

Epidemiological Analysis of Site Relationships of Synchronous and Metachronous Multiple Primary Cancers in the National Cancer Center, Japan, 1962-1996

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Background: Multiple primary cancer (MPC) has been recognized as a problem commonly encountered in routine medical practice. A study of MPC is necessary not only to provide insights into the etiology of cancer, but also to provide information for effective medical care by clinical oncologists.

Methods: A cohort of 49 751 cancer patients who were admitted to the National Cancer Center Hospital between 1962 and 1996 was used to study the site relationship of MPC. Logistic and Poisson regression analyses using an internal reference group within the cohort were applied for the calculation of the prevalence odds ratio (POR) for site relationships of synchronous MPC and the incidence rate ratio (IRR) for those of metachronous MPC.

Results: Three site combinations with elevated risks for both synchronous and metachronous MPCs, eight with elevated risk for synchronous MPC, five with elevated risk for metachronous MPC and six with decreased risk for synchronous MPC were identified with statistical significance. Among them, the increased risk of metachronous stomach cancer following lymphoma and myeloma (POR = 1.0 and 1.1, $P > 0.05$; IRR = 2.5, $P < 0.05$) and the inverse site-correlation of synchronous MPC between [trachea, bronchus and lung] and other sites of the upper aerodigestive tract [lip, oral cavity and pharynx] (POR = 0.5 and 0.3, $P < 0.05$) and esophagus (POR = 0.7 and 0.3, $P < 0.05$) have not been reported previously.

Conclusions: Our results suggest that interventions for lymphoma and myeloma might affect the development of subsequent stomach cancer and additional etiological factors other than tobacco smoking are associated with the development of cancer in the upper aerodigestive tract.

Key words: multiple primary neoplasms – second primary neoplasms – epidemiology

INTRODUCTION

In Japan, approximately 40% of males and 20% of females will develop a cancer by the age of 79. Based on these figures and assuming that half of the cancer patients will survive at least 5 years, 4% of males and 1% of females are expected to develop multiple primary cancer (MPC) in their lifetime (1). This clearly shows that MPC should be regarded as a problem commonly encountered in routine medical practice rather than a rare and

unusual event to be reported as case reports. Furthermore, it has been reported that certain combinations of sites are more likely to be diagnosed as MPC than expected from the national incidence rate (2). Therefore, clinical oncologists should be provided with information on the risk of MPC to give effective medical care to cancer survivors.

The site combinations of MPC also provide insights into the etiology of cancer. First, the occurrence of MPC may sometimes be associated with exposure to agents carcinogenic to multiple organs. Second, it may sometimes reflect the existence of people who are highly susceptible to cancer at multiple sites owing to genetic abnormality. Third, it sometimes results from the carcinogenicity of therapeutic agents applied to the first primary cancer (3-6).

In order to reveal such etiological factors, a systematic epidemiological study on MPCs is essential. In several countries, epidemiological studies on MPC based on a large-scale population-based cancer registry have provided some insights into MPC from the etiological point of view. In Japan, several studies have reported the risks of MPCs following first primary cancers (7-8) of the colon and rectum (9), non-Hodgkin's lymphoma (10),

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Abbreviations: MPC, multiple primary cancer; POR, prevalence odds ratio; IRR, incidence rate ratio; NCCH, National Cancer Center Hospital; HNPCC, hereditary non-polyposis colorectal cancer

thyroid gland (11), stomach (12–13), pharynx and larynx (14–15), uterine cervix (16), head and neck (17) and breast (18). Since the cancer incidence pattern in Japan is known to be very different from that in Western countries, it is hoped that these studies of MPCs in Japan will provide some additional insights into the etiology of cancer.

In 1991, Kobayashi et al. (19) reported on site relationships of MPCs using the National Cancer Center Hospital (NCCH) Registry. Since the number of registered cases in the registry has increased and the survival rate among cancer patients has improved, a re-analysis on the site relationships of MPCs is expected to yield more reliable risk estimates than the previous study. In this paper, we present the results of our investigation on the site relationships of MPCs using this cohort of cancer patients in the National Cancer Center Hospital Registry.

SUBJECTS AND METHODS

SUBJECTS

The cohort of this study consisted of 49 751 cancer patients with cancer at 23 categorized sites (52 989 cancer diagnoses) in the National Cancer Center Hospital (NCCH) from 1962 through 1996. Among them, 2219 patients (2270 diagnoses) of the cohort were simultaneously diagnosed as having two or more cancer sites on their first admissions: 2170 with two cancer sites, 47 with three cancer sites and two with four cancer sites. We defined MPCs identified during the first admission as synchronous MPCs. The remaining 47 532 patients were diagnosed for a single cancer site on the first admission. Among synchronous MPC cases, patients who had cancers at three or more sites were excluded from this study for simplicity. Finally, 49 702 patients including 2170 patients with two synchronous cancer sites (51 872 cases) and 47 532 patients with a single cancer site were included in the study population. The demographic characteristics of the cohort in detail are shown in Table 1.

