-year age categories

(1) **Hypopharyngeal cancer (Figures 1 and 2).** The crude mortality rates of hypopharyngeal cancer for males in 5-year age categories are shown in Figure 1 (50-69 years of age) and Figure 2 (70 years of age and older). In the group 50-59 years of age, the crude mortality rate has been almost constant. However, in the groups aged 70 years and older, it has been rapidly increasing.

(2) **Oropharyngeal cancer (Figures 3 and 4).** The changes in the crude mortality rates of oropharyngeal cancer were similar to those of hypopharyngeal cancer. In the group aged 50-59 years, the crude mortality rate remained stable. However, in the groups 70 years of age and older, it has been rapidly increasing. Using the data shown in Figures 1-4, correlation coefficients (year at death vs. crude mortality rate) were calculated (Table 3). For both cancers correlation coefficients increased as the age increased. Based on the data shown in Figures 1-4, the X coefficient and the Y intercept of a formula for each of the regression lines were calculated (Table 4). For both cancers, the X coefficient increased and the Y intercept decreased as age increased. That is, the slope of the regression lines became steeper.

4. Age-adjusted mortality rates of hypopharyngeal and oropharyngeal cancers (Table 5)

For males, the age-adjusted mortality rate of hypopharyngeal cancer has been increasing. In 2012 it reached 12.2 per million, and there has been no clear sign of a decrease. The ratio of males/females has also been increasing. This is because the age-adjusted mortality rate for females has remained almost constant.

For males, the age-adjusted mortality rate of oropharyngeal cancer has been increasing as well, and in 2016 it reached 7.66. There has been no sign of a decrease.

5. Number of cigarettes consumed per smoker per day

The Ministry of Health, Labor and Welfare reports the annual amounts of cigarettes sold (<http://www.health-net.or.jp/tobacco/product/pd070000.html>). Using these data, the numbers of persons (20 years of age or older) and the smoking rates, the annual number of cigarettes consumed per smoker per day was calculated (Table 6). It has been increasing.

6. Percentage of heavy drinkers

Using the number of heavy drinkers (drinking 150 mL/day or more alcohol) in the report by Tanaka^[7] and the numbers of persons (20 years old or older), the annual percentage of heavy drinkers was calculated (Table 7). Since 1970, it has been almost constant.

DISCUSSION

According to a study in Japan whose subjects were 722 patients with hypopharyngeal cancer, the overall 5-year survival rate has been improving from 34% (1993-1997), to 39% (1998-2002), 54% (2003-2007) and 60% (2008-2012)^[8].

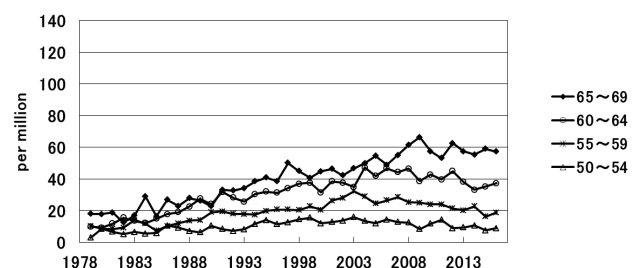


Figure 1 Crude mortality rate of hypopharyngeal cancer (male, 50-69 yrs).

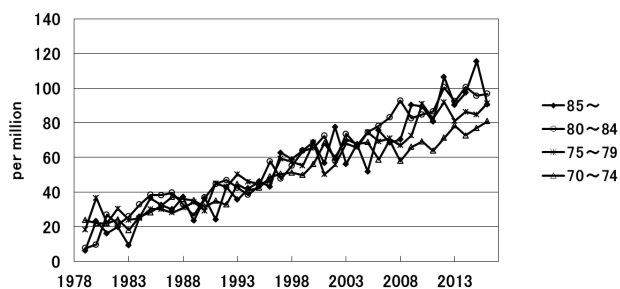


Figure 2 Crude mortality rate of hypopharyngeal cancer (male, 70- yrs).

