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Incidence of metachronous second primary cancers in Osaka, Japan: Update of analyses using population-based cancer registry data

Takahiro Tabuchi,[1] Yuri Ito, Akiko Ioka, Isao Miyashiro and Hideaki Tsukuma

Center for Cancer Control and Statistics, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan

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Cancer survivors are at excess risk of developing second primary cancers, but the precise level of risk in Japanese patients is not known. To investigate the risk of survivors developing second primary cancers, we conducted a retrospective cohort study using data from the Osaka Cancer Registry. The study subjects comprised all reported patients aged 0–79 years who were first diagnosed with cancer between 1985 and 2004 in Osaka and who survived for at least 3 months, followed-up through to December 2005. A metachronous second primary cancer was defined as any invasive second cancer that was diagnosed between 3 months and 10 years after the first cancer diagnosis. The main outcome measures were incidence rates per 100 000 person-years, cumulative risk and standardized incidence ratios (SIR) of second primary cancer. Metachronous second primary cancers developed in 13 385 of 355 966 survivors (3.8%) after a median follow-up of 2.5 years. Sex-specific incidence rates of metachronous second primary cancer per 100 000 person-years increased with age, and were higher among men than women (except for the 0–49 years age group), but these rates did not differ over the study period. The 10-year cumulative risk was estimated as 13.0% for those who first developed cancer at 60–69 years of age (16.2% for men, 8.6% for women). The SIR among those with first cancer diagnosed at 0–39 and 40–49 years of age were 2.13 and 1.52, respectively, in both sexes, whereas the SIR among cancers of the mouth/pharynx, esophagus and larynx were much higher than one as for site relationships. We showed that cancer survivors in Osaka, Japan, were at higher risk of second primary cancers compared with the general population. Our findings indicate that second primary cancers should be considered as a commonly encountered major medical problem. Further investigations are required to advance our understanding to enable the development of effective measures against multiple primary cancers. (*Cancer Sci* 2012; 103: 1111–1120)

Approximately 50% of men and 40% of women will develop a cancer during their lifetime,[1] and half of all cancer patients in Japan will survive for at least 5 years.[2] Because of the longer survival times for several forms of cancer and the aging of the population, it is estimated that 5–10% of all cancer patients develop a further, independent primary cancer.[3,4] A better understanding of multiple primary cancers should yield greater insights into the shared etiological factors and basic mechanisms of carcinogenesis and could thus provide a more sound basis for the management of cancer patients, including the development of protective measures.[5]

In a previous study using data from the Osaka Cancer Registry (2000 Census population; 8.8 million), one of the largest population-based cancer registries in the world, we reported that 2.0% of cancer patients developed metachronous second primary cancer between 1966 and 1986.[4] We also calculated the 10-year cumulative risk for metachronous second primaries to be approximately 10% for those who developed their first cancer at 60–69 years of age between 1978 and 1983.[4] However, investigations into trends or site combinations could not be completed owing to the short cancer registration period. In the present study, we updated the data for the incidence of metachronous second primary cancers in Osaka, Japan, according to sex, age groups, calendar year at diagnosis, primary cancer sites, and follow-up interval. This was done not only to provide an insight into the etiology of cancer, but also to provide information for effective medical care by clinical oncologists.

Materials and Methods

Study subjects and definition of metachronous second primary cancer. The present study was designed as a retrospective cohort study. Individual case records were obtained from the Osaka Cancer Registry, which was founded in 1962 for the purpose of registering all malignant tumors and benign intracranial tumors arising in Osaka Prefecture.[6] The study subjects were all reported patients aged 0–79 years in Osaka who were initially diagnosed as having a first primary cancer between 1985 and 2004 and had survived for at least 3 months. The incidence of second primary cancers among the study subjects was examined through to the end of 2005 for a maximum of 10 years after the first cancer diagnosis.

Metachronous second primary cancer was defined as any invasive second cancer that was diagnosed between 3 months and 10 years after diagnosis of the first cancer. *In situ* carcinomas, benign intracranial tumors, and any third or fourth (or more) primaries were excluded. Each cancer site was categorized into 16 selected major groups according to International Classification of Diseases Tenth Revision (ICD-10)[7], to analyze the cancer site relationships between first and second cancer. The ICD-10 codes used in the present study are given as mouth/pharynx (C00-14), esophagus (C15), stomach (C16), colorectum (C18-20), liver (C22), gallbladder (C23, C24), pancreas (C25), larynx (C32), lung (C33, C34), breast (female) (C50), uterus (C53-55), ovary (C56), prostate (C61), kidney/urinary tract/bladder (C64-68), thyroid (C73) and blood (C81-85, C88, C90, C91-96).

Statistical analysis. To estimate the risk for second primary cancer, person-years at risk were calculated as the time from 3 months after diagnosis of the first cancer until whichever of the following came first: (i) December 31, 2005; (ii) the date of diagnosis of the metachronous second primary cancer; (iii) the date of death; (iv) the date when a patient reached 80 years of age; or (v) the date 10 years after the diagnosis of the first cancer.[8]

The incidence rate per 100 000 person-years and cumulative risk[9] for metachronous second primary cancer were estimated

[1]To whom correspondence should be addressed.
E-mail: tabuti-ta@mc.pref.osaka.jp

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according to sex, age group and calendar year at the time of diagnosis of the first cancer.

