Jpn. J. Cancer Res. 85, 339–345, April 1994

Incidence of Second Primary Cancers in Osaka Residents, Japan, with Special Reference to Cumulative and Relative Risks

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This study was conducted to examine the incidence rates and cumulative risks of second primary cancers in Osaka and to compare the observed number of second primary cancers with the expected number calculated using cancer incidence rates among Osaka residents. Study subjects were all reported cases aged 0–79 who were first diagnosed as having a first primary cancer between 1966–86. Incidence of second primary cancer among the study subjects was examined through to the end of 1989. The total number of study subjects was 217,307. During the follow-up period (mean duration: 3.7 years), second primary cancers developed in 5,071 patients (2.3%). Incidence of synchronous (interval <3 months) and metachronous (interval ≥ 3 months) second primary cancers increased in the later years. Incidence rates of second primary cancers were significantly associated with gender (male), age and calendar year at diagnosis of the first cancer. Based on the incidence rates, cumulative risk of developing metachronous second primary cancer was calculated. The ten-year cumulative risk was estimated as 10% for those who developed their first cancer during their sixties in 1978-83. The observed number of second primary cancers (including synchronous) was compared with the expected number. The ratios of observed-to-expected numbers were generally lower than 1.0 among those who developed their first cancer in 1966–77, while these ratios were higher than 1.0 among those who developed their first cancer in 1978–86. The ratios were much higher than 1.0 among those who developed their first cancer in their childhood and youth. Patients who had developed cancer of the colon, larynx, lung, bladder, or breast (female) showed significantly higher risk of developing second primary cancer during the period 1–4 years after diagnosis of the first cancer.

Key words: Second primary cancer — Time trend — Incidence rate — Cumulative risk — Ratio of observed-to-expected numbers

With increasing survival after treatment for many forms of cancer, and the use of chemotherapeutic agents and radiations in the treatment of malignant tumors, it is estimated that at present some 5% of all cancer patients develop a further independent primary cancer.[1–3] Although hospital-based studies have the advantage of diagnostic refinement, they are often limited by the relatively small number of patients with multiple primary cancer known to a single institution, which results in unstable risk estimates. These difficulties were overcome, for the most part, with the establishment of large population-based cancer registries.[4] Using a data file from the Osaka Cancer Registry, one of the oldest and largest population-based cancer registries in Japan,[5] we examined the incidence of second primary cancers developing in a relatively large and unselected population of cancer patients in Osaka.

MATERIALS AND METHODS

Outline of the Osaka Cancer Registry The Osaka Cancer Registry was founded in 1962 for the purpose of registering all malignant tumors and benign intracranial tumors arising in Osaka Prefecture (1990 Census population; 8.7 millions).[5] The Registry assigns a unique registration number to each patient, and thus second or later multiple primary cancers can be easily identified. For each tumor, the site of origin, histologic findings, clinical stage, and primary treatment are identified. An additional code for multiple primary cancers is assigned which identifies each primary cancer. Follow-up information is also available, including the last date of contact and vital status.

Study subjects and definition of multiple primary cancers Study subjects were all reported cases aged 0–79 who were initially diagnosed as having a first primary cancer (invasive cancer and benign intracranial tumor) between 1966–86. The incidence of a second primary cancer among the study subjects was examined through to the end of 1989.

In this study, we have followed the rules suggested by the IARC as well as by the ICD-O second edition[6–8] to define the circumstances under which an individual is considered to have more than one cancer.

Analysis of metachronous second primary cancers Incidence rates of metachronous second primary cancers were calculated using a computer program developed by

Monson.[9] Metachronous second primary cancers were defined as all invasive tumors and intracranial tumors which were diagnosed at least 3 months after diagnosis of the first cancer. *In situ* carcinomas and any third or fourth (or more) primaries were excluded. The period of observation used in calculating the risks for second primary cancers began at the date of diagnosis of the first cancer and ended at either the date of diagnosis of the metachronous second primary cancer, the date of reaching 80 years old, the date of death, or December 31, 1989, whichever came first. Patients who were diagnosed as having a second primary cancer within 3 months (synchronous second primaries) or who did not survive for 3 months or more after diagnosis of the first cancer were all excluded from the analysis of metachronous second primary cancer risk.

Using the age-, sex-, and period-specific incidence rates calculated above, cumulative risks[10] of developing metachronous second primary cancers were estimated according to age and calendar year at diagnosis of the first cancer and number of elapsed years thereafter.