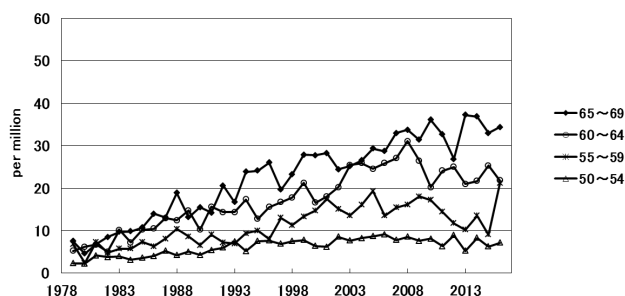


Figure 3 Crude mortality rate of oropharyngeal cancer (male, 50-69 yrs).

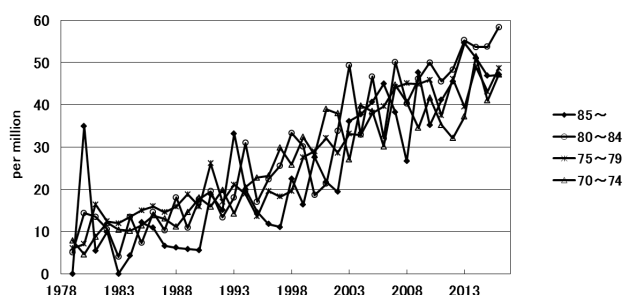


Figure 4 Crude mortality rate of oropharyngeal cancer (male, 70- yrs).

In a study of 38 patients with oropharyngeal cancer who were newly diagnosed from 1978 to 1985, the overall 5-year survival rate was 34%^[9]. In another study of 95 patients with oropharyngeal cancer who were newly diagnosed from 1971 to 1990, the overall 5-year survival rate was 42%^[10]. According to a study in Japan whose subjects were 523 patients with oropharyngeal cancer who were newly diagnosed from 2005 to 2007, the overall 5-year survival rate was 69.9%^[11].

Thus, in Japan, the prognoses for the present 2 cancers have been improving. Since their age-adjusted mortality rates have been increasing, it is also certain that their incidences have been increasing.

Since the percentage of heavy drinkers has been almost stable, smoking may have a large contribution to the increase in the age-adjusted mortality rates of the 2 cancers. In Japan, after World War 2, the age-adjusted mortality rate of lung cancer for males increased, but after 1995, it has been decreasing^[12]. On the other hand, the peak of the smoking rate was recorded in 1966^[12]. Thus, there is a time lag of 30 years between the peak of the age-adjusted mortality rate of lung cancer and that of the smoking rate. However, the age-adjusted mortality rates of the present 2 cancers have not yet begun to decrease. Consequently, it is possible that the latent periods of the 2 cancers are longer than that of lung cancer.

The smoking rate has been decreasing, but the number of cigarettes per smoker has been increasing. However, the number of cigarettes per smoker is not involved in calculating the smoking rate. It is also

Table 1 Number of deaths due to hypopharyngeal and oropharyngeal cancers.

