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Second Primary Cancer Following Laryngeal Cancer with Special Reference to Smoking Habits

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The risk of developing a second primary cancer following laryngeal cancer was estimated by following-up 472 male laryngeal cancer patients for an average of 8.6 years by means of record linkage to the Osaka Cancer Registry. Of these patients, 115 developed a second cancer other than laryngeal cancer, whereas the expected number derived from the incidence rates among Osaka residents was 51.4 (relative risk (RR) = 2.2, 95% confidence interval = 1.85–2.69). Cumulative risk of developing a second primary cancer was estimated to be 31.1% at 15 years after laryngeal cancer. By site, the risks were significantly increased for tobacco-related cancers, RR = 24.5, 6.1 and 2.3 for cancers of the oral cavity & pharynx, esophagus and lung, respectively. Also, the risks were higher among heavy smokers for cancer of the oral cavity & pharynx and esophagus than among light smokers. No adverse effects of radiotherapy for laryngeal cancer on the development of thyroid cancer, lymphoma and leukemia were observed. The present study suggests the necessity of following-up laryngeal cancer patients ovar a long period in order to enable the early detection of tobacco-related cancer.

Key words: Second primary cancer — Laryngeal cancer — Smoking habit — Population-based cancer registry

Population-based and hospital-based studies[1-5] have revealed that laryngeal cancer patients have a high risk of developing second primary cancers, especially those which are related to cigarette smoking; i.e., oral cavity & pharynx, esophagus and lung. These results are due to common etiologic factors associated with the initial cancer.[6,7] Population-based studies on second primary cancers have advantages in estimating the risks with a large number of registered cases and in the long-term follow-up of these cases. However, they present difficulties in estimating the risks from the viewpoint of exposure levels of etiologic factors for the initial cancers, such as the number of cigarettes smoked. On the other hand, hospital-based studies present difficulties in following-up the patients over a long time, leading to underestimation of risks.

In the present study, we followed-up male laryngeal cancer patients diagnosed at one hospital by collating their files to the files of the population-based cancer registry and estimated the risks of developing second primary cancer after laryngeal cancer, with special reference to cigarette smoking habits at the diagnosis of laryngeal cancer.

MATERIALS AND METHOD

Male laryngeal cancer patients who had initially been diagnosed by one of the authors (S.T.) between 1965 and 1975, and who had resided in Osaka Prefecture at the diagnosis of laryngeal cancer were followed-up by referring to their medical records or to their resident offices. Copies of death certificates were obtained from Local Justice Bureaus with the approval of the Ministry of Justice. Their files were also collated with the files of the Osaka Cancer Registry to obtain information on the occurrence of second primary cancer, not only for those who continued to visit the department of oto-rhinolaryngology but also for those who had stopped.

The period of observation used in calculating the risks for second primary cancers begins at the date of diagnosis of laryngeal cancer and ends at either the data of diagnosis of the second primary cancer, the date of death or December 31st 1985, whichever comes first. Site-specific sex, 5-year age group and 5-year calendar period incidence rates for each cancer among Osaka residents were applied to the appropriate person-years at risk to obtain the numbers of second primary cancers to be expected had these patients experienced the same rates as were prevailing in the corresponding general population. Analysis was also carried out according to the number of cigarettes smoked per day at the diagnosis of laryngeal cancer. The statistical methods used were based on the assumption that the observed number of cancers followed a Poisson distribution. Tests of significance for observed/expected values (O/E) were calculated using the exact Poisson probabilities, and 95% confidence intervals (CI) of the O/E ratios were based on the formulation derived by Byar.[8]

RESULTS

Four hundred and seventy-two patients were included in the present study, and the age distribution at diagnosis is shown in Table I. Of these, 451 were regular smokers and they were categorized into 3 groups according to the number of cigarettes smoked per day (1–19, 20–39 and more than 40 cigarettes) at the diagnosis of laryngeal cancer (Table I). On December 31st 1985, 163 were alive, 291 had died and 18 (3.8%) were lost in follow-up.