The Statistics Survey Section of the hospital followed up 47 532 patients with a single cancer site at the time of the first admission for subsequent development of MPCs by reviewing the hospital chart, surgical pathology results and autopsy records if available. Fifteen patients were excluded from the analysis because of insufficient information on follow-up date. Among the remaining eligible patients of the cohort, 771 were diagnosed for second primary cancers during their follow-up period, 715 with one, 49 with two and seven with three second primary cancers. We defined such cases as metachronous MPCs. Finally, 47 517 patients with a single cancer site on the first admission and 834 metachronous MPC cases ($715 + 49 \times 2 + 7 \times 3$) were used for the analysis of site relationships of metachronous MPCs. The overall demographic data of the cohort for the analysis of metachronous MPCs are displayed in Table 2 and in the first row of Table 4. A detailed explanation of Table 2 is given in the following section.

In this study, each diagnosis was categorized into 23 sites, according to the ICD-9 between 1962 and 1995 and ICD-10 between 1995 and 1996 for each admission to the NCCH, in order to analyze descriptively the cancer site relationships (Table 2).

STATISTICAL METHODS

For the analysis of site relationships of synchronous MPCs, site-specific prevalence odds ratios (PORs) at the time of the first admission were calculated using the logistic regression method adjusting for gender, age and calendar year of the first admission. The prevalence of synchronous MPC was compared between patients with cancer at a certain site and the remaining patients as the internal reference. In calculating the POR of site *A* among patients with cancer at site *B*, for example, the reference group was all patients with cancer other than at site *B*. Likewise, in calculating the POR of site *B* among patients with cancer at site *A*, the reference group was all patients with cancer other than at site *A*. Therefore, two PORs were calculated for a specific site relationship of *A* and *B*. A combination of two sites was regarded as significant if the number of MPC cases exceeded five and two PORs were both statistically significant at the 5% level in the same direction.

For the analysis of site relationships of metachronous MPCs, site-specific incidence rate ratios (IRRs) were calculated based on the Poisson regression method assuming that the number of incidence cases of second primary cancers followed a Poisson distribution. The IRR was adjusted for gender, age and calendar year of the first admission. The person time contributed to by each patient is the period from the date of the first admission to either the date of admission for a specific second primary cancer of interest or, for those who did not develop an MPC at the specific site of interest, to the last date when the vital status was confirmed. For those who developed MPCs at sites other than the specific site of interest, the last date of follow-up was also set as the last date when the vital status was confirmed. In this analysis, patients who had a second primary cancer at a site identical with that of the first primary cancer were excluded from the reference group, because we could not distinguish their cancer from recurrent cancer. The SAS statistical package (version 6.12) was used for data-handling and Poisson and logistic regression analyses with GENMOD and LOGISTIC procedures, respectively.

RESULTS

The number of patients enrolled in the study for site relationship of synchronous MPCs was 49 702. Among them, 2170 patients, 1480 male and 690 female cases, were diagnosed as having two cancer sites. The PORs of synchronous MPCs are shown in Table 3. Among them, 19 combinations of cancer sites, 13 positively correlated and six negatively correlated, were statistically significant in the same direction in the risk of having synchronous MPC for the site combination. The combinations positively correlated were site combinations of [lip, oral cavity and pharynx] versus esophagus, [lip, oral cavity and pharynx] versus larynx, [lip, oral cavity and pharynx] versus thyroid gland, esophagus versus stomach, esophagus versus thyroid gland, colon versus [rectosigmoid junction and rectum], pancreas versus thyroid gland, [gall bladder and extrahepatic bile duct] versus thyroid gland, larynx versus thyroid gland, corpus uteri versus ovary, prostate versus bladder and bladder versus [kidney and ureter]. Those inversely correlated were [lip, oral cavity and pharynx] versus stomach,

[lip, oral cavity and pharynx] versus colon, [lip, oral cavity and pharynx] versus [rectosigmoid junction and rectum], [lip, oral cavity and pharynx] versus [trachea, bronchus and lung], esophagus versus [trachea, bronchus and lung] and breast versus cervix uteri.