The observed number of metachronous second primary cancers was compared with the expected number according to sex, age group, selected site of the first and second cancer, and follow-up interval. A standardized incidence ratio (SIR) was then obtained by dividing the observed number of cases of a second primary cancer by the expected number. Thus, the SIR is used to estimate the risk of a cancer patient developing a second primary malignancy compared with the incidence of cancer among the general population. In the analyses for site relationship between the first and second cancer, we report only the cancer site combinations where more than 10 eligible metachronous second primary cancers were obtained. The significance and 95% confidence intervals (CI) for the SIR were tested by Poisson distribution analysis.

In Osaka, we used the rules suggested by the International Agency for Research on Cancer (IARC)[10] and the third edition of the ICD-O[11] to define the circumstance under which an individual is considered to have more than one cancer. The IARC's definition does not accept any tumors in the same site as a second primary cancer unless their major histological type differs from that of the first primary cancer. Therefore, the SIR for all sites will be underestimated, particularly in the case of first cancers with high person-years, such as cancer of the stomach, colorectum, liver, lung, and breast. To avoid such underestimations, we excluded both the observed and expected numbers of second primary cancer in the same site as the first cancer from the SIR calculations for all sites. Therefore, in the present study a second primary cancer of the same site (as defined by the three-digit rubric of the ICD with some exceptions according to the rules) was excluded even if its histological type differed from that of the first primary cancer when we used the variable of cancer site in the analyses.[8]

Probability values for statistical tests were two-tailed and $P < 0.05$ was considered significant. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

Results

The total number of study subjects was 355 966, of whom 79.7% were histologically verified. During the follow-up period (median follow-up duration 2.5 years; mean 3.9 years), metachronous second primary cancers developed in 13 385 subjects (3.8%). Figure 1 shows age- and sex-specific incidence rates of metachronous second primary cancers per 100 000 person-years, in which study subjects were classified into four groups according to calendar year at diagnosis of the first cancer. The incidence rates increased remarkably with an increase in age and were higher among men than women, except in the 0–39 and 40–49 years age groups. In terms of calendar year at the time of diagnosis of the first cancer, age-specific incidence rates did not differ within either sex.

Table 1 shows the cumulative risks of metachronous second primary cancers according to age and calendar year at diagnosis of the first cancer. The 10-year cumulative risk was estimated as 13.0% for those who developed their first cancer at 60–69 years of age (16.2% for men, 8.6% for women). No difference or increasing trend was observed during the study period.

Table 2 shows the SIR according to sex, age at diagnosis of the first cancer, and follow-up interval. The SIR and 95% CI among those (of both sexes) who developed their first cancer at 0–39 and 40–49 years of age were 2.54 (1.43–3.66) and 1.75 (1.41–2.10), respectively, for the first year; 2.34 (1.86–2.82) and 1.61 (1.46–1.77), respectively, for the next 4 years; 1.90 (1.51–2.29) and 1.39 (1.25–1.53), respectively, for the next 5–10-year period; and 2.13 (1.84–2.43) and 1.52 (1.42–1.62), respectively, for all 10 years after diagnosis of the first cancer. These ratios were higher than those in the total and other age groups. During the period 1–5 years after the diagnosis of the first cancer, 38% and 48% excess risk of metachronous second primary cancers was observed among men and women, respectively, who developed their first cancer at 50–59 years of age. Women aged 50–79 years had a tendency for a higher SIR of metachronous second primaries than men aged 50–79 years, whereas women aged 0–49 years had a tendency for a lower SIR than men aged 0–49 years.

Table 3 lists the SIR according to selected sites of the first cancer and the follow-up interval. There were no clear increasing or decreasing trends of SIR for any site of the first cancer for the duration of follow-up. The highest SIR (~2.0–2.5) were observed for cancers of the mouth/pharynx, esophagus, and larynx, followed by cancers of the lung, breast, uterus, ovary, thyroid, and blood (~1.4–1.7). The ratios for the remaining

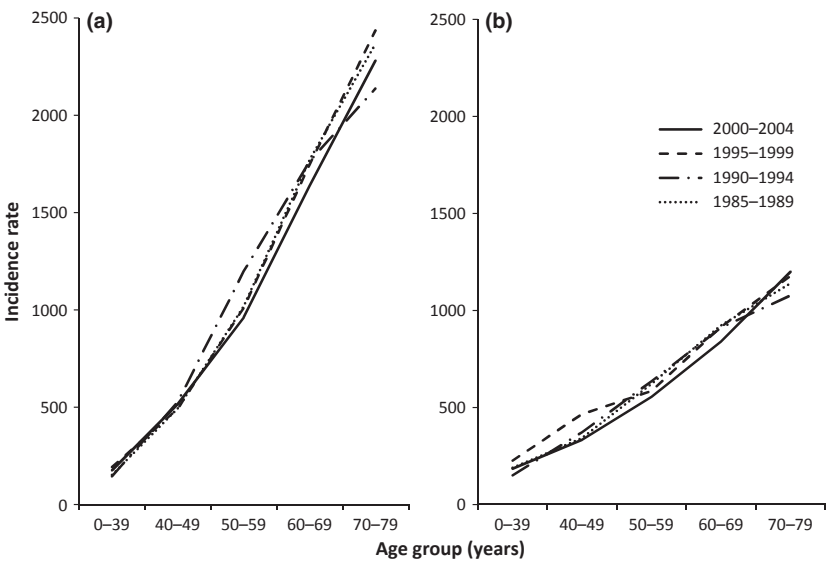

Fig. 1. Age-specific incidence rates of metachronous second primary cancer per 100 000 person-years in (a) men and (b) women according to the calendar year at diagnosis of the first cancer, Osaka, 1985–2004.