Poisson regression analysis was performed to estimate the incidence rate ratios of metachronous second primary cancers for each of the possible relating factors, together with their 95% confidence intervals, and to control possible confounding factors simultaneously. This analysis was implemented with the statistical package for generalized linear interactive modelling, developed by the Working Party on Statistical Computing of the Royal Statistical Society.[11]

External comparison The observed number (O) of second primary cancers (including synchronous) for all sites was compared with the expected number (E), according to selected site of the first cancer and number of elapsed years thereafter. The IARC's definition[6-8] does not accept any tumors in the same site (ICD-9 3 digit level) as the first primary cancer as a second primary cancer, unless their major histologic types differ from the first primary cancer's. Therefore, the O/E ratios for all sites must be underestimated, particularly in the case of first cancers with large person-years, such as cancers of the stomach, colon, rectum, larynx, lung, bladder, thyroid, breast (female), and uterus. To avoid such underestimations in the case of those first cancers, we excluded both of the observed and the expected numbers of second primary cancers in the same site as the first cancer from the O/E for all sites.

Patients who were diagnosed as having a second primary cancer or who died within 3 months after diagnosis of the first cancer were included in this analysis.

A computer program developed by Monson[9] was used for these calculations. The significance of the O/E ratios

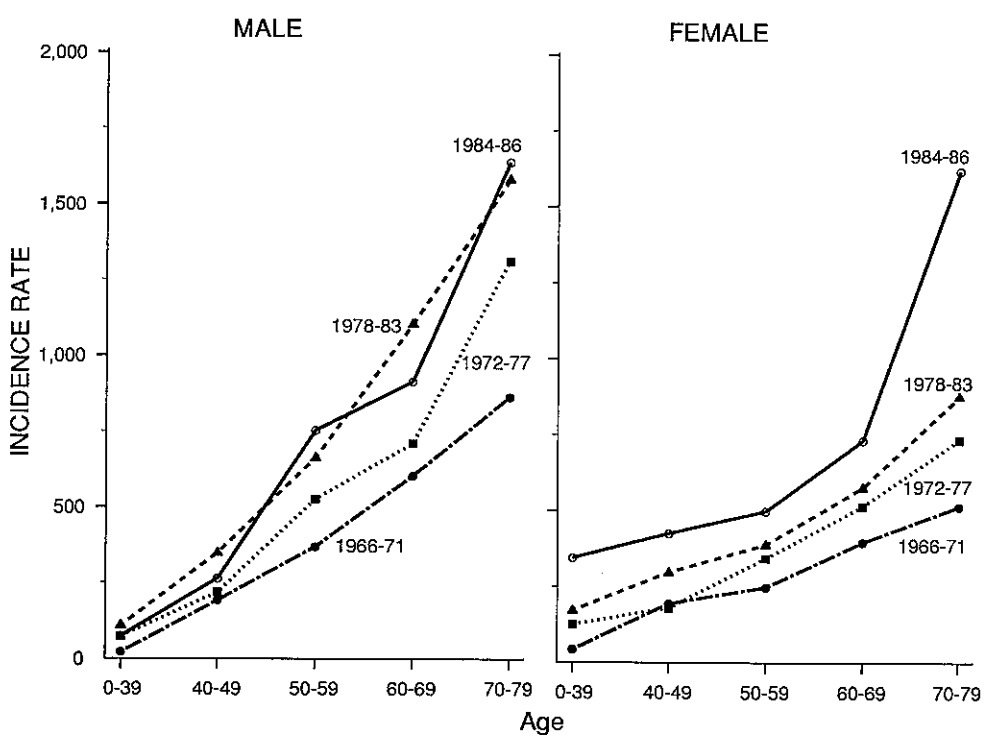

Fig. 1. Age-specific incidence rates of metachronous second primary cancers per 100,000 person-years, according to sex and calendar year at diagnosis of the first cancer, Osaka, 1966–86.

was tested by Poisson distribution analysis,[12] while their 95% confidence intervals were calculated using the CIA statistical package.[13]

Reported *P*-values were all two-tailed.

RESULTS

The total number of study patients was 217,307. During the follow-up period (mean follow-up duration: 3.7 years), second primary cancers developed in 5,071 patients (2.3%), of which 4,436 cases were metachronous second primary cancers.

Metachronous second primary cancers Fig. 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 4 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 males than among females except for age groups of 0–39 and 40–49 years old. Age-specific incidence rates increased with calendar year at diagnosis of the first cancer, in particular, for females.

In order to elucidate risk factors relating to the development of primary second cancers, Poisson regression analysis was performed on the incidence data of metachronous second primary cancers obtained during the first 0–4 years after diagnosis of the first cancer (Table I). Calendar year and age at diagnosis of the first cancer, as well as sex (male), were found to be independent significant risk factors for developing a second primary cancer.