The number of patients included in the analysis of metachronous MPCs was 47 517 with a single diagnosed cancer at the time of the first admission, 24 131 males and 23 386 females. The overall person years of follow-up are displayed in Table 2. The overall person years that contributed to the cohort was 281 302 and the mean follow-up period was 5.92 years. The mean age at the first admission for a first primary cancer was 55.9 years. Table 4 shows the distribution of the sites of second primary cancers in the first row and the adjusted IRRs by Poisson regression analysis. Significant ($P < 0.05$ and observed second primary cancer > 5) relationships of the sites are displayed in Table 5, together with site combinations which were found to be significantly correlated in the analysis of synchronous MPCs. Eight site combinations showed a significantly positive correlation and none of the site combinations showed significantly inverse correlation. The positively correlated site combinations were esophagus cancer following cancer at the site of [lip, oral cavity and pharynx] (IRR = 4.9), cancer at the site of [lip, oral cavity and pharynx] following esophagus cancer (IRR = 11.2), cancer at the site of [lip, oral cavity and pharynx] following larynx cancer (IRR = 7.4), 4 esophagus cancer following larynx cancer (IRR = 2.7); cancer at the site of [trachea, bronchus and lung] following larynx cancer (IRR = 4.0); thyroid gland cancer following cancer at the site of [trachea, bronchus and lung] (IRR = 2.6); colon cancer following corpus uteri cancer (IRR = 7.3); and stomach cancer following [lymphoma and myeloma] (IRR = 2.5). (Table 5)

DISCUSSION

We identified 13 positively and six inversely correlated site combinations of cancer with statistical significance in the analysis of synchronous MPCs and eight positively correlated site combinations in the analysis of metachronous MPCs. By comparing the results for synchronous and metachronous MPCs, the site combinations can be categorized into four groups: (1) site combinations in which the risks of both synchronous and metachronous MPCs are significantly elevated; (2) site combinations in which only risks of synchronous MPC are significantly elevated; (3) site combinations in which only risks of metachronous MPC are significantly elevated; and (4) site combinations in which only risks of synchronous MPC are significantly decreased (Table 5). Although site combinations in the same group might be interpreted in the same way from an etiological point of view, each site combination should be carefully interpreted taking into account the following four factors which play important roles in the etiology of MPC: genetic susceptibility, common exposure status (exposure to an agent carcinogenic to both sites), treatment effects and chance.

If two cancers at different sites share common risk factors such as genetic susceptibility and common exposure status, the risk of

having MPC, either synchronous or metachronous, should increase. Such site combinations can be seen in the first group in Table 5. The combination of [lip, oral cavity and pharynx] versus esophagus has been reported as significantly correlated in several papers (14,20–23) and the correlation is thought to be attributable to tobacco smoking and alcohol consumption. We also identified a marginally correlated site combination among tobacco-related cancers, [lip, oral cavity and pharynx] versus larynx. Such site combinations could be explained by the concept of field cancerization (24). The other site combination found to be correlated was that of colon versus [rectosigmoid junction and rectum], although the observed number in the analysis of metachronous MPC did not meet our criterion of at least five observed. The positive correlation of the site relationship agrees with those in past reports (9,25).

When interpreting the site combinations in the second group in Table 5, the so-called screening effect should be taken into account. The probability of detecting synchronous MPC usually increases during the first admission, because systematic examinations are made of cancer patients to identify co-existing abnormalities. The probability of detecting metachronous MPC also increases during the follow-up period, for the same reason. By the analogy of detecting pre-clinical cancers by mass screening, this increase in detection of pre-clinical cancers is often called the 'screening effect' (26). The magnitude of the screening effect for synchronous MPC is related to the length of the pre-clinical detectable period of the cancer to be diagnosed as MPC. The incidence of metachronous MPC is also influenced by the screening effect, because at least some parts of metachronous MPCs, which would also be detected during the follow-up period, would be detected as synchronous MPC during the first admission or would be detected at an early point in time during the follow-up period. As a result of the screening effect, the risk of MPC among cancer patients is often overestimated when it is compared with cancer incidence rates of the general population (23,26,27). When they are compared with an internal reference within the cohort, the overestimation of the risk of MPC due to the screening effect can be improved, because the patients in the cohort will receive a similar quality and quantity of physical check-ups during their follow-up periods. Even if they are compared with the internal reference, however, the probability of detecting MPC at adjacent sites would be increased more than those at other sites. Four out of seven site combinations in the second group of Table 5 include cancer of the thyroid gland. Since cancer of the thyroid gland is known to have a long pre-clinical period, the observed site combinations are possibly affected by the screening effect. Other site combinations could also have resulted from the screening effect, especially those cancers whose locations are anatomically adjacent. However, the results of adjacently located site combinations should be interpreted with caution, because anatomically adjacent sites are also likely to have been surgically removed together. Therefore, the risk of metachronous MPC can become lower than expected or cannot be calculated owing to the lack or a small number of observations, even if cancers at the sites develop under a common etiological background.