Table I. Characteristics of Study Subjects by Smoking Habit at Diagnosis

Age	Total	Number of cigarettes smoked/day		
		1–19	20–39	40–
–39	9	3	3	2
40–49	42	2	23	15
50–59	147	27	73	42
60–69	194	43	105	42
70–	80	22	35	14
Total	472	97	239	115
Mean age at diagnosis (yr)	61.7	63.6	61.4	60.1
Average length of follow-up (yr)	8.6	8.9	8.7	8.4

Table II. Observed (O) and Expected (E) Numbers of Second Primary Cancer Cases Following Laryngeal Cancer

Site	O	E	O/E	(95%CI)
All sites except larynx	115	51.4	2.2*	(1.85–2.69)
Oral cavity, pharynx	22	0.9	24.5**	(15.34–37.08)
Esophagus	13	2.1	6.1**	(3.25–10.46)
Stomach	27	18.5	1.5	(0.96–2.12)
Colon	5	2.1	2.3	(0.74–5.37)
Rectum	2	2.1	1.0	(0.11–3.52)
Liver	6	5.1	1.2	(0.43–2.57)
Pancreas	1	1.6	0.6	(0.01–3.53)
Lung	20	8.6	2.3**	(1.42–3.59)
Urinary bladder	4	1.7	2.4	(0.63–6.03)
Thyroid gland	4	0.2	25.9**	(6.96–66.26)
Non-Hodgkin lymphoma	2	0.8	2.7	(0.39–9.63)
Leukemia	0	0.5	0.0	(0.00–9.63)

* $P<0.05$. ** $P<0.01$.

Overall, 115 second primary cancers other than laryngeal cancer developed during the observation period, 2.2 times higher than the expected number, and the difference was significant (Table II). By site, the O/E ratios were significantly high for cancers of the oral cavity & pharynx (O/E=24.5, 95% CI=15.34–37.08), esophagus (O/E = 6.1, 95% CI = 3.25–10.46), lung (O/E = 2.3, 95%CI=1.42–3.59) and thyroid gland (O/E=25.9, 95%CI=6.96–66.26). The occurrence of non-Hodgkin lymphoma was 2.7 times higher than the expected number, though the difference was not significant. No leukemia developed during the observation period.

To clarify the risks over time after the diagnosis of laryngeal cancer, the observation period was divided into four categories: within one year, 1–4 years, 5–9 years and more than 10 years after diagnosis. Table III shows the O/E ratios according to the length of follow-up for those cancers which had significantly higher risks in Table II. The O/E ratio for cancer of the oral cavity & pharynx was 77.2 within one year after diagnosis of laryngeal cancer and decreased with time elapsed, though the risk was still higher than that among the general population even 10 or more years after the diagnosis of laryngeal cancer. The O/E ratios for esophageal cancer were rather constant, 4.3–9.1 for the entire follow-up period. The differences were significant during the periods of 1–4 years and 10 or more years after diagnosis of laryngeal cancer. No lung cancer developed within one year of diagnosis of laryngeal cancer; however, the risks increased after one or more years (2.3–2.9), though a significant difference was observed only 1–4 years after diagnosis of the initial cancer because of the small observed number. Three cancer cases of the thyroid gland were diagnosed within one year, but no cancer of the thyroid gland developed five or more years after the diagnosis of laryngeal cancer.

Table III. Observed/Expected(O/E) Ratio of Second Primary Cancer by Years after Diagnosis of Laryngeal Cancer

Second primary	O/E ratio							
	<1 yr		1–4 yr		5–9 yr		10+ yr	
All sites except larynx	4.0**	(16)	2.9**	(40)	1.8**	(30)	1.9**	(29)
Oral cavity, pharynx	77.2**	(6)	35.0**	(9)	16.3**	(5)	7.8	(2)
Esophagus	5.0	(1)	9.1**	(6)	4.3	(3)	5.4*	(3)
Lung	0.0	(0)	2.9*	(6)	2.4	(7)	2.3	(7)
Thyroid gland	273.2**	(3)	24.7	(1)	0.0	(0)	0.0	(0)

* $P<0.05$. ** $P<0.01$.
Numbers in parentheses are observed numbers.

