Jpn. J. Cancer Res. 82, 1356–1365, December 1991

Second Primary Cancers Following Colon and Rectal Cancer in Osaka, Japan

Hideo Tanaka,[1] Tomohiko Hiyama,[2] Aya Hanai[1] and Isaburo Fujimoto[1]

[1]Department of Field Research and [2]Division of Epidemiology, Research Institute, Center for Adult Diseases, Osaka, 1-3-3 Nakamichi, Higashinari-ku, Osaka 537

The frequencies of second primary cancers following colon and rectal cancers were estimated using the Osaka Cancer Registry's population-based data for Osaka, Japan. A series of 7,312 colon and 6,923 rectal cancer cases newly diagnosed in the period of 1966–1986 were followed up until the end of 1986. The average follow-up period was 3.6 years for colon cancer and 3.7 years for rectal cancer. Significantly elevated risks of second primary cancers following colon cancer were observed for cancers of the rectum (O/E= 2.0; 95% confidence interval (CI)=1.1–3.4 among males, O/E=4.3; 95% CI=2.4–7.2 among females), corpus uteri (O/E=8.2; 95% CI=3.3–16.9), ovary (O/E=4.3; 95% CI=1.0–5.0), and female thyroid gland (O/E=4.7; 95% CI=1.7–8.8). These findings were more notable among right-sided colon cancer patients than left-sided colon cancer patients. The elevated risks of second primary cancers were particularly evident among patients younger than 50 years of age at the time of diagnosis of the initial cancer (colon cancer: O/E=3.1 among males, 3.4 among females, rectal cancer: O/E=1.7 among males, 1.3 among females). These findings suggest that younger colorectal cancer patients should undergo more careful checkups throughout their lives.

Key words: Second primary cancer — Colon cancer — Rectal cancer — Population-based cancer registry

In recent years, the incidence rate of colorectal cancer in Japan has been increasing remarkably: it was estimated at 10.6 per 100,000 population in 1970, and 27.2 in 1985.[1)] At the same time, the prognosis of colorectal cancer patients has been improving steadily in Japan.[2)] These trends provide increased opportunities of developing second primary cancers among these cancer patients.

Several studies on second primary cancers among colon and rectal cancer cases have been conducted in western countries where these cancers are prevalent. These studies have shown increased risks of second primary cancers for the sites of colon,[3)] rectum,[3, 5)] gallbladder and bile ducts,[5)] skin,[6)] breast,[3, 6)] corpus uteri,[3–6)] ovary,[3, 4, 6)] kidney and bladder,[6)] brain,[3)] and thyroid gland.[3)] No population-based study results concerning this issue are yet available in Japan.

This study was conducted using the population-based data accumulated in the Osaka Cancer Registry in order to 1) estimate the risks of second primary cancers following colon and rectal cancers, 2) to present the necessary data for planning the medical follow-up of colorectal cancer patients, and 3) to obtain clues to clarify the etiological factors of colorectal cancer.

SUBJECTS AND METHODS

The Osaka Cancer Registry has been operating since December 1962 with the cooperation of the Osaka Medical Association, the Osaka Prefectural Health Department and the Center for Adult Diseases, Osaka. It covers all of Osaka, whose population was 8.7 million in 1985. It registers cancer cases using cancer reports notified by doctors in hospitals and clinics, and death certificates of Osaka residents collected from health centers in Osaka. Registered cases have been followed up year by year by using these two sources of information. Most of the registered cases were reported as invasive cases. The proportion of carcinoma *in situ* among 22,577 cases registered in 1987 was very low (1.2%, 265 cases).[7)]

A series of 8,476 colon and 7,649 rectal cancer cases who had been diagnosed between January 1, 1966 and September 30, 1986 were identified from the Osaka Cancer Registry's files. Registered cases based on the death certificate only were not included in the study. To reduce possible errors in differentiating development of a new second primary cancer from a metastatic growth, and to avoid detection bias (as cancer patients are under detailed medical examination there is an increased chance for detection of new latent cancers), simultaneous primary cancers, defined as those occurring within three months from the date of diagnosis of the initial cancer, were excluded. The following cases were consequently excluded from further analysis; 1,164 colon cancer cases (1,128 died within three months from the date of diagnosis of the initial cancer, and 36 with simultaneous primary cancers within the same period), and 726 rectal cancer cases (695 died within three months from the date of diagnosis of the initial cancer, and 31 with simultaneous primary cancers within the same period). The remaining 7,312 colon and 6,923 rectal cancer cases were studied as the final cohort (Table I).