In five site combinations in the third group in Table 5, elevated risks of metachronous MPC following a first primary cancer were identified: cancer of the thyroid gland following cancer of the trachea, bronchus and lung, esophagus cancer following larynx cancer, colon cancer following cancer of the corpus uteri, cancer of the trachea, bronchus and lung following larynx and stomach cancer following lymphoma and myeloma. According to a personal communication with a therapeutic radiologist of the National Cancer Center, about 10–20% of lung cancer patients who receive radiation therapy are also exposed to radiation at the site of the thyroid gland in its radiation field. Thus, the increased risk of thyroid cancer following cancer of the trachea, bronchus and lung might be due to radiation therapy for cancer at those sites (28). The increased risk of esophagus cancer following cancer of the larynx might be due to an adverse effect of radiation therapy for larynx cancer, although the effect of common risk factors, such as tobacco smoking and alcohol consumption, cannot be ruled out. The increased risk of colon cancer following cancer of the corpus uteri might be explained by the contribution of hereditary non-polyposis colorectal cancer (HNPCC) (29). The risk of cancer of the corpus uteri following colon cancer also increased, although not significantly. The increased risk of stomach cancer following lymphoma and myeloma cannot be explained by the adverse effects of therapeutic agents for the first cancer. More specific epidemiological studies on the carcinogenic effects of cancer treatment are needed in the future.

The site combinations in the fourth group in Table 5 are more difficult to interpret than the others. The inverse site relationship of breast cancer and cancer of the cervix uteri could be explained by the difference in risk factors related to socioeconomic status, that is, difference in standard of living, education level and experienced number of parity (30,31).

The site combinations of [lip, oral cavity and pharynx] and stomach, colon and [rectosigmoid junction and rectum] in the fourth group in Table 5 could have resulted from an increased probability of synchronous MPC in the reference group due to the strong site-correlation between [lip, oral cavity and pharynx] and esophagus or larynx in the first group in Table 5. However, the inverse site-correlation of [trachea, bronchus and lung] and cancers in the upper aerodigestive tract in the analysis of synchronous MPC seems to be inconsistent with those of other studies which concluded that they have the same risk factor of tobacco smoking and have increased risk of MPC for each other.

One possibility is that the interaction of tobacco smoking and alcohol consumption causes a difference between site relationships of lung cancer and other cancers of the upper aerodigestive tract. Alcohol intake does not play any role in lung cancer, whereas it plays a substantial role in upper aerodigestive cancer. The other possibility is that damage to the muco-ciliary transportation system which can transport carcinogens (32) out of the respiratory system makes the difference between them. The upper aerodigestive tract is more likely to be exposed to inhaled carcinogens when the muco-ciliary transportation system is intact, but the lung will begin to be exposed to inhaled carcinogens after the muco-ciliary system is damaged. The latter

hypothesis could also explain the time lag (~5 years) in the age of patients with cancer of the lung and the [lip, oral cavity and pharynx]. Further studies are needed to explain these apparently inconsistent results.

In summary, we identified several site combinations of MPC of possible medical significance from the etiological point of view. We also showed the appropriateness of the use of an internal reference group in an epidemiological study of MPC, in comparison with a study using the general population as a reference group, in order to reduce the possibility of being biased owing to the screening effect. Further epidemiological studies, hopefully multi-institutional, are necessary to elucidate the reason for the inverse site-correlation between [lip, oral cavity and pharynx] and [trachea, bronchus and lung], esophagus and [trachea, bronchus and lung] and the reason for the increased risk of stomach cancer following lymphoma and myeloma.

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Table 1. Site combinations of synchronous multiple primary cancers on the first admission and the observed numbers

cancer sites on the first admission	cases	% of male	mean age	site of synchronous MPCs diagnosed at the time of the first admission												
				oral	esoph	stom	col	rect	liver	gb	panc	lary	lung	bone	skin	breast/cervix/body ovary
lip, oral cavity, pharynx	3,086	71.4%	57.3													
esophagus	2,346	86.6%	62.8													
stomach	10,223	67.7%	58.8	101	133											
colon	2,551	60.1%	60.0	10	16	93										
rectosigmoid junction, rectum	2,151	61.6%	57.5	5	8	42	88									
liver	2,157	81.2%	58.7	8	7	63	16	14								
gall bladder, extrahepatic bile duct	456	53.5%	62.7	2	1	18	6	5	2							
pancreas	723	62.9%	60.6	3	2	24	4	2	0	3						
larynx	992	92.8%	62.7	22	14	20	8	4	11	1	2					
trachea, bronchus, lung	6,935	75.7%	62.1	20	28	133	36	21	19	2	8	35				
bone, articular cartilage	309	59.9%	28.2	0	0	1	1	0	0	0	0	0	0	0		
skin	664	59.0%	60.4	2	4	15	5	2	2	0	0	1	14	0		
breast	7,290	0.5%	51.1	4	2	57	23	13	12	3	4	1	28	1	5	
cervix uteri	4,480	0.0%	55.0	0	2	15	12	12	2	0	0	0	9	1	1	21
corpus uteri	900	0.0%	56.5	0	0	6	5	6	0	0	1	0	2	0	1	18
ovary	604	0.0%	49.8	0	1	3	5	1	0	0	2	0	2	0	0	13
prostate	589	100.2%	67.8	6	4	26	12	5	7	0	2	1	35	1	0	0
bladder	990	76.7%	61.5	4	4	27	6	6	6	1	2	6	14	1	2	6
kidney, ureter	717	70.6%	56.2	5	5	21	8	4	5	0	1	4	18	0	1	6
brain	329	58.4%	36.3	0	0	0	1	0	0	0	0	0	0	0	1	4
thyroid gland	1,015	30.3%	52.3	17	17	16	14	0	8	5	7	11	25	2	3	2
lymphoma, myeloma	1,563	63.7%	49.8	10	4	31	13	3	8	3	0	0	12	0	1	12
leukemia	702	62.5%	27.8	2	2	7	0	1	0	0	1	1	4	0	0	5
total(diagnoses)	51,872	52.7%	56.9													
total(patients)	49,702	52.0%	56.6													