Year	Hypopharyngeal cancer		Oropharyngeal cancer		Ratio (Hypo/Oro)	
	male	female	male	female	male	female
1979	149	73	74	23	2.01	3.17
1980	183	55	66	20	2.77	2.75
1981	188	55	105	19	1.79	2.89
1982	185	81	100	18	1.85	4.50
1983	208	76	109	21	1.91	3.62
1984	238	78	112	17	2.13	4.59
1985	234	63	135	25	1.73	2.52
1986	302	65	152	22	1.99	2.95
1987	315	80	165	44	1.91	1.82
1988	346	74	195	37	1.77	2.00
1989	366	62	205	26	1.79	2.38
1990	396	73	191	33	2.07	2.21
1991	479	94	242	30	1.98	3.13
1992	459	81	240	24	1.91	3.38
1993	519	118	248	33	2.09	3.58
1994	558	84	303	32	1.84	2.63
1995	611	92	298	33	2.05	2.79
1996	636	110	328	32	1.94	3.44
1997	740	104	351	44	2.11	2.36
1998	764	103	385	51	1.98	2.02
1999	788	103	450	52	1.75	1.98
2000	830	110	442	64	1.88	1.72
2001	904	107	486	56	1.86	1.91
2002	901	122	503	73	1.79	1.67
2003	1024	114	534	80	1.92	1.43
2004	1063	110	586	87	1.81	1.26
2005	1085	133	655	91	1.66	1.46
2006	1106	131	598	109	1.85	1.20
2007	1181	112	722	98	1.64	1.14
2008	1189	147	727	117	1.64	1.26
2009	1235	126	718	128	1.72	0.98
2010	1311	103	743	133	1.76	0.77
2011	1259	121	697	112	1.81	1.08
2012	1411	127	707	114	2.00	1.11
2013	1351	125	740	135	1.83	0.93
2014	1373	138	855	140	1.61	0.99
2015	1415	123	780	162	1.81	0.76
2016	1440	149	889	145	1.62	1.03

possible, therefore, that the contribution of the number of cigarettes per smoker to the pathogenesis of these 2 cancers may be larger than that of the smoking rate.

For males, in the groups aged 70 years and older, rapid increases in the crude mortality rates were observed for the present 2 cancers. The increases as a whole are mainly due to the increases in these age groups. It is difficult to explain why the increase in the crude mortality rate is rapid in older age groups. The life expectancy of Japanese people is becoming longer. For example, for males in 1955 it was 63.60 years, and then rose to 74.78 in 1985 and 80.75 in 2015. As a result, the number of aged persons is increasing. It is possible that among them there are not a few who have smoked heavily since their youth, and their risk for the present 2 cancers would thus be high.

Table 2 Crude mortality rates of hypopharyngeal and oropharyngeal cancers (per million) .

Year	Hypopharyngeal cancer			Oropharyngeal cancer		
	male	female	ratio (M/F)	male	female	ratio (M/F)
1979	2.62	1.25	2.10	1.3	0.39	3.33
1980	3.2	0.93	3.44	1.15	0.34	3.38
1981	3.26	0.92	3.54	1.82	0.32	5.69
1982	3.19	1.35	2.36	1.72	0.3	5.73
1983	3.56	1.26	2.83	1.87	0.35	5.34
1984	4.05	1.28	3.16	1.9	0.28	6.79
1985	3.96	1.03	3.84	2.29	0.41	5.59
1986	5.08	1.06	4.79	2.56	0.36	7.11
1987	5.27	1.29	4.09	2.76	0.71	3.89
1988	5.77	1.19	4.85	3.25	0.6	5.42
1989	6.08	1	6.08	3.41	0.42	8.12
1990	6.57	1.17	5.62	3.17	0.53	5.98
1991	7.93	1.5	5.29	4	0.48	8.33
1992	7.57	1.29	5.87	3.96	0.38	10.42
1993	8.55	1.87	4.57	4.08	0.52	7.85
1994	9.17	1.33	6.89	4.98	0.51	9.76
1995	10.03	1.45	6.92	4.89	0.52	9.40
1996	10.41	1.73	6.02	5.37	0.5	10.74
1997	12.09	1.63	7.42	5.73	0.69	8.30
1998	12.46	1.61	7.74	6.28	0.8	7.85
1999	12.84	1.61	7.98	7.33	0.81	9.05
2000	13.5	1.72	7.85	7.19	1	7.19
2001	14.68	1.66	8.84	7.89	0.87	9.07
2002	14.63	1.89	7.74	8.17	1.13	7.23
2003	16.62	1.77	9.39	8.67	1.24	6.99
2004	17.26	1.7	10.15	9.51	1.35	7.04
2005	17.61	2.06	8.55	10.63	1.41	7.54
2006	17.96	2.03	8.85	9.71	1.69	5.75
2007	19.2	1.73	11.10	11.74	1.52	7.72
2008	19.36	2.28	8.49	11.84	1.81	6.54
2009	20.13	1.95	10.32	11.71	1.99	5.88
2010	21.29	1.59	13.39	12.07	2.05	5.89
2011	20.49	1.87	10.96	11.34	1.73	6.55
2012	23.01	1.97	11.68	11.53	1.76	6.55
2013	22.08	1.94	11.38	12.09	2.09	5.78
2014	22.49	2.14	10.51	14.01	2.17	6.46
2015	23.19	1.91	12.14	12.78	2.52	5.07
2016	23.66	2.32	10.20	14.61	2.26	6.46