In the Registry, colon cancer cases have been classified into subsites according to the 9th revision of the International Classification of Diseases.[8] In our analysis, colon was categorized as all colon (153.0–153.9), right-sided (appendix, cecum, ascending colon, hepatic flexure and transverse colon: ICD=153.0+153.1+153.4+153.5+153.6), and left-sided (splenic flexure, descending colon and sigmoid colon: ICD=153.2+153.3+153.7). All colon includes colon multiple and subsite unknown (ICD =153.8, 153.9).

Person-years at risk were calculated from the date of diagnosis of the initial cancer until the date of diagnosis of the second primary cancer, date of death, or the closing date, December 31, 1986, whichever occurred first. The patients for whom there were no matching death certificates were assumed to be alive at the closing date. The observed numbers of second primary cancers were compared with the expected numbers calculated using a computer program developed by Monson,[9] applying the 5-year age-, 5-year calendar period-, sex-, and site-specific incidence rates for Osaka residents.

The risks for new primary cancers were expressed as the ratios of the observed (O) number to the expected (E) number (O/E ratio). The statistical significance of differences between the observed and expected figures was tested under the assumption that the observed number followed a Poisson distribution.

RESULTS

Characteristics of study subjects Table I presents the descriptive characteristics of the study subjects by sex. The number of study subjects for colon cancer was 3,862 for males and 3,450 for females, and for rectal cancer was 4,045 for males and 2,878 for females. Average length of follow-up was 3.6–3.8 years on each site for both sexes. Of these, 86% of colon cancer cases and 87% of rectal cancer cases were diagnosed histologically.

Table II shows the descriptive characteristics of the study subjects according to age category at the date of diagnosis of the first cancer; less than 50 years (younger-age group), 51 to 69 years (elder-age group) and more than 70 years (old-age group). The number of study subjects for the elder-age group was the largest of the three groups. Average follow-up periods became shorter with advancing age.

Table I. Characteristics of Study Subjects

	Colon						Rectum[d]	
	Male			Female			Male	Female
	Colon[a]	RSC[b]	LSC[c]	Colon[a]	RSC[b]	LSC[c]		
No. of subjects	3,862	1,180	1,828	3,450	1,195	1,485	4,045	2,878
Average follow-up period (yr)	3.64	3.56	3.42	3.65	3.57	3.50	3.65	3.83
Average age at initial diagnosis (yr)	60.6	59.8	61.5	60.9	62.0	60.2	59.7	59.2
Histological diag.[e] (%)	87.2	88.1	90.5	85.6	86.3	89.4	87.4	87.6

a) ICD 9=153.0–153.9.
b) Right-sided colon; ICD 9=153.0, 153.1, 153.4, 153.5, 153.6.
c) Left-sided colon; ICD 9=153.2, 153.3, 153.7.
d) ICD 9=154.0–154.9.
e) Percentage of subjects diagnosed histologically.

Table II. Characteristics of Study Subjects by Age

	Colon						Rectum					
	Male			Female			Male			Female		
Age	≤50	51–69	≥70 yr	≤50	51–69	≥70 yr	≤50	51–69	≥70 yr	≤50	51–69	≥70 yr
No. of subjects	897	1,896	1,069	783	1,724	943	1,028	2,031	986	803	1,373	702
Average follow-up period (yr)	4.68	3.61	2.82	4.56	3.82	2.58	4.26	3.72	2.87	4.09	4.16	2.89
Average age at intial diagnosis (yr)	42.1	60.9	75.6	42.4	61.0	76.1	42.2	60.8	75.7	41.5	60.8	76.3

Table III-A. Observed (O) and Expected (E) Numbers of Second Primary Cancers among Colon Cancer Patients, Male