The cumulative risk of developing second primary cancer after laryngeal cancer was estimated by the life table method (Fig. 1). The cumulative risk at 15 years after diagnosis of laryngeal cancer was estimated to be 31.1%, and is higher among heavy smokers than light smokers.

In Table IV, O/E ratios are shown according to the number of cigarettes smoked per day at the diagnosis of laryngeal cancer. The O/E ratio for cancer of the oral cavity & pharynx increased with increase in the number of cigarettes smoked per day. The O/E ratios for esophageal cancer were 3.9 for those who smoked 1–19 cigarettes per day, 7.3 for those who smoked 20–39 cigarettes per day and 6.6 for those who smoked more than 40 cigarettes per day. The O/E ratio for lung cancer among those who smoked 20–39 cigarettes per day was 3.1, which is higher than that among those who smoked 1–19 cigarettes per day. However, the O/E ratio among those who smoked more than 40 cigarettes per day was 1.1, which is lower than that among those who smoked less.

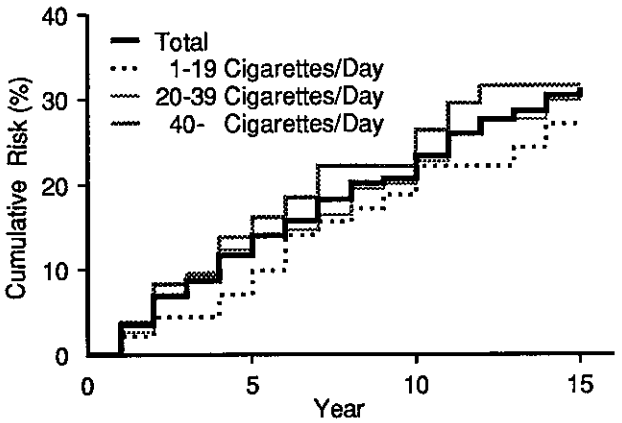

Fig. 1. Cumulative risk of developing second primary cancer after laryngeal cancer according to the number of cigarettes smoked per day.

DISCUSSION

In the present study, male laryngeal cancer patients were followed-up individually for vital status (the proportion lost to follow-up was 3.8%) and the occurrence of second primary cancer after laryngeal cancer was surveyed by referring not only to their medical records but also to the Osaka Cancer Registry files. The Osaka Cancer Registry registers cancer patients who reside in Osaka Prefecture, and no information on those who moved out of Osaka Prefecture and developed a second primary cancer at another location is available. Under such circumstances, we could not obtain any information

Table IV. Observed (O) and Expected (E) Numbers of Second Primary Cancer Cases Following Laryngeal Cancer by Smoking Habit

Site	Consumption of cigarettes per day								
	1–19			20–39			40+		
	O	E	O/E	O	E	O/E	O	E	O/E
All sites except larynx	23	11.7	2.0**	58	26.6	2.2**	28	11.3	2.5**
Oral cavity, pharynx	0	0.2	0.0	12	0.5	25.8**	10	0.2	48.7**
Esophagus	2	0.5	3.9	8	1.1	7.3**	3	0.5	6.6*
Stomach	10	4.4	2.3*	8	9.6	0.8	6	4.0	1.5
Colon	0	0.5	0.0	2	1.1	1.8	2	0.5	4.1
Rectum	1	0.5	2.1	0	1.1	0.0	1	0.4	2.3
Liver	1	1.1	0.9	3	2.6	1.1	1	1.2	0.9
Pancreas	0	0.4	0.0	0	0.8	0.0	1	0.4	2.8
Lung	3	2.0	1.5	14	4.5	3.1*	2	1.9	1.1
Urinary bladder	2	0.4	5.0	2	0.9	2.3	0	0.4	0.0
Thyroid gland	1	0.1	28.4	3	0.1	37.7**	0	0.1	0.0
Non-Hodgkin lymphoma	1	0.2	5.9	1	0.4	2.6	0	0.2	0.0

* $P<0.05$. ** $P<0.01$.