Table 3 Correlation coefficients (year at death vs. crude mortality rate).

Age	Hypopharyngeal cancer	Oropharyngeal cancer
50-54	0.527	0.786
55-59	0.750	0.784
60-64	0.879	0.901
65-69	0.954	0.956
70-74	0.965	0.940
75-79	0.964	0.945
80-84	0.974	0.933
85~	0.949	0.851

All of them are significant ($p < 0.05$)

Table 4 X coefficient and Y intercept of regression lines (year at death vs. crude mortality rate).

Age	Hypopharyngeal cancer		Oropharyngeal cancer	
	X coefficient	Y intercept	X coefficient	Y intercept
50-54	0.16	-299.7	0.14	-271.7
55-59	0.44	-851.9	0.32	-629.4
60-64	0.90	-1759.6	0.57	-1117.0
65-69	1.32	-2603.7	0.82	-1621.8
70-74	1.65	-3236.6	1.10	-2164.7
75-79	1.94	-3817.4	1.12	-2206.2
80-84	2.33	-4606.6	1.39	-2750.7
85~	2.42	-4771.3	1.25	-2481.2

Table 5 Age-adjusted mortality rates of hypopharyngeal and oropharyngeal cancers (per million).

Year	Hypopharyngeal cancer			Oropharyngeal cancer		
	male	female	ratio (M/F)	male	female	ratio (M/F)
1979	3.35	1.32	2.54	1.64	0.41	4.00
1980	4.01	0.96	4.18	1.55	0.34	4.56
1981	4.01	0.93	4.31	2.22	0.32	6.94
1982	3.9	1.34	2.91	2.05	0.29	7.07
1983	4.14	1.21	3.42	2.16	0.34	6.35
1984	4.72	1.21	3.90	2.17	0.26	8.35
1985	4.53	0.93	4.87	2.54	0.37	6.86
1986	5.59	0.95	5.88	2.79	0.31	9.00
1987	5.63	1.13	4.98	2.88	0.6	4.80
1988	5.99	1	5.99	3.33	0.5	6.66
1989	6.09	0.8	7.61	3.36	0.35	9.60
1990	6.36	0.93	6.84	3.1	0.41	7.56
1991	7.44	1.19	6.25	3.78	0.38	9.95
1992	6.94	1	6.94	3.64	0.27	13.48
1993	7.71	1.39	5.55	3.65	0.38	9.61
1994	8.01	0.93	8.61	4.31	0.36	11.97
1995	8.51	1.03	8.26	4.13	0.35	11.80
1996	8.62	1.21	7.12	4.44	0.33	13.45
1997	9.72	1.04	9.35	4.63	0.47	9.85
1998	9.79	1.03	9.50	4.93	0.52	9.48
1999	9.83	0.98	10.03	5.61	0.51	11.00
2000	10.03	1	10.03	5.38	0.63	8.54
2001	10.64	1.04	10.23	5.69	0.53	10.74
2002	10.25	1.16	8.84	5.8	0.69	8.41
2003	11.44	1.01	11.33	6	0.7	8.57
2004	11.46	1.02	11.24	6.38	0.71	8.99
2005	11.38	1.15	9.90	6.92	0.72	9.61
2006	11.44	0.99	11.56	6.22	0.9	6.91
2007	11.76	0.94	12.51	7.27	0.83	8.76
2008	11.58	1.16	9.98	7.28	0.93	7.83
2009	11.66	1.08	10.80	6.9	1.04	6.63
2010	12.1	0.81	14.94	7.05	1.06	6.65
2011	11.56	0.91	12.70	6.51	0.85	7.66
2012	12.2	0.96	12.71	6.39	0.87	7.34
2013	11.64	0.93	12.52	6.32	1.01	6.26
2014	11.53	1.02	11.30	7.34	1.04	7.06
2015	11.38	0.89	12.79	6.53	1.11	5.88
2016	11.62	1.01	11.50	7.66	1	7.66