Second primary cancer sites	Colon[a]			Right-sided colon[b]			Left-sided colon[c]		
	O	E	O/E	O	E	O/E	O	E	O/E
All sites	156	161.93	1.0	53	45.70	1.2	67	76.48	0.9
All sites except initial sites	148	154.07	1.0	50	43.49	1.2	62	72.74	0.9
Stomach	67	53.06	1.3	16	15.01	1.1	29	24.93	1.2
Colon	8	7.86	1.0	3	2.21	1.4	5	3.74	1.3
Rectum	14	6.92	2.0*	11	1.96	5.6**	1	3.28	0.3
Liver	16	18.27	0.9	5	5.24	1.0	9	8.60	1.1
Gall bladder, bile ducts	3	3.30	0.9	1	0.92	1.1	2	1.57	1.3
Pancreas	2	5.11	0.4	1	1.44	0.7	1	2.41	0.4
Larynx	1	2.99	0.3	0	0.85	0.0	0	1.41	0.0
Lung, bronchus	17	28.05	0.6*	7	7.82	0.9	8	13.35	0.6
Prostate gland	6	4.72	1.3	2	1.30	1.5	1	2.29	0.4
Bladder	6	5.78	1.0	1	1.62	0.6	2	2.76	0.7
Thyroid gland	0	0.53	0.0	0	0.15	0.0	0	0.25	0.0
Malignant lymphoma	3	2.91	1.0	2	0.83	2.4	0	1.36	0.0
Leukemia	0	1.73	0.0	0	0.50	0.0	0	0.80	0.0

*; $P<0.05$. **; $P<0.01$.
a), *b*) and *c*) Refer to the footnotes in Table I.

Table III-B. Observed (O) and Expected (E) Numbers of Second Primary Cancers among Colon Cancer Patients, Female

Second primary cancer sites	Colon[a]			Right-sided colon[b]			Left-sided colon[c]		
	O	E	O/E	O	E	O/E	O	E	O/E
All sites	106	76.12	1.4**	39	26.89	1.5	42	31.02	1.4
All sites except initial sites	101	71.42	1.4**	35	25.23	1.4	41	29.20	1.4*
Stomach	26	20.14	1.3	7	7.24	1.0	11	8.07	1.4
Colon	5	4.70	1.1	4	1.66	2.4	1	1.93	0.5
Rectum	14	3.25	4.3**	9	1.15	7.8**	5	1.32	3.8*
Liver	5	5.04	1.0	1	1.79	0.6	2	2.05	1.0
Gall bladder, bile ducts	3	2.91	1.0	1	1.03	1.0	1	1.19	0.8
Pancreas	4	2.71	1.5	0	0.96	0.0	3	1.11	2.7
Lung, bronchus	11	6.84	1.6	3	2.44	1.2	4	2.78	1.4
Breast	5	6.28	0.8	2	2.10	1.0	2	2.67	0.8
Cervix uteri	4	6.75	0.6	0	2.28	0.0	2	2.82	0.7
Corpus uteri	7	0.85	8.2**	3	0.28	10.7**	2	0.37	5.4
Ovary	7	1.64	4.3**	3	0.55	5.4*	2	0.69	2.9
Bladder	2	1.34	1.5	0	0.49	0.0	1	0.54	1.9
Thyroid gland	5	1.07	4.7**	2	0.37	5.4	1	0.45	2.2
Malignant lymphoma	0	1.22	0.0	0	0.43	0.0	0	0.50	0.0
Leukemia	1	0.88	1.1	1	0.30	3.3	0	0.37	0.0

*; $P<0.05$. **; $P<0.01$.
a), *b*) and *c*) Refer to the footnotes in Table I.

Occurrence of second primary cancers by first primary site Overall, 156 second primary cancers were observed among male colon cancer patients (O/E=1.0; 95% confidence interval=0.8–1.1) (Table III-A). Observing the risks according to the site of second primary cancers, the risk for rectal cancer was high (O/E=2.0; 95% CI=1.1–3.4) for males. Elevated risk was observed among the right-sided colon cancer patients (O/E=5.6;

Table IV. Observed (O) and Expected (E) Numbers of Second Primary Cancers among Rectal Cancer Patients

Second primary cancer sites	Male			Female		
	O	E	O/E	O	E	O/E
All sites	104	163.92	0.6**	50	64.87	0.8
All sites except initial sites	104	156.95	0.7**	50	62.09	0.8
Stomach	32	54.37	0.6**	8	17.53	0.5*
Colon	8	7.82	1.0	6	3.90	1.5
Rectum	0	6.96	0.0	0	2.77	0.0
Liver	11	18.61	0.6	4	4.24	0.9
Gall bladder, bile ducts	3	3.27	0.9	1	2.38	0.4
Pancreas	3	5.16	0.6	1	2.24	0.5
Larynx	3	3.07	1.0	1	0.23	4.3
Lung, bronchus	17	28.00	0.6*	4	5.71	0.7
Breast	0	0.10	0.0	6	5.34	1.1
Cervix uteri	—	—	—	4	5.79	0.7
Corpus uteri	—	—	—	0	0.71	0.0
Ovary	—	—	—	1	1.37	0.7
Prostate gland	4	4.59	0.9	—	—	—
Bladder	2	5.75	0.4	1	1.15	0.9
Thyroid gland	1	0.53	0.9	0	0.90	0.0
Malignant lymphoma	1	2.95	0.3	0	1.01	0.0
Leukemia	2	1.74	1.2	3	0.74	4.1

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

95% CI=2.80–10.07). The risk of developing lung cancer was significantly low (O/E=0.6; 95% CI=0.4–1.0) for males.