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Table 1. Cumulative risk of metachronous second primary cancer (%), according to sex, age and calendar year at the time of diagnosis of the first cancer

Sex/age (years)	Duration	Year of diagnosis of first cancer				
		1985–1989	1990–1994	1995–1999	2000–2004	Total
Male						
0–39	3 months–5 years	0.4	0.9	1.0	0.9	0.8
	3 months–10 years	1.5	1.4	1.8	–	1.6
40–49	3 months–5 years	2.2	2.0	2.1	2.3	2.1
	3 months–10 years	5.1	4.8	4.9	–	5.0
50–59	3 months–5 years	4.9	4.1	4.6	4.5	4.5
	3 months–10 years	11.4	9.8	9.5	–	10.2
60–69	3 months–5 years	7.2	7.3	7.9	7.5	7.5
	3 months–10 years	16.4	16.5	15.7	–	16.2
70–79	3 months–5 years	9.2	10.1	10.8	10.2	10.2
	3 months–10 years	20.8	22.5	21.7	–	21.8
Female						
0–39	3 months–5 years	0.7	0.6	0.9	0.8	0.7
	3 months–10 years	1.9	1.5	2.3	–	1.9
40–49	3 months–5 years	1.5	1.9	1.9	1.6	1.7
	3 months–10 years	3.3	3.5	4.6	–	3.7
50–59	3 months–5 years	2.7	2.7	2.8	2.6	2.7
	3 months–10 years	6.0	6.1	5.5	–	5.8
60–69	3 months–5 years	4.0	3.9	4.3	3.9	4.1
	3 months–10 years	8.7	8.6	8.4	–	8.6
70–79	3 months–5 years	4.9	4.7	5.6	5.5	5.2
	3 months–10 years	11.7	11.0	10.1	–	11.0
All patients						
0–39	3 months–5 years	0.6	0.7	1.0	0.8	0.8
	3 months–10 years	1.7	1.5	2.1	–	1.8
40–49	3 months–5 years	1.7	1.9	2.0	1.8	1.9
	3 months–10 years	3.9	4.0	4.7	–	4.2
50–59	3 months–5 years	3.9	3.5	3.7	3.5	3.7
	3 months–10 years	8.8	8.1	7.5	–	8.1
60–69	3 months–5 years	5.8	6.0	6.6	6.1	6.2
	3 months–10 years	12.8	13.3	12.9	–	13.0
70–79	3 months–5 years	7.3	7.7	8.6	8.4	8.1
	3 months–10 years	16.4	17.2	16.8	–	17.0

cancer sites were approximately 1.1–1.3 and usually > 1.0 regardless of the significance.

Table 4 lists the SIR according to selected sites of the first and second primary cancers. Some specific associations were observed between the sites of the first and second primary cancers; specifically, the SIR for cancers of the mouth/pharynx, esophagus, and larynx were much higher. That is, the SIR between these three sites ranged between 4 and 22; however, the SIR for lung and the three sites was estimated to be approximately 2–3. The site relationships between breast, uterus, and ovary were relatively high, especially after first breast cancer (i.e. the SIR [95% CI] was 2.07 [1.71–2.43] for first breast to second uterus; 2.16 [1.62–2.70] for first breast to second ovary; 1.40 [1.10–1.71] for first uterus to second breast; and 1.43 [0.82–2.04] for first ovary to second breast). In addition, a high SIR for second thyroid cancer, but not first thyroid cancer, was observed.

Discussion

The present study shows that in Osaka, Japan, 3.8% of study subjects (of both sexes) developed metachronous second primary cancers within 10 years of the first primary cancer between 1985 and 2005. Compared with our previous study, in which we reported that 2.0% of cancer patients developed metachronous second primary cancers between 1966 and 1986,[4] the proportion of multiple primary cancers has approximately doubled in the past 20 years. Although constantly elevated SIR was not observed in the first decade in our previous study,[4] elevated SIR for metachronous second primary cancers was observed among almost all sex and age groups over the study period in the present study. Almost all cancer patients were more likely to develop metachronous second primary cancers than the general population, as also found in another recent study in Australia.[12] A possible explanation for this finding could be the accumulation or concentration of cancer risk factors, such as smoking, alcohol drinking, radiotherapy treatment, and other potential factors, including genetic factors, within an individual. It may be difficult to improve cancer patients' lifestyle. For example, smoking cessation is challenging even for patients recovering from lung cancer with curative treatment because a significant proportion of smokers with cancer do not receive formal assistance to quit.[13] However, detection or surveillance bias may also play a part in the results, as evidenced in the elevated SIR of second thyroid cancer.[14]

We also found that the 10-year cumulative risk for second primaries was 13.0% for those who developed their first cancer at 60–69 years of age. Although this finding was slightly higher than our previous results, with an approximate 10% 10-year cumulative risk for second primaries for those who developed their first cancer at 60–69 years of age in 1978–1983,[4] we added sex-stratified information on cumulative risk for second primaries. Men with their first cancer diagnosed when they were at 60–69 years of age had a high cumulative risk of

Table 2. Observed numbers and standardized incidence ratios of metachronous second primary cancer according to sex, age at diagnosis of the first cancer and years after diagnosis of the first cancer, 1985–2004