Table II indicates cumulative risks of the metachronous second primary cancers, according to age and calen-

Table I. Risk Factors Relating to Development of Metachronous Second Primary Cancers: Poisson Regression Analysis

Factor		Adjusted rate ratio	95% CI
Year at diagnosis of first cancer	1966–71	1.00	
	1972–77	1.59	1.33–1.90
	1978–83	2.89	2.47–3.38
	1984–86	2.89	2.45–3.40
Age at diagnosis of first cancer	0–49	1.00	
	50–59	1.88	1.64–2.14
	60–69	2.94	2.60–3.32
	70–79	3.50	3.07–3.99
Sex	Male	1.00	
	Female	0.67	0.62–0.73

Table II. Cumulative Risk of Metachronous Second Primary Cancers, According to Age and Calendar Year at Diagnosis of the First Cancer: Both Sexes

Age	Duration (years)	Year at diagnosis of the first cancer				Total
		1966–71	1972–77	1978–83	1984–86	
0–14	5	0.7%	0.0%	0.2%	0.2%	0.2%
	10	0.7	0.6	0.4	–	0.6
	15	1.2	0.9	–	–	0.9
	20	1.2	–	–	–	0.9
15–29	5	0.0	0.9	1.1	0.7	0.7
	10	0.2	1.6	1.7	–	1.2
	15	0.6	2.1	–	–	1.6
	20	0.9	–	–	–	2.0
30–39	5	0.5	0.5	1.1	0.7	0.8
	10	1.3	1.2	2.0	–	1.5
	15	2.7	2.6	–	–	2.9
	20	4.3	–	–	–	4.4
40–49	5	1.0	1.1	1.9	1.7	1.5
	10	2.4	3.5	3.9	–	3.4
	15	4.6	5.6	–	–	5.6
	20	6.7	–	–	–	7.9
50–59	5	1.0	1.5	2.9	3.1	2.3
	10	3.3	5.2	6.1	–	5.3
	15	6.6	9.1	–	–	8.7
	20	10.8	–	–	–	13.0
60–69	5	1.5	2.7	4.7	4.5	3.6
	10	4.7	8.3	10.4	–	8.6
	15	9.0	13.1	–	–	13.1
	20	13.2	–	–	–	17.1

dar year at diagnosis of the first cancer. The 10-year cumulative risk was estimated as around 10% for those who developed their first cancer in their sixties in 1978–83.

Observed and expected numbers of second primary cancers The observed number (O) of second primary cancers (including synchronous) was compared with the expected number (E).

Table III shows the O/E ratios according to sex, calendar year at diagnosis of the first cancer, and number of elapsed years thereafter. The ratios among those who developed their first cancer during the earlier study period (1966–77) were generally lower than 1.0, while among those who developed their first cancer during the later study period (1978–86) the ratios were higher than 1.0. During the period 1–4 years after diagnosis of the first cancer, 8% and 20% excess risk of second primaries was observed among males and females, respectively, who developed their first cancer in 1978–86. The O/E ratios during the 5–9 year period after diagnosis of the first cancer among those who developed their first cancer in 1978–86, which are parenthesized in Table III, should be revised in the next several years, because of the high proportion of censored data.

Table IV shows the O/E ratios according to age at diagnosis of the first cancer and the number of elapsed years. The ratios among those who developed their first cancer in childhood (0–14 years old) and youth (15–29 years old) were 24.1 and 15.9 for the first year, 4.2 and 5.1 for the next 4 years, and 7.3 and 2.2 for the next 5–9 year period, respectively, after diagnosis of the first cancer. These ratios were much higher than the ratios among the total age groups. The observed numbers of second primary cancers among those who developed their first cancer in childhood and youth were so small that we have only presented the O/E ratios for the entire study period.

The O/E ratios among those who developed their first cancer in 1978–86 were further examined according to selected sites of the first cancer (Table V). Because of the high proportion of censored data, the O/E ratios during

Table III. Observed and Expected Numbers of Second Primary Cancers, According to Years after Diagnosis of the First Cancer: Relation to Calendar Year at Diagnosis of the First Cancer and Sex

Sex	Year at diagnosis of the first cancer	Years after diagnosis of the first cancer					
		0		1–4		5–9	
		Obs	O/E (95% CI)	Obs	O/E (95% CI)	Obs	O/E (95% CI)
Male	1966–77	86	0.43 [b] (0.35–0.54)	227	0.62 [b] (0.55–0.71)	365	0.95 (0.86–1.05)
	1978–86	649	1.50 [b] (1.39–1.62)	858	1.08 [a] (1.00–1.15)	334	[1.02] (0.91–1.13)
Female	1966–77	74	0.67 [b] (0.53–0.85)	230	0.88 (0.77–1.00)	304	1.03 (0.92–1.15)
	1978–86	358	2.01 [b] (1.94–2.38)	496	1.20 [b] (1.10–1.31)	219	[1.07] (0.93–1.21)

a) $P<0.05$. *b*) $P<0.01$. [ ]: see text.