Table V. Studies on Second Primary Cancer after Laryngeal Cancer

Authors (ref. no.) Study design	Country; Period	No. of subjects	Average follow-up	Findings
Boice *et al.* (1) Population-based	USA; 1935–82	M 3,653	5.3 yr	Elevated risks: oropharynx (2.6), esophagus (2.8), colon (1.5), liver (2.1) lung (3.1)
Olsen (2) Population-based	Denmark; 1943–80	M 3,344	5.9 yr	Elevated risks: oropharynx (2.0), pancreas (2.4)
Kobayashi *et al.* (4) Hospital-based	Japan; 1962–87	M 1,127 F 88	6.6 yr 6.7 yr	Elevated risks: oropharynx (8.8), esophagus (2.8), lung (1.9) Lower risk: stomach (0.5)
Wagenfeld *et al.* (3) Hospital-based	Canada; 1970–74	163	NA	Supraglottic cancer only. Estimated only cancers of respiratory system. Elevated risk: respiratory system (14)
Kawamoto *et al.* (5) Hospital-based	Japan; 1967–78	M 590 F 64	NA	Estimated only cancers of upper digestive tract and respiratory system. Elevated risks: head & neck (19.5), esophagus (8.1)
Hiyama *et al.* (present paper) Hospital-based	Japan; 1965–75	M 472	8.6 yr	Elevated risks: oropharyx (24.5), esophagus (6.1), lung (2.3),

NA; not available. M; male. F; female.
Numbers in parentheses are O/E ratios.

on the occurrence of second primary cancer among those who moved out of Osaka Prefecture and were alive at the end of 1985. In this regard, the observed number of second primary cancer cases represents the minimum of the actual number of developed second primary cancers among the study subjects, which leads to underestimated O/E ratios compared with actual figures.

Two population-based studies[1, 2] and one hospital-based study[4] estimated the risks of developing second primary cancer for all sites except that of the initial cancer. Two other hospital-based studies[3, 5] whose study subjects were laryngeal cancer patients undergoing radiotherapy, estimated the risks limited to cancers of the upper digestive tract and respiratory system. The results of our study are substantially consistent with those of these other studies (Table V). In our study, the risk of developing second primary cancer other than the initial cancer was estimated to be 2.2, significantly higher than the expected number. The risks of developing second primary cancers other than the initial cancer were estimated to be significantly high in the two population-based studies, though the difference was not significant in the hospital-based study. Kobayashi *et al.*[4] estimated the risk in their hospital-based study to be 1.1, though this figure might be underestimated due to underestimation of the occurrence of second primary cancers among those who stopped visiting their hospital. Actually, the O/E ratios for cancers with better prognosis, such as stomach cancer or colorectal cancer, were under unity at five or more years after the diagnosis of the initial cancer. This figure might indicate a disadvantage with hospital-based studies in surveying the occurrence of cancer for a long time after the diagnosis of the initial cancer without collation with the population-based cancer registry files. In the present study, we obtained information for 48 second primary cancer cases (41.8%) by referring to their medical charts, and for 31 cases (27.0%), information was obtained from the death certificates only.

A study on multiple primary cancer might provide clues to understanding the common etiologic factors between the initial cancer and the subsequently developed cancer, the adverse effects of therapy for the initial cancer, genetic predisposition and so forth. In the present study, increased risks are observed for cancers of the oral cavity & pharynx, esophagus and lung (Table II). These increased risks can be mainly explained by the common risk factor with the initial cancer, i.e. cigarette smoking, as cigarette smoking is strongly connected with laryngeal cancer and these 3 sites of cancer.[6, 7] A comparison of the observed number of second primary cancers with the expected number derived from the incidence rates among smokers could clarify the effects of other factors other than cigarette smoking, but the incidence rates by smoking habits are not available. The observed dose-response relationship between the number of cigarettes smoked at the diagnosis of laryngeal cancer and the risk of developing second primary cancer of the oral cavity & pharynx and the esophagus might support this explanation, though the possibility of effects from genetic predisposition and other factors can not be ruled out. Information on drinking habit, which is one of the etiologic factors of cancer of the oral cavity & pharynx and cancer of the esophagus, was not available for this study.