Age at diagnosis of the first cancer (years)	Years after diagnosis of the first cancer															
	3 months–1 year				1–5 years				5–10 years*				Total (3 months–10 years)			
	No. second primary cancers	Person-years	SIR	95% CI	No. second primary cancers	Person-years	SIR	95% CI	No. second primary cancers	Person-years	SIR	95% CI	No. second primary cancers	Person-years	SIR	95% CI
Male patients																
0–39	9	5 739	4.59	1.59–7.59	34	20 737	3.88	2.58–5.19	27	16 937	2.34	1.46–3.23	70	43 414	3.15	2.41–3.88
40–49	37	10 557	1.81	1.23–2.39	170	35 274	1.89	1.61–2.18	164	27 466	1.50	1.27–1.73	371	73 298	1.69	1.52–1.86
50–59	282	31 382	1.53	1.35–1.70	927	93 355	1.38	1.29–1.47	731	59 066	1.22	1.13–1.30	1940	183 805	1.33	1.27–1.39
60–69	655	47 644	1.05	0.97–1.13	2279	130 211	1.19	1.14–1.23	1311	66 678	1.07	1.01–1.13	4245	244 535	1.13	1.09–1.16
70–79	638	32 168	0.93	0.86–1.01	1581	65 729	1.10	1.05–1.16	346	12 526	1.19	1.06–1.31	2565	110 423	1.07	1.03–1.11
Total (0–79)	1621	127 490	1.07	1.02–1.12	4991	345 305	1.21	1.18–1.24	2579	182 673	1.15	1.11–1.20	9191	655 475	1.17	1.14–1.19
Female patients																
0–39	11	8 811	1.86	0.76–2.97	57	34 455	1.89	1.40–2.38	65	28 115	1.76	1.33–2.19	133	71 383	1.82	1.51–2.13
40–49	64	16 943	1.72	1.30–2.15	247	67 177	1.47	1.28–1.65	224	55 039	1.32	1.15–1.49	535	139 162	1.43	1.30–1.55
50–59	144	25 098	1.64	1.37–1.90	503	86 858	1.48	1.35–1.61	389	59 469	1.34	1.21–1.48	1036	171 427	1.45	1.36–1.53
60–69	211	27 930	1.24	1.07–1.41	799	88 050	1.35	1.25–1.44	524	54 128	1.17	1.07–1.27	1534	170 110	1.27	1.20–1.33
70–79	240	21 790	1.14	0.99–1.28	568	49 613	1.16	1.06–1.25	148	11 723	1.20	1.01–1.39	956	83 127	1.16	1.08–1.23
Total (0–79)	670	100 573	1.31	1.21–1.41	2174	326 153	1.34	1.28–1.4	1350	208 474	1.27	1.20–1.33	4194	635 209	1.31	1.27–1.35
All patients (both sexes)																
0–39	20	14 550	2.54	1.43–3.66	91	55 192	2.34	1.86–2.82	92	45 052	1.90	1.51–2.29	203	114 796	2.13	1.84–2.43
40–49	101	27 500	1.75	1.41–2.10	417	102 451	1.61	1.46–1.77	388	82 505	1.39	1.25–1.53	906	212 460	1.52	1.42–1.62
50–59	426	56 480	1.56	1.41–1.71	1430	180 213	1.42	1.34–1.49	1120	118 535	1.26	1.18–1.33	2976	355 232	1.37	1.32–1.42
60–69	866	75 575	1.09	1.02–1.16	3078	218 260	1.22	1.18–1.27	1835	120 805	1.10	1.05–1.15	5779	414 645	1.16	1.13–1.19
70–79	878	53 958	0.98	0.92–1.05	2149	115 342	1.12	1.07–1.16	494	24 249	1.19	1.09–1.30	3521	193 550	1.09	1.05–1.13
Total (0–79)	2291	228 063	1.13	1.08–1.18	7165	671 459	1.25	1.22–1.28	3929	391 147	1.19	1.15–1.23	13385	1 290 684	1.21	1.19–1.23

CI, confidence interval. *Because of the high proportion of censored data, the low reliability of the standardized incidence ratios (SIR) among the population aged 70–79 years for the period 5–10 years after diagnosis of the first cancer should be kept in mind.

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Table 3. Observed numbers and standardized incidence ratios of second primary cancer according to site of the first cancer and follow-up interval after diagnosis of the first cancer, 1985–2004, for both sexes combined