Table 6 Number of cigarettes consumed per smoker per day.

Year	Smoking rate (%)		Population (≥20 yrs.)		Number of smokers			Number of cigarettes	Number of cigarettes
	male	female	male	female	male	female	total	sold (100 million)	(per smoker per day)
1960	81	14	26864468	29178889	21760219	4085044	25845264	1227.6	13.0
1965	82.3	15.7	29951342	32305549	24649954	5071971	29721926	1714.49	15.8
1970	77.5	15.6	33463043	36012633	25933858	5617971	31551829	2221.32	19.3
1975	76.2	15.1	36860218	39464148	28087486	5959086	34046572	2898.42	23.3
1980	70.2	14.4	38995839	41783867	27375079	6016877	33391956	3039.74	24.9
1985	64.6	13.7	41258800	44168300	26653185	6051057	32704242	3032	25.4
1990	60.5	14.3	43655387	46695943	26411509	6677520	33089029	3220	26.7
1995	58.8	15.2	46394896	49544686	27280199	7530792	34810991	3347	26.3
2000	53.5	13.7	48276508	51551056	25827932	7062495	32890426	3245	27.0

Table 7 Number and percentage of heavy drinkers.

Year	Number	Percentage*
1965	1030000	1.8
1970	1400000	2.2
1975	1705000	2.5
1980	1905000	2.5
1985	2023000	2.5
1990	2058000	2.4
1995	2316000	2.6
1999	2270000	2.4

*Percentage within population aged 20 yrs or older.

Recently, it was reported that the incidence of oropharyngeal cancer whose pathogenesis is human papillomavirus (HPV) is increasing in the USA, northern Europe, and Japan^[13-16]. HPV was detected in about 50% of 157 oropharyngeal squamous cell carcinoma patients according to a recent multicenter study in Japan^[16]. In the US, the incidence increased significantly among persons aged 40-59 years^[13]. However, as far as the present results are concerned, the crude mortality for persons 50-59 years of age was almost stable. It is mainly oropharyngeal cancer in which HPV is involved in the pathogenesis. For males, however, the ratio of the numbers from deaths of hypopharyngeal cancer/oropharyngeal cancer has been almost constant. These results might be explained by the fact that the prognosis for oropharyngeal cancer due to HPV is good^[17]. At present, the influence of HPV on oropharyngeal cancer is not apparent in the data on mortality.