Table IV. Observed and Expected Numbers of Second Primary Cancers, According to Years after Diagnosis of the First Cancer: Relation to Age at Diagnosis of the First Cancer, 1966–86, Both Sexes

Age at diagnosis of the first cancer	Years after diagnosis of the first cancer					
	0		1–4		5–9	
	Obs	O/E (95% CI)	Obs	O/E (95% CI)	Obs	O/E (95% CI)
0–14	10	24.1 [b] (11.7–44.9)	4	4.2 [a] (1.15–10.8)	4	7.3 [b] (1.98–18.6)
15–29	11	15.9 [b] (7.96–28.5)	13	5.1 [b] (2.71–8.72)	8	2.2 [b] (0.94–4.27)
0–79	1167	1.3 [b] (1.20–1.34)	1811	1.0 (0.94–1.03)	669	1.0 (0.91–1.06)

a) $P<0.05$. *b*) $P<0.01$.

Table V. Observed and Expected Numbers of Second Primary Cancers, According to Years after Diagnosis of the First Cancer: Relation to Site of the First Cancer, 1978–86, Both Sexes

Site of the first cancer	Years after diagnosis of the first cancer					
	0		1–4		5–9	
	Obs	O/E (95% CI)	Obs	O/E (95% CI)	Obs	O/E (95% CI)
Stomach	237	1.48[b] (1.30–1.68)	332	0.93 (0.84–1.04)	154	[0.88] (0.74–1.03)
Colon	62	1.46[b] (1.12–1.87)	115	1.21[a] (1.00–1.46)	49	[1.35] (1.00–1.79)
Rectum	58	1.57[b] (1.19–2.02)	63	0.74[a] (0.57–0.95)	34	[0.96] (0.67–1.34)
Larynx	40	2.65[b] (1.89–3.60)	71	1.60[b] (1.25–2.02)	29	[1.26] (0.84–1.80)
Lung	117	1.60[b] (1.32–1.92)	90	1.27[a] (1.02–1.57)	24	[1.22] (0.78–1.82)
Bladder	49	1.84[b] (1.36–2.43)	97	1.36[b] (1.10–1.66)	39	[1.22] (0.87–1.67)
Thyroid	11	1.85 (0.92–3.30)	27	1.34 (0.89–1.96)	15	[1.39] (0.78–2.30)
Breast (Female)	56	2.24[b] (1.62–2.91)	117	1.35[b] (1.12–1.62)	53	[1.12] (0.84–1.47)
Uterus	35	1.26 (0.88–1.76)	100	1.16 (0.94–1.41)	52	[0.95] (0.71–1.25)

a) $P<0.05$. *b*) $P<0.01$. [ ]: see text.

the 5–9 year period, which are parenthesized in Table V, should be revised in the next several years. Within the first year of diagnosis, the O/E ratios were significantly higher than 1.0 for almost all of these sites, due, in large part, to the possible detection bias.[4] During the next 4 years after diagnosis of the first cancer, the ratios were nearly equal to or under 1.0 for cancers of the stomach, rectum and uterus. Meanwhile significantly elevated risks were observed for cancers of the colon, larynx, lung, bladder and breast (female).

DISCUSSION

This study showed that the incidence rates of second primary cancers were significantly associated with gender (male), age and calendar year at diagnosis of the first cancer. The O/E ratios of second primary cancers during the period 1–4 years after diagnosis of the first cancer were generally lower than 1.0 among those who developed their first cancer in 1966–77, and higher than 1.0 among those who developed their first cancer in 1978–86.

Risk of second primary cancer can be modified ostensibly by improvement in medical scrutiny and notification of cancer patients.[4] Observed O/E ratios lower than 1.0 during the earlier study period might be indicative of underestimation of the risks for second primary cancers, since the reliability of such registration indices as 'the proportion of cases registered by death certificate only' and 'the proportion of the cases verified histologically' were not so favorable in Osaka during the earlier period.[5] Recent increases in the risk of second primary cancer, therefore, seem partly attributable to improvements in medical scrutiny and notification of cancer patients, as well as to improvements in the survival length of cancer patients.