Site of the first cancer	ICD-10	Follow-up interval after diagnosis of the first cancer															
		3 months–1 year				1–5 years				5–10 years				Total (3 months–10 years)			
		No. second primary cancers	Person-years	SIR	95% CI	No. second primary cancers	Person-years	SIR	95% CI	No. second primary cancers	Person-years	SIR	95% CI	No. second primary cancers	Person-years	SIR	95% CI
Mouth/pharynx	C00–14	107	5 578	2.27	1.84–2.70	368	16 439	2.66	2.39–2.93	187	9 621	2.26	1.93–2.58	662	31 638	2.47	2.28–2.65
Esophagus	C15	109	5 460	1.96	1.59–2.32	205	9 576	2.04	1.76–2.32	86	3 570	2.10	1.66–2.55	400	18 606	2.03	1.83–2.23
Stomach	C16	432	47 535	1.17	1.06–1.28	1522	145 980	1.33	1.26–1.39	1013	96 018	1.27	1.19–1.34	2967	289 536	1.28	1.24–1.33
Colorectum	C18–20	376	36 192	1.29	1.16–1.42	1301	114 495	1.36	1.29–1.43	793	66 397	1.34	1.25–1.43	2470	217 085	1.34	1.29–1.39
Liver	C22	239	22 872	1.14	1.00–1.29	619	53 731	1.19	1.10–1.29	138	13 654	1.00	0.84–1.17	996	90 258	1.15	1.08–1.22
Gallbladder	C23, C24	34	3 613	0.98	0.65–1.31	81	6 205	1.40	1.10–1.71	34	2 703	1.35	0.90–1.81	149	12 522	1.27	1.06–1.47
Pancreas	C25	36	3 824	1.02	0.68–1.35	45	3 730	1.37	0.97–1.77	13	1 339	1.14	0.52–1.76	94	8 893	1.18	0.94–1.42
Larynx	C32	63	2 269	2.32	1.75–2.90	259	8 158	2.52	2.22–2.83	148	5 220	2.03	1.70–2.35	470	15 647	2.32	2.11–2.53
Lung	C33, C34	284	22 705	1.32	1.16–1.47	533	39 087	1.47	1.34–1.59	162	13 571	1.24	1.05–1.43	979	75 364	1.38	1.29–1.47
Breast (females)	C50	115	25 252	1.44	1.18–1.71	509	102 282	1.49	1.36–1.62	383	70 034	1.47	1.32–1.61	1007	197 571	1.48	1.38–1.57
Uterus	C53–55	46	9 606	1.25	0.89–1.61	232	36 008	1.63	1.42–1.84	204	28 203	1.66	1.43–1.88	482	73 819	1.59	1.45–1.74
Ovary	C56	24	3 592	1.78	1.07–2.50	67	10 212	1.81	1.38–2.24	33	5 840	1.54	1.01–2.07	124	19 644	1.72	1.42–2.03
Prostate	C61	88	5 436	1.03	0.82–1.25	302	15 868	1.18	1.05–1.31	95	4 756	1.16	0.92–1.39	485	26 061	1.15	1.04–1.25
Kidney/urinary tract/bladder	C64–68	128	9 816	1.26	1.04–1.48	493	33 330	1.42	1.30–1.55	272	20 392	1.24	1.09–1.39	893	63 539	1.34	1.25–1.43
Thyroid	C73	30	3 432	1.81	1.16–2.46	97	14 893	1.36	1.09–1.63	83	11 953	1.43	1.12–1.74	210	30 278	1.44	1.25–1.64
Blood	C81–85, C88, C90, C91–96	93	10 121	1.45	1.15–1.74	258	28 528	1.56	1.37–1.75	126	15 685	1.54	1.27–1.80	477	54 334	1.53	1.39–1.67

CI, confidence interval; SIR, standardized incidence ratios.

Table 4. Observed numbers and standardized incidence ratios of second primary cancer according to the site of first and second primary cancer, 1985–2004, in both sexes

First cancer site	Second cancer site	No. second primary cancers	Person-years	SIR	95% CI
Mouth/pharynx	Esophagus	137	32 483	13.62	11.34–15.90
Mouth/pharynx	Stomach	81	32 571	1.38	1.08–1.68
Mouth/pharynx	Colorectum	53	32 558	1.35	0.99–1.71
Mouth/pharynx	Liver	66	32 599	1.49	1.13–1.85
Mouth/pharynx	Gallbladder	11	32 684	1.52	0.62–2.41
Mouth/pharynx	Pancreas	17	32 684	1.57	0.82–2.31
Mouth/pharynx	Larynx	12	32 674	4.35	1.89–6.81
Mouth/pharynx	Lung	113	32 562	2.45	2.00–2.90
Mouth/pharynx	Prostate	18	32 657	1.73	0.93–2.53
Mouth/pharynx	Kidney/urinary tract/bladder	16	32 656	1.30	0.66–1.94
Mouth/pharynx	Blood	28	32 661	2.39	1.50–3.27
Esophagus	Mouth/pharynx	94	19 043	21.63	17.26–26.00
Esophagus	Stomach	58	19 128	1.32	0.98–1.66
Esophagus	Colorectum	33	19 117	1.15	0.76–1.54
Esophagus	Liver	40	19 154	1.21	0.83–1.58
Esophagus	Pancreas	16	19 193	2.00	1.02–2.97
Esophagus	Larynx	14	19 181	6.38	3.04–9.72
Esophagus	Lung	62	19 129	1.71	1.29–2.14
Esophagus	Prostate	14	19 181	1.51	0.72–2.30
Esophagus	Kidney/urinary tract/bladder	19	19 173	2.00	1.10–2.90
Esophagus	Blood	16	19 174	1.89	0.97–2.82
Stomach	Mouth/pharynx	89	294 635	1.54	1.22–1.86
Stomach	Esophagus	171	294 528	1.68	1.42–1.93
Stomach	Colorectum	563	293 399	1.40	1.28–1.51
Stomach	Liver	486	293 978	1.07	0.97–1.16
Stomach	Gallbladder	91	294 693	1.17	0.93–1.41
Stomach	Pancreas	134	294 709	1.18	0.98–1.38
Stomach	Larynx	39	294 685	1.36	0.94–1.79
Stomach	Lung	632	294 047	1.26	1.16–1.36
Stomach	Breast (female)	126	294 397	1.63	1.34–1.91
Stomach	Uterus	35	294 742	1.09	0.73–1.45
Stomach	Ovary	15	294 779	1.04	0.51–1.56
Stomach	Prostate	157	294 497	1.36	1.15–1.57
Stomach	Kidney/urinary tract/bladder	163	294 433	1.26	1.07–1.45
Stomach	Thyroid	31	294 695	1.86	1.20–2.51
Stomach	Blood	137	294 653	1.14	0.95–1.33
Colorectum	Mouth/pharynx	47	222 016	1.13	0.81–1.45
Colorectum	Esophagus	95	221 949	1.31	1.05–1.57
Colorectum	Stomach	558	220 824	1.28	1.17–1.39
Colorectum	Liver	352	221 454	1.07	0.96–1.19
Colorectum	Gallbladder	58	222 035	0.97	0.72–1.22
Colorectum	Pancreas	109	222 020	1.28	1.04–1.52
Colorectum	Larynx	29	222 010	1.50	0.96–2.05
Colorectum	Lung	410	221 554	1.14	1.03–1.25
Colorectum	Breast (female)	91	221 774	1.22	0.97–1.47
Colorectum	Uterus	50	221 961	1.64	1.19–2.10
Colorectum	Ovary	34	222 048	2.43	1.61–3.24
Colorectum	Prostate	107	221 886	1.31	1.06–1.56
Colorectum	Kidney/urinary tract/bladder	120	221 805	1.30	1.07–1.53
Colorectum	Thyroid	42	221 956	3.00	2.09–3.91
Colorectum	Blood	108	221 970	1.20	0.97–1.43
Liver	Mouth/pharynx	31	91 628	1.51	0.98–2.04
Liver	Esophagus	58	91 598	1.56	1.16–1.96
Liver	Stomach	264	91 223	1.22	1.08–1.37
Liver	Colorectum	170	91 367	1.19	1.01–1.37
Liver	Gallbladder	22	91 655	0.82	0.48–1.17
Liver	Pancreas	34	91 647	0.85	0.57–1.14
Liver	Lung	146	91 519	0.82	0.69–0.95
Liver	Breast (female)	24	91 633	1.26	0.75–1.76
Liver	Ovary	12	91 658	3.23	1.40–5.06