REFERENCES

1. Maier H, Diez A, Gewelke U, Heller WD, Weidauer H. Tobacco and alcohol and the risk of head and neck cancer. *Clin Investig* 1992;70:320-327. [PMID: 1521046]
2. Schlecht NF, Franco EL, Pintos J, Negassa A, Kowalski LP, Oliveira BV, Curado MP. Interaction between tobacco and alcohol consumption and the risk of cancers of the upper aero-digestive tract in Brazil. *Am J Epidemiol* 1999;150:1129-1137. [PMID: 10588073]
3. Braakhuis BJJ, Visser O, Leemans CR. Oral and oropharyngeal cancer in The Netherlands between 1989 and 2006: increasing incidence, but not in young adults. *Oral Oncol* 2009;45:e85-89. [DOI: 10.1016/j.oraloncology.2009.03.010].
4. Robinson KL, Macfarlane GJ. Oropharyngeal cancer incidence and mortality in Scotland: are rates still increasing? *Oral Oncol* 2003;39:31-36. [PMID: 12457719]
5. Yoshino K. Epidemiology and clinical statistics of oropharyngeal and hypopharynx carcinoma. *Stomach Intestine* 2005;40:1229-1238. [DOI: 10.11477/mf.1403100148]
6. Tsukuma H, Ioka A, Ooshima A, Ajiki W. Cancer incidences and head and neck cancers in Japan. *Head Neck Cancer* 2006;32:292-299. [DOI: 10.5981/jjhnc.32.292]
7. Tanaka K. The development of policies and of issues for alcohol-related problems in Japan. *Segi Gakuen Kiyou* 2007;8:103-110. NAID: 110006337284
8. Suzuki M, Fujii T, Yoshii T, Otozai S, Kitamura K, Kanamura R, Omori Y, Minamino T. Trends in the detail of the stage and survival rate in hypopharyngeal cancer over 20 years. *J Otolaryngol Jpn* 2016;119:949-954. [DOI: 10.3950/jibiinkoka.119.949]
9. Koja S, Itokazu T. Treatment results of mesopharynx carcinoma. *Otologia Fukuoka* 1993;39:157-160. [DOI: 10.11334/jibi1954.39.2_157]
10. Tanaka S, Matsuoka H, Sakaguchi S, Hirano M. Results of treatment and control-of primary lesion in carcinoma of oropharynx. *Head Neck Cancer* 1993;19:249-253. [DOI: 10.5981/jjhnc1974.19.249]
11. Homma A, Hayashi R, Kawabata K, Yoshino K, Iwae N, Hasegawa Y, Kanou S, Nibu K, Kato T, Shiga K, Matsuura K, Kadota S, Fujii M. The current status of treatment for oropharyngeal cancer in Japan. *Head Neck Cancer* 2013;39:449-455. [DOI: 10.5981/jjhnc.39.449]
12. Nishi M. Lifestyle and cancer after the Second World War in Japan. *J Tumor* 2014;2:197-201. [DOI: 10.6051/j.issn.1819-6187.2014.02.48]
13. Chaturvedi AK, Engels EA, Anderson WF, Gillison ML. Incidence trends for human papillomavirus-associated and -unrelated oral squamous cell carcinomas in the United States. *J Clin Oncol* 2008;26:612-619. [PMID: 18235120]
14. Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, Xiao W, Kim E, Jiang B, Goodman MT, Sibug-Saber M, Cozen W, Liu L, Lynch CF, Wentzensen N, Jordan RC, Altekruze S, Anderson WF, Rosenberg PS, Gillison ML. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol* 2011;29:4294-4301. [DOI: 10.1200/JCO.2011.36.4596].
15. Hammarstedt L, Lindquist D, Dahlstrand H, Romanitan M, Dahlgren LO, Joneberg J, Creson N, Lindholm J, Ye W, Daliansis T, Munck-Wikland E. Human papillomavirus as a risk factor for the increase in incidence of tonsillar cancer. *Int J Cancer* 2006;119:2620-2623. [PMID: 16991119]; [DOI: 10.1002/ijc.22177]
16. Hama T, Tokumaru Y, Fujii M, Yane K, Okami K, Kato K, Masuda M, Mineta H, Nakashima T, Sugawara M, Sakihama N, Yoshizaki T, Hanazawa T, Kato H, Hirano S, Imanishi Y, Kuratomi Y, Otsuki N, Ota I, Sugimoto T, Suzuki S. Prevalence of human papillomavirus in oropharyngeal cancer: a multicenter study in Japan. *Oncology* 2014;87:173-182. [DOI: 10.1159/000360991]
17. Fakhry C, Westra WH, Li S, Cmelak A, Ridge JA, Pinto H,

Forastiere A, Gillison ML. Improved survival of patients with human papillomavirus–positive head and neck squamous cell carcinoma in a prospective clinical trial. JNCI 2008;100:261–269.

[DOI: 10.1093/jnci/djn011]

Peer Reviewer: Sherif Abdelwahab