*49,702 eligible patients (47,532 with a single cancer and 2,170 with two cancers diagnosed) for this study were admitted to the National Cancer Center Hospital along with 51,872 cancer diagnosed sites from 1962 through 1996.

abbreviations: oral-lip, oral cavity, and pharynx; esoph-esophagus; stom-stomach; col-colon; rect-rectosigmoid junction and rectum; liver-liver; gb-gall bladder, extrahepatic bile duct; panc-pancreas; lary-larynx; lung-trachea, bronchus, lung; bone-bone, articular cartilage; bres-breast; cervix-cervix uteri; body-corpus uteri; prost-prostate; bladd-bladder; kid-kidney and ureter; thyro-thyroid gland; lymph-lymphoma and myeloma

Table 2. Criterion of categorization into 23 parts of cancer sites according to ICD-9 and ICD10 and characteristics of the cohort for the analysis of site relationships of metachronous multiple primary cancers in the National Cancer Center Hospital Registry, 1962–1996

site of initial primary cancer	ICD-9	ICD-10	cases	% of male	mean age*	person-years†	PY/patient
lip, oral cavity, pharynx	140.1-149.9	C00.0-C14.8	2,815	70.1%	56.5	15,978	5.68
esophagus	150.0-150.9	C15.0-C15.9	1,991	85.6%	62.3	4,887	2.45
stomach	151.0-151.9	C16.0-C16.9	9,422	66.9%	57.8	57,574	6.11
colon	153.0-153.9	C18.0-C18.9	2,169	58.4%	59.0	10,948	5.05
rectosigmoid junction, rectum	154.0-154.1	C19.0-C20.0	1,909	61.0%	56.6	11,159	5.85
liver	155.0	C22.0	1,967	81.0%	57.7	5,203	2.65
gall bladder, extrahepatic bile duct	156.0-156.9	C23.0-C24.9	403	52.4%	61.9	575	1.43
pancreas	157.0-157.9	C25.0-C25.9	655	62.4%	59.6	742	1.13
larynx	161.0-161.9	C32.0-C32.9	850	92.7%	61.8	7,056	8.30
trachea, bronchus, lung	162.0-162.9	C33.0-C34.9	6,466	75.5%	61.3	17,538	2.71
bone, articular cartilage	170.0-170.9	C40.0-C41.9	300	60.7%	27.3	1,332	4.44
skin	173.0-173.9	C44.0-C44.9	605	57.4%	59.6	4,144	6.85
breast	174.0-174.9	C50.0-C50.9	7,030	0.4%	50.4	61,144	8.70
cervix uteri	180.0-180.9	C53.0-C53.9	4,358	0.0%	54.4	46,371	10.64
corpus uteri	182.0-182.9	C54.0-C54.9	821	0.0%	56.2	7,023	8.55
ovary	183.0-183.9	C56.0-C56.9	545	0.0%	49.2	2,195	4.03
prostate	185.0-185.9	C61.0-C61.9	453	100.0%	66.6	1,614	3.56
bladder	188.0-188.9	C67.0-C67.9	825	75.8%	60.5	5,283	6.40
kidney, frotter	189.0-189.9	C64.0-C66.9	578	67.8%	54.4	2,350	4.07
brain	191.0-191.9	C70.0-C71.9	324	58.6%	35.7	1,189	3.67
thyroid gland	193.0-193.9	C73.0-C73.1	828	27.1%	50.5	8,837	10.67
lymphoma, myeloma	200.0-203.9	C81.0-C90.9	1,533	63.4%	48.2	6,710	4.38
leukemia	204.0-208.9	C91.0-C95.9	670	63.0%	25.9	1,448	2.16
total			47,517	50.8%	55.9	281,302	5.92

* mean age; mean age at the time of the first admission to the NCCCH

† The person years shown in this table are the period from the date of the first admission to the date when the vital status was confirmed.