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Table 4. (continued)

First cancer site	Second cancer site	No. second primary cancers	Person-years	SIR	95% CI
Liver	Prostate	47	91 597	1.09	0.78–1.41
Liver	Kidney/urinary tract/bladder	52	91 585	1.13	0.82–1.44
Liver	Thyroid	11	91 647	2.14	0.88–3.41
Liver	Blood	67	91 605	1.60	1.21–1.98
Gallbladder	Stomach	27	12 699	1.11	0.69–1.53
Gallbladder	Colorectum	33	12 669	1.92	1.26–2.57
Gallbladder	Liver	13	12 696	0.74	0.34–1.14
Gallbladder	Lung	27	12 705	1.37	0.85–1.89
Pancreas	Stomach	14	8 994	0.83	0.39–1.26
Pancreas	Colorectum	18	8 991	1.55	0.83–2.26
Pancreas	Lung	18	8 998	1.33	0.72–1.94
Larynx	Mouth/pharynx	26	16 492	6.03	3.71–8.35
Larynx	Esophagus	45	16 471	5.56	3.94–7.19
Larynx	Stomach	84	16 291	1.81	1.43–2.20
Larynx	Colorectum	41	16 431	1.44	1.00–1.88
Larynx	Liver	47	16 472	1.32	0.94–1.70
Larynx	Gallbladder	10	16 527	1.92	0.73–3.11
Larynx	Pancreas	12	16 534	1.50	0.65–2.35
Larynx	Lung	136	16 336	3.48	2.90–4.07
Larynx	Prostate	11	16 517	1.10	0.45–1.75
Larynx	Kidney/urinary tract/bladder	20	16 490	1.98	1.11–2.85
Larynx	Blood	13	16 525	1.54	0.70–2.38
Lung	Mouth/pharynx	35	76 773	2.14	1.43–2.84
Lung	Esophagus	60	76 748	2.04	1.52–2.55
Lung	Stomach	250	76 462	1.39	1.22–1.57
Lung	Colorectum	146	76 533	1.24	1.04–1.44
Lung	Liver	107	76 694	0.82	0.66–0.97
Lung	Gallbladder	30	76 798	1.27	0.82–1.73
Lung	Pancreas	46	76 789	1.36	0.96–1.75
Lung	Larynx	21	76 778	2.51	1.44–3.58
Lung	Breast (female)	34	76 724	1.66	1.10–2.21
Lung	Uterus	11	76 806	1.30	0.53–2.07
Lung	Prostate	62	76 713	1.67	1.26–2.09
Lung	Kidney/urinary tract/bladder	64	76 730	1.65	1.25–2.06
Lung	Thyroid	20	76 780	4.29	2.41–6.17
Lung	Blood	43	76 777	1.22	0.86–1.59
Breast (female)	Mouth/pharynx	16	200 696	1.40	0.71–2.08
Breast (female)	Esophagus	20	200 702	1.92	1.08–2.76
Breast (female)	Stomach	180	200 292	1.40	1.20–1.61
Breast (female)	Colorectum	152	200 362	1.20	1.01–1.40
Breast (female)	Liver	88	200 620	1.18	0.93–1.43
Breast (female)	Gallbladder	36	200 686	1.28	0.86–1.69
Breast (female)	Pancreas	42	200 705	1.27	0.88–1.65
Breast (female)	Lung	103	200 563	1.24	1.00–1.48
Breast (female)	Uterus	126	200 389	2.07	1.71–2.43
Breast (female)	Ovary	61	200 574	2.16	1.62–2.70
Breast (female)	Kidney/urinary tract/bladder	26	200 631	1.24	0.77–1.72
Breast (female)	Thyroid	83	200 359	5.06	3.97–6.15
Breast (female)	Blood	43	200 682	1.08	0.76–1.41
Uterus	Stomach	54	74 675	1.06	0.78–1.35
Uterus	Colorectum	75	74 568	1.56	1.21–1.92
Uterus	Liver	29	74 741	0.98	0.62–1.33
Uterus	Gallbladder	19	74 751	1.62	0.89–2.35
Uterus	Pancreas	21	74 753	1.63	0.93–2.32
Uterus	Lung	82	74 668	2.60	2.03–3.16
Uterus	Breast (female)	82	74 497	1.40	1.10–1.71
Uterus	Kidney/urinary tract/bladder	15	74 735	1.86	0.92–2.80
Uterus	Thyroid	13	74 711	2.12	0.97–3.27
Uterus	Blood	35	74 733	2.32	1.55–3.10
Ovary	Stomach	11	19 858	0.99	0.40–1.57