Another explanation for the increase in the risk of second primary cancer may be the increase in the risk factors of cancer in our environment, such as smoking and dietary habits, because time trends in the age-specific incidence rates of second primary cancers were in large part correlated with the incidence rates of cancer among Osaka residents (Fig. 1). Furthermore, we have to consider the etiological roles of chemotherapy and/or radiotherapy in the development of metachronous second primary cancers, because many reports suggest increased risk of second primary cancer among those patients treated with chemotherapeutic agents and/or radiation.[4]

The incidence rates or cumulative risks of second primary cancers were not so high among children and youths, but the O/E ratios were much higher than 1.0 (Table IV). Similar findings have also been reported by other researchers.[14, 15] Because of the limited number of cases, it was difficult to find any specific associations between the first and second primary cancers. Genetic predispositions, as well as treatment with chemotherapeutic agents and/or radiation, might play rather signifi-

Table VI. Specific Associations by Site of First and Second Primary Cancers, 1978–86

First cancer	Second primary		Male		Female	
	Site	(ICD-9)	Obs	O/E	Obs	O/E
Stomach	Colon	(153)	73	1.73[b]	18	1.22
	Rectum	(154)	59	1.87[b]	16	1.84[a]
	Breast	(174)	–	–	32	1.54[a]
Colon	Stomach	(151)	50	1.41[a]	18	1.36
	Rectum	(154)	14	2.62[b]	11	4.38[b]
	Ovary	(183)	–	–	9	5.95[b]
Rectum	Colon	(153)	13	1.88[a]	7	2.29
	Liver	(155)	10	0.53[a]	3	0.93
Larynx	Oral etc.	(140–149)	6	4.03[b]	1	16.33
	Esophagus	(150)	13	4.74[b]	0	–
	Liver	(155)	20	1.72[a]	0	–
	Lung	(162)	31	2.09[b]	5	9.30[b]
	Bladder	(188)	7	2.55[a]	0	–
	Thyroid	(193)	4	15.19[b]	2	25.50[b]
Lung	Colon	(153)	22	2.38[b]	1	0.45
	Prostate	(185)	11	2.23[a]	–	–
	Kidney etc.	(189.0–.1)	7	3.13[a]	2	6.33
	Thyroid	(193)	1	1.81	3	6.39[a]
Bladder	Uterus	(179–182)	–	–	6	3.57[a]
	Prostate	(185)	18	5.04[b]	–	–
Breast	Stomach	(151)	–	–	53	1.33[a]
(Female)	Colon	(153)	–	–	22	1.72[a]
	Lung	(162)	–	–	24	1.60[a]
	Thyroid	(193)	–	–	16	4.61[b]
Uterus	Lung	(162)	–	–	36	2.20[b]
	Hematopoietic	(200–208)	–	–	17	2.11[b]

a) $P<0.05$. *b*) $P<0.01$.

cant roles in the etiology of second primaries among children and youth.[16]

Our study has demonstrated that successfully treated cancer patients are still subject to increased risk of second primary cancers. Close surveillance is therefore recommended, in order to detect and treat second primary cancer as early as possible. In addition, health education should be conducted so that these patients have the chance to reduce their risk of developing second primary cancers.

Table VI shows some specific associations by site of first and second primary cancers, where the O/E ratios for males or females or both were found to be significantly greater or smaller than 1.0. Although we need to analyze these associations in more detail for a better understanding, some hypotheses can be put forward. For example, reciprocal associations may be explained by shared risk factors.[17] Such associations were demonstrated between colon and rectal cancer in the present study. Similar associations were also observed in part among smoking-related cancers for males, such as larynx, oral cavity, esophagus, lung and bladder.

When the association between two malignancies is not reciprocal, other possible explanations must be sought, such as a treatment effect or detection bias.[17] Increased risks of prostate cancer after bladder cancer, as well as thyroid cancer after laryngeal cancer,[18] and rectal cancer after stomach cancer,[19] were all supposed to be explained in large part by detection bias.

Further studies will be needed to clarify the relationships between first and second primary cancers more completely, and to assess the etiological roles of treatment with chemotherapeutic agents and/or radiation in the development of second primary cancers.

ACKNOWLEDGMENTS

This study was supported in part by a Grant-in-Aid for Cancer Research from the Ministry of Health and Welfare, and by a Grant-in-Aid for Medical Research from the Daido-seimei-kousei-jigyo-dan. We are grateful to all medical institutions in Osaka and the Osaka Medical Association which provided us with cancer incidence data.

(Received October 8, 1993/Accepted January 12, 1994)

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