The risk of developing second primary cancer by the length of follow-up period was estimated in two population-based studies and one hospital-based study. In the present study, the O/E ratio for the oral cavity & pharynx was highest within one year of diagnosis of laryngeal cancer and declined with the passage of time, though it was still higher than unity. This result is consistent with those of the other three studies. The O/E ratios for esophageal cancer and lung cancer were higher shortly after the diagnosis of the initial cancer. This might be partly due to the detection bias: cancer patients are under closer scrutiny, especially shortly after the diagnosis of the initial cancer. Another possible explanation is the cessation of smoking after the diagnosis of laryngeal cancer. Lubin *et al.*[9] reported that cessation of smoking lowered the risk of developing lung cancer and that the protective effect became greater with the time elapsed since cessation. Moore[10] reported that the risk of developing second primary cancers related to cigarette smoking was lower among those cancer patients of the oral cavity & pharynx and larynx who stopped smoking than among those who continued smoking. In the present study, information on smoking habits after the diagnosis of laryngeal cancer was not available. Laryngeal cancer patients with laryngectomy are not supposed to continue smoking after undergoing operation. In the present study, 239 out of 471 laryngeal cancer patients had laryngectomy.

We estimated the risk of developing second primary cancer related to cigarette smoking according to the number of cigarettes smoked per day at the diagnosis of laryngeal cancer. The O/E ratios for cancers of all sites except the larynx increased with increase in the number of cigarettes smoked per day at the diagnosis of laryngeal cancer. This result could be explained by the fact that heavy smokers have a higher risk of developing tobacco-related cancers. By site, a dose-response relationship was observed for cancer of the oral cavity & pharynx. The O/E ratios for esophageal cancer were higher among those who smoked 20–39 cigarettes or more than 40 cigarettes per day than among those who smoked less than 20 cigarettes. However, the O/E ratio for lung cancer among those who smoked heavily (more than 40 cigarettes per day) was estimated to be 1.1, which is lower than that among light smokers (1–19 cigarettes per day), though the observed number was too small for reliable estimation. A plausible explanation is that the proportion of those who continued smoking after the diagnosis of laryngeal cancer was higher among light smokers than heavy smokers. The risk of developing second primary lung cancer among heavy smokers was compared with that among light smokers by applying a multiplicative Poisson regression model to control the effects of laryngectomy, which is a substitute for smoking habits after the diagnosis of laryngeal cancer. Heavy smokers showed lower risks than light smokers. Another plausible explanation is that heavy smokers might have died from other competitive tobacco-related diseases before lung cancer developed. Laryngeal cancer patients who smoked heavily had poor survival compared with those who smoked lightly. The 15-year relative survival rates were 65.5% for light smokers and 58.8% for heavy smokers.

It this study, O/E ratio was increased for thyroid cancer, however this increased risk might be due to a detection bias, not to the adverse effects of radiotherapy for laryngeal cancer: three of the observed thyroid cancer cases were diagnosed within one year of laryngeal cancer diagnosis and the remaining one case was diagnosed at 1–4 years. In summary, laryngeal cancer patients have higher risks of developing second primary cancers even 10 or more years after the diagnosis of laryngeal cancer, and this risk was higher among heavy smokers. It is recommended that all laryngeal cancer patients undergo close medical follow-up over a long period of time to enable the early detection of second primary cancers, especially the tobacco-related cancers. Needless to say, such patients should be encouraged to quit smoking after the diagnosis of laryngeal cancer.

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