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Table 4. (continued)

First cancer site	Second cancer site	No. second primary cancers	Person-years	SIR	95% CI
Ovary	Colorectum	33	19 802	3.04	2.00–4.07
Ovary	Lung	12	19 876	1.73	0.75–2.71
Ovary	Breast (female)	21	19 844	1.43	0.82–2.04
Ovary	Blood	13	19 876	3.74	1.71–5.78
Prostate	Mouth/pharynx	21	26 800	2.47	1.41–3.52
Prostate	Esophagus	14	26 833	0.82	0.39–1.25
Prostate	Stomach	119	26 628	1.23	1.01–1.46
Prostate	Colorectum	80	26 698	1.35	1.05–1.65
Prostate	Liver	59	26 741	0.87	0.65–1.09
Prostate	Gallbladder	16	26 825	1.41	0.72–2.09
Prostate	Pancreas	21	26 824	1.21	0.69–1.73
Prostate	Lung	62	26 777	0.67	0.50–0.83
Prostate	Kidney/urinary tract/bladder	50	26 763	2.21	1.60–2.83
Prostate	Blood	22	26 822	1.24	0.72–1.75
Kidney/urinary tract/bladder	Mouth/pharynx	17	65 125	1.21	0.64–1.79
Kidney/urinary tract/bladder	Esophagus	36	65 118	1.41	0.95–1.88
Kidney/urinary tract/bladder	Stomach	167	64 815	1.12	0.95–1.29
Kidney/urinary tract/bladder	Colorectum	122	64 847	1.26	1.04–1.49
Kidney/urinary tract/bladder	Liver	111	64 975	1.00	0.81–1.19
Kidney/urinary tract/bladder	Gallbladder	25	65 137	1.35	0.82–1.88
Kidney/urinary tract/bladder	Pancreas	33	65 147	1.21	0.80–1.62
Kidney/urinary tract/bladder	Lung	177	64 960	1.41	1.20–1.61
Kidney/urinary tract/bladder	Breast (female)	12	65 136	0.97	0.42–1.52
Kidney/urinary tract/bladder	Uterus	12	65 116	2.32	1.01–3.64
Kidney/urinary tract/bladder	Prostate	64	65 005	2.08	1.57–2.59
Kidney/urinary tract/bladder	Blood	34	65 108	1.18	0.78–1.58
Thyroid	Stomach	32	30 711	1.24	0.81–1.67
Thyroid	Colorectum	27	30 689	1.25	0.78–1.72
Thyroid	Liver	12	30 753	0.70	0.30–1.10
Thyroid	Lung	26	30 716	1.43	0.88–1.98
Thyroid	Breast (female)	37	30 666	1.97	1.34–2.61
Thyroid	Blood	13	30 746	1.93	0.88–2.97
Blood	Mouth/pharynx	14	55 012	2.18	1.04–3.32
Blood	Esophagus	17	55 027	1.61	0.84–2.37
Blood	Stomach	79	54 898	1.20	0.94–1.47
Blood	Colorectum	55	54 931	1.20	0.88–1.51
Blood	Liver	82	54 916	1.71	1.34–2.07
Blood	Lung	71	54 957	1.38	1.06–1.70
Blood	Breast (female)	10	55 005	0.65	0.25–1.04
Blood	Prostate	19	55 015	1.77	0.98–2.57
Blood	Kidney/urinary tract/bladder	24	54 990	1.77	1.06–2.47
Blood	Thyroid	14	55 017	5.54	2.64–8.43

CI, confidence interval; SIR, standardized incidence ratios.

16.2%, compared with an 8.6% risk in women. These figures clearly show that second primary cancer should be regarded as a problem commonly encountered in routine medical practice rather than a rare and unusual event to be described in case reports.