The person years used in the analysis are the period from the date of the first admission to either the date of admission for a specific second primary cancer of interest or, for those who did not develop a MPC at the specific site of interest, to the last date when the vital status was confirmed. For those who developed MPCs at sites other than the specific site of interest, the last date of follow-up was also set at the last date when the vital status was confirmed.

The person years in this table are shown in order to summarize the cohort.

Table 3. Prevalence odds ratios (PORs) of synchronous multiple primary cancer adjusted for gender, age and calendar year of the first admission

cancer sites on the first admission	site of synchronous MPCs diagnosed at the time of the first admission															
	oral	esoph	stom	col	rect	liver	gb	panc	lary	lung	bone	skin	breas	cervix	body	ovary
lip, oral cavity, pharynx	5.0*	0.7	0.4*	0.3*	0.6	0.6	0.7	2.2*	0.5*	0.5	0.3	0.8	0.6	0.3	0.5	0.5
esophagus	8.2*	2.2*	0.6	0.5	0.3	0.4	1.2	0.7	1.0	0.4	0.8	0.6	0.3*	0.3*	0.5	1.7
stomach	0.7	1.7*	1.1	0.7	1.5*	1.9	1.9*	0.5	1.0	0.8	1.1	1.2	0.7	0.6	0.4	0.6
colon	0.5*	0.5*	1.4*	0.8	0.7	0.8	0.7	0.8	2.8	1.3	1.2	1.8	1.1	1.7	1.1	0.5
rectosigmoid junction, rectum	0.3*	0.4*	0.8	5.6*	1.3	2.2	0.6	0.5	0.7	0.7	0.9	2.4*	2.1	0.5	0.7	0.5
liver	0.3*	0.2*	0.9	0.6	0.9	0.7	4.0	0.6	0.4	0.5*	0.8	0.8	0.7	0.5	0.5	0.9
gall bladder, extrahepatic bile duct	0.7	0.2	1.7*	1.4	2.0	0.9*	3.4*	0.7	0.7	0.7	0.8	0.8	0.5	0.5	0.5	0.9
pancreas	0.6	0.3	1.3	0.5	0.5	0.9*	0.4*	0.6	0.4	0.4	0.8	0.8	0.6	0.4	0.4	3.0
larynx	3.2*	1.3	0.7	0.9	0.7	2.3*	0.8	1.2	2.4*	0.6	2.0	0.6	0.2	1.4	1.1	0.2
trachea, bronchus, lung	0.3*	0.6*	0.4*	0.4*	0.4*	0.4*	0.2*	0.5	1.1	1.3	0.9	0.7	0.3	0.4	1.0	0.3*
bone, articular cartilage	-	-	0.4	0.8	-	-	-	-	-	0.5	3.0	0.5	5.1	2.3	15.7	2.3
skin	0.5	0.7	-	0.8	0.5	0.6	-	0.4	1.4	1.4	0.4	1.4	0.4	0.5	1.1	1.2
breast	0.2*	1.1	0.5*	0.4*	1.3	0.6	0.6	0.3	1.0	0.4	1.4	0.4	0.4*	0.6*	0.5*	0.5
cervix uteri	-	0.4	0.4*	0.7	0.9	0.4	-	-	0.5	1.4	0.4	0.4*	1.3	0.9	0.4	0.8
corpus uteri	-	-	0.8	0.9	1.7	-	-	1.1	-	0.4	1.8	1.2	2.5*	11.0*	1.5	1.0
ovary	-	1.4	0.6	1.7	0.4	-	-	4.5	-	0.9	-	1.2	2.3*	11.0*	1.3	1.6
prostate	0.8	0.3*	1.0	1.3	1.0	1.2	-	1.2	0.2	2.2*	42.0	-	-	-	6.3*	1.1
bladder	0.5	0.4*	1.0	0.6	1.0	1.1	0.7	1.1	1.3	0.8	11.8	1.2	1.6	1.1	2.7	2.1
kidney, ureter	0.9	0.7	1.5	1.1	0.9	1.3	-	0.9	1.4	1.8*	1.0	1.6	2.3	1.2	1.7	6.4*
brain	-	-	-	0.5	-	-	-	-	-	-	4.6	0.4	-	-	-	1.1
thyroid gland	5.0*	4.3*	1.2	2.4*	-	3.4*	7.0*	7.8*	8.0*	3.9*	11.1	3.7	2.6*	3.7*	0.9	1.8
lymphoma, myeloma	1.0	0.3*	1.0	1.0	0.4	1.3	2.1	-	-	0.7	-	0.5	1.2	1.4	0.9	1.6
leukemia	0.6	0.7	1.2	-	0.4	-	-	3.0	1.1	1.4	-	1.3	1.4	1.0	0.8	1.9

Bold: statistically significant. (p<0.05)