The SIR for metachronous second primary cancers from the first cancer of the mouth/pharynx, esophagus, and larynx, generally accepted as smoking and alcohol related, was higher than those from the other first cancers, including lung cancer. Robust site relationships of first and second primary cancers within these three cancer sites (mouth/pharynx to esophagus, mouth/pharynx to larynx, esophagus to larynx and each others) were found (see Table 4). Tobacco smoking is clearly one of the major causes of second primary cancers, as it is for first cancers.[15] Generally, cigarette smokers had an approximate 15–30-fold higher risk of lung cancer than non-smokers, whereas an approximate 2–10-fold higher risk of cancer of the mouth/pharynx, esophagus, or larynx has been reported for cigarette smokers.[16] In the present study, a lower SIR between smoking-related lung cancer and cancers of the mouth/pharynx, esophagus, or larynx was obtained than the SIR between these three sites. This may be due to combined effects of not only tobacco smoking, but also alcohol drinking, radiotherapy, or other potential factors,[17] as well as to the relatively lower relative risk of cigarette smoking for lung cancer in Japan than in Western countries (i.e. 4.4 for men and 2.8 for women in Japan).[18] The risk of developing a tobacco- or alcohol-related second cancer has been linked mainly to patients' habits before the onset of the initial cancer, although continued smoking and drinking may enhance the risk.[5,19]

Breast, uterine, and ovarian cancers had the next highest SIR for second primaries. Furthermore, we found that women aged 50–79 years had a higher SIR for second primaries than men aged 50–79 years. The site relationships between breast, uterus, and ovary were relatively high, especially after first breast cancer, whereas a robust site relationship between

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colorectal cancer and ovarian cancer was observed (see Table 4). These findings are consistent with previous evidence that women have slightly higher risk for second cancer compared with men because of the good survival rates for common female cancers.[3] Female-specific causes, such as hormonal environment due to menopause, may affect these relationships.[17] Although the constellation of multiple cancers of the breast, uterine corpus, ovary, and colon has long intrigued investigators, nutritional and hormonal interactions, such as dietary habits (e.g. high fat intake) and reproductive factors (e.g. nulliparity), may contribute to the development of multiple primaries at these sites.[5]

The risk of second primary cancer can be modified ostensibly by improving medical scrutiny and notification of cancer patients.[5] In our previous study, underestimation of the risk of second primary cancer may have been possible, with the incidence of second primaries differing substantially between 1966 and 1986. This may be due to the reliability of the registration indices because the number of cases registered by death certificate only and the number of cases verified histologically were not so favorable in Osaka during in the 1960s–1970s.[4] The present study shows that the incidence rates per 100 000 person-years for metachronous second primary cancers were approximately the same across all study periods (1985–2005) among both sexes in Osaka. This finding seems partly attributable to soundness of medical scrutiny and notification of cancer patients, as well as to stability in the registration indices.

One of the interesting relationships that emerged from the present analysis was that between hematological tumors and cancer of the mouth/pharynx, esophagus, uterus, ovary, and liver. Although there is evidence that hepatocellular carcinoma and lymphoma share a common risk factor, namely the hepatitis virus,[20] the relationships between hematological tumors and cancer of the mouth/pharynx, esophagus, uterus, and ovary have been relatively unclear. Because of the age distribution or potential etiologies of hematological tumors, analyses using disease types (lymphoma, leukemia, and myeloma) and specific age categories, such as childhood, adolescence, and young adults, should be considered in future research.[21] Although multiple primary cancers in some individuals provide a clue to understanding cancer etiology, including genetics,[5,22] a number of associations remain without apparent explanation.[5] Because it is possible that other factors, such as socioeconomic status, genetics, lifestyle, or social network, may vary between people who have been diagnosed with cancer and those who have not,[23] further investigations are required to identify the mechanisms underlying these relationships in the incidence of multiple primary cancers for specific interventions.

There are several limitations to the present study. First, we should keep in mind the changes in the completeness of cancer registration in Osaka when we evaluate incidence. The percentage of cases registered by death certificate only, which is often regarded as an index of completeness, was approximately 10–15% and registration has been stable in the Osaka Cancer Registry for the most recent two decades.[24] Therefore, we considered that the effects of changes in completeness on incidence rates over the study periods are likely to be small. Second, some misclassifications for second primaries will be unavoidable in cancer registries, especially in cases registered by death certificate only. The IARC rules for second primaries are rather conservative compared with clinical practice; therefore, the risk for second primaries may be underestimated. Third, patients with second primary cancers may be followed-up in hospitals where the completeness of registration of cancer cases is higher than average compared with other hospitals in Osaka. This could result in an overestimation for second primaries to some degree. Fourth, patients with cancer differ in many respects from the general population, and these characteristics may affect the risk of subsequent cancer. For example, women with cervical cancer tend to smoke more, bear children at an earlier age, and are of lower socioeconomic status than women in the general population.[5] Because of the nature of cancer registries, these potential risk factors were not included in the data collection.

In conclusion, we have shown that cancer survivors in Osaka, Japan, are at higher risk of second primary cancer compared with the general population, in accordance with previous studies.[11,25–27] More than one-tenth of cancer survivors aged over 60 years (specifically men over 50 years of age) will develop metachronous second primary cancer within 10 years of diagnosis of the first cancer. This clearly shows that second primary cancer should be considered as a commonly encountered major medical problem. The evaluation of second primary cancer identifies groups of cancer patients in need of increased surveillance for early cancer detection and management. Preventive measures are needed to reduce the occurrence of subsequent cancer and mortality.[5] Because we obtained acceptably stable statistics for second primary cancer in Osaka, further studies are required to advance our understanding of effective measures against multiple primary cancers.

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Disclosure Statement

The authors have no conflict of interest.

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