*: observed number exceeds five and POR is statistically significant. (p<0.05)

†: observed number exceeds five, and two PORs are both statistically significant. (p<0.05)

-: no observation

aberrations: same as in table 1; leuk-leukemia

Table 4. Incidence rate ratios (IRRs) of metachronous multiple primary cancer adjusted for gender, age and calendar year of the first admission

cancer sites on the first admission	site of metachronous MPC																									
	cases of second primary																									
	35	62	159	73	43	24	13	18	15	84	4	15	50	22	20	18	32	33	22	7	53	26	6	934 (total)		
lip, oral cavity, pharynx																										
esophagus	11.2*	4.9*	0.9	1.1	1.0	0.5	-	0.8	2.1	0.9	4.8	1.9	1.2	1.6	1.4	1.8	0.6	0.8	0.6	-	0.7	-	-	3.7	-	
stomach	0.2	0.6	-	1.8	0.5	0.9	1.6	1.4	2.7	7.2	1.6	-	-	3.7	3.3	-	-	3.3	3.7	4.1	-	3.7	-	-	-	
colon	-	-	1.4	1.0	1.0	0.7	0.3	0.7	0.4	0.7	-	0.3	1.1	0.9	0.4	1.6	0.4	0.5	0.1	3.0	0.7	2.1	-	-		
rectosigmoid junction, rectum	0.6	0.3	1.3	3.2*	6.0*	1.9	2.2	-	1.2	-	0.9	-	4.5	1.2	1.4	6.0	6.7	0.6	0.7	3.0	-	2.0	1.1	5.4		
liver	-	-	1.3	-	-	-	-	-	-	-	0.9	-	1.6	1.7	1.2	2.2	2.5	2.7	1.4	1.1	-	-	-	-		
gall bladder, extrahepatic bile duct	-	-	-	-	-	-	-	-	-	-	-	-	-	4.0	-	-	2.9	-	-	-	-	-	-	-		
pancreas	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	49.4	-	12.2	-	-	-		
larynx	7.4*	2.7*	0.5	0.7	1.0	0.5	0.6	2.3	-	4.0*	-	4.6	-	5.8	-	-	-	-	-	-	-	-	-	-		
trachea, bronchus, lung	1.0	0.6	0.8	0.3	0.6	1.6	-	1.3	-	-	-	0.9	0.5	1.4	-	-	0.5	1.0	-	-	2.0	2.7	-	-		
bone, articular cartilage	0.0	-	1.5	-	-	-	-	-	-	-	-	-	-	-	-	-	1.0	2.0	2.0	-	2.6*	0.7	-	-		
skin	-	-	1.2	2.0	3.7	1.5	-	-	1.0	1.5	-	-	2.4	-	-	-	1.0	-	-	-	-	-	-	14.9		
breast	1.1	2.5	0.9	0.6	0.3	3.7	1.0	1.8	6.7	0.7	-	0.4	-	0.6	1.6	1.8	0.0	1.1	-	22.2	1.2	1.0	0.6	-		
cervix uteri	0.4	0.4	0.7	0.7	1.1	0.5	0.8	0.9	-	0.8	-	2.0	0.4	-	0.2	0.1	-	1.7	1.2	-	2.2	0.8	-	-		
corpus uteri	-	-	1.2	7.3*	1.1	-	-	-	0.9	49.4	-	-	1.1	1.6	-	-	-	2.0	9.2	-	0.7	3.0	-	-		
ovary	-	-	2.2	-	8.5	-	-	-	-	5.0	-	-	3.3	-	5.0	-	-	-	-	-	7.4	-	-	-		
prostate	-	-	0.8	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
bladder	-	0.5	0.7	1.7	-	1.1	-	2.7	-	1.6	22.2	-	3.3	3.0	-	-	2.6	-	3.7	6.7	-	2.0	-	-		
kidney, ureter	-	-	2.1	-	2.2	3.3	4.1	9.0	5.5	1.2	-	-	-	-	-	-	3.7	-	-	-	-	-	-	-		
brain	-	-	-	-	-	-	-	-	-	-	-	-	10.0	-	-	-	-	-	-	-	-	-	-	-		
thyroid gland	2.3	-	0.6	1.6	-	1.3	1.4	-	-	1.0	-	-	1.6	1.0	-	-	3.0	1.5	1.9	-	-	-	-	5.8		
lymphoma, myeloma	1.3	-	2.6*	0.6	0.8	1.4	1.6	-	-	-	6.0	-	-	-	3.3	3.0	3.5	-	-	-	1.1	-	-	7.4		
leukemia	-	-	-	-	-	-	-	-	-	-	-	-	-	-	23.1	-	-	-	-	-	14.2	-	-	-		

Bold: statistically significant ($p < 0.05$)*: observed number exceeds five and IRR is statistically significant ($p < 0.05$)

-: no observation

aberrations: same as in table 1

Table 5. Significant site relationships in synchronous and metachronous multiple primary cancers

site of first primary cancer	site of second cancer	synchronous cases				metachronous cases			
		adjusted POR	95%CI	adjusted POR	95%CI	adjusted IRR	95%CI	adjusted IRR	95%CI
1) Site-combinations, in which the risks of both synchronous and metachronous MPCs are significantly elevated									
lip, oral cavity, pharynx	esophagus	4.9	(3.8 - 6.2)	8.2	(6.3 - 10.6)	4.9	(2.9 - 8.5)	11.2	(4.9 - 25.6)
lip, oral cavity, pharynx	larynx	2.3	(1.4 - 3.6)	3.2	(2.0 - 4.9)	2.1	(0.6 - 7.5)	7.4	(3.2 - 16.7)
colon	rectosigmoid junction, rectum	8.1	(6.2 - 10.7)	5.6	(4.4 - 7.2)	6.0¶	(2.7 - 13.4)	3.2¶	(1.6 - 6.5)
2) site-combinations, in which only risks of synchronous MPC are significantly elevated									
lip, oral cavity, pharynx	thyroid gland	1.7	(1.0 - 2.8)	5.0	(3.0 - 8.4)	0.7	(0.2 - 2.7)	2.3	(0.5 - 10.0)
esophagus	stomach	2.2	(1.8 - 2.7)	1.7	(1.4 - 2.1)	1.8	(1.0 - 3.4)	0.6	(0.3 - 1.1)
esophagus	thyroid gland	2.3	(1.4 - 3.8)	4.3	(2.6 - 7.1)	3.6	(1.1 - 11.9)	-	-
pancreas	thyroid gland	2.5	(1.2 - 5.3)	7.8	(3.5 - 17.4)	-	-	-	-
larynx	thyroid gland	4.0	(2.1 - 7.5)	8.0	(4.2 - 15.0)	2.0	(0.6 - 6.8)	-	-
corpus uteri	ovary	11.1	(6.3 - 19.4)	10.5	(6.2 - 17.9)	-	-	4.9	(0.6 - 38.4)
prostate	bladder	6.4	(4.0 - 10.1)	6.4	(4.0 - 10.0)	-	-	2.6	-
bladder	kidney, ureter	19.3	(13.4 - 27.9)	22.7	(15.9 - 32.5)	3.6	(0.8 - 15.9)	-	-
3) site-combinations, in which only risks of metachronous MPC are significantly elevated									
trachea, bronchus, lung	thyroid gland	0.9	(0.6 - 1.4)	3.9¶	(2.6 - 5.9)	2.6	(1.1 - 6.3)	1.0	(0.2 - 4.2)
esophagus	larynx	1.2	(0.7 - 2.2)	1.1	(0.4 - 3.1)	7.2¶	(2.2 - 24.3)	2.7	(1.4 - 5.4)
larynx	trachea, bronchus, lung	2.4¶	(1.7 - 3.5)	1.1	(0.8 - 1.6)	4.0	(2.2 - 7.0)	1.3	(0.3 - 5.7)
corpus uteri	colon	0.9	(0.3 - 2.7)	1.1	(0.5 - 2.8)	7.3	(3.0 - 18.1)	6.0	-
lymphoma, myeloma	stomach	1.0	(0.7 - 1.5)	1.1	(0.7 - 1.7)	2.5	(1.4 - 4.7)	2.1	(0.9 - 4.9)
4) site-combinations, in which only risks of synchronous MPC are significantly decreased									
lip, oral cavity, pharynx	stomach	0.7	(0.2 - 0.7)	0.7	(0.5 - 0.9)	0.9	(0.6 - 1.6)	0.2¶	(0.0 - 0.5)
lip, oral cavity, pharynx	colon	0.4	(0.2 - 0.7)	0.5	(0.2 - 0.9)	1.1	(0.5 - 2.5)	-	-
lip, oral cavity, pharynx	rectosigmoid junction, rectum	0.3	(0.2 - 0.7)	0.4	(0.2 - 0.8)	1.0	(0.3 - 3.2)	0.6	(0.1 - 4.5)
lip, oral cavity, pharynx	trachea, bronchus, lung	0.5	(0.3 - 0.7)	0.3	(0.2 - 0.4)	0.9	(0.4 - 2.0)	1.0	(0.3 - 3.5)
esophagus	trachea, bronchus, lung	0.7	(0.4 - 1.0)	0.3	(0.2 - 0.4)	1.6	(0.6 - 4.5)	0.6	(0.2 - 1.7)
breast	cervix uteri	0.4	(0.3 - 0.7)	0.3	(0.2 - 0.5)	0.6	-	0.4	-

bold: significant and observed number equal to five or over.

‡ : significant, but observed number > 5

- : no observed data or not available