Among females, 106 second primary cancers were observed. The risk was significantly high (O/E=1.4; 95% CI=1.1–1.7) (Table III-B). Observing the risks according to the site of second primary cancers, significantly increased risks were found for cancers of the rectum (O/E=4.3; 95% CI=2.4–7.2), corpus uteri (O/E=8.2; 95% CI=3.3–16.9), ovary (O/E=4.3; 95% CI=1.0–5.0), and thyroid gland (O/E=4.7; 95% CI=1.7–8.8). These risks were higher among right-sided colon cancer patients than left-sided colon cancer patients.

Table IV shows that 104 male rectal cancer patients developed second primary cancers, corresponding to an O/E ratio significantly lower than unity (O/E=0.7; 95% CI=0.5–0.8). Significantly decreased risks were also found for cancers of the stomach (O/E=0.6; 95% CI=0.4–0.8) and lung (O/E=0.6; 95% CI=0.4–1.0).

Fifty female patients with rectal cancer developed second primary cancers (Table IV). The risk of developing stomach cancer was significantly lower than unity (O/E=0.5; 95% CI=0.2–0.9).

Analysis according to the length of follow-up In order to clarify the risks according to the length of follow-up, the period was divided into four categories: less than 1 year (excluding the first 3 months), 1–4 years, 5–9 years, and 10 or more years (Tables V and VI).

As shown in Table V, the risks of developing rectal cancer were consistently high in the periods 1–4 years, 5–9 years, and 10+ years for both males (O/E=2.6, 1.3, 3.5) and females (O/E=5.9, 5.4, 4.5). A similar trend was observed in the development of endometrial cancer (O/E=5.4, 15.8, 9.9). The greatest risks for cancers of the ovary and female thyroid gland were found in the 1–4 year period (O/E=8.4, 8.7, respectively). In the development of stomach cancer, a significantly elevated risk (O/E=2.0) was observed in the 5–9 year period among males.

Table VI shows risks of developing second primary cancers among rectal cancer cases according to the length of follow-up. The risks of developing stomach or lung cancer following male rectal cancer were consistently low throughout the follow-up periods (stomach, 0.4–0.7; lung, 0.3–0.8).

Analysis according to age category Table VII shows the risks for the two age categories at the diagnosis of colon cancer; less than 50 years (younger-age group) and 51 to 69 years (elder-age group). We excluded subjects more than 70 years of age (old-age group). The reasons were 1) the reliability of diagnosing carcinoma would decrease

Table V. Observed (O) Numbers and O/E Ratios of Second Primary Cancers by Years after Diagnosis of Colon Cancer

Sex	Second primary cancer sites	<1 yr		1–4 yr		5–9 yr		10+ yr	
		O	O/E	O	O/E	O	O/E	O	O/E
Male	All sites	20	0.6**	72	1.0	42	1.2	22	1.2
	All sites except initial sites	19	0.6**	69	1.0	40	1.2	20	1.1
	Stomach	8	0.7	27	1.2	23	2.0**	9	1.5
	Rectum	1	0.7	8	2.6*	2	1.3	3	3.5
	Lung	2	0.3	6	0.5	8	1.3	1	0.3
Female	All sites	21	1.2	50	1.6**	22	1.3	13	1.3
	All sites except initial sites	20	1.3	47	1.6**	22	1.4	12	1.3
	Stomach	6	1.3	10	1.2	5	1.1	5	2.0
	Rectum	0	0.0	8	5.9**	4	5.4*	2	4.5
	Lung	2	1.4	5	1.8	4	2.6	0	0.0
	Corpus uteri	1	5.2	2	5.4	3	15.8**	1	9.9
	Ovary	1	2.7	6	8.4**	0	0.0	0	0.0
	Thyroid gland	0	0.0	4	8.7**	0	0.0	1	7.2

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

Table VI. Observed (O) Numbers and O/E Ratios of Second Primary Cancers by Years after Diagnosis of Rectal Cancer

Initial sites	Second primary cancer sites	<1 yr		1–4 yr		5–9 yr		10+ yr	
		O	O/E	O	O/E	O	O/E	O	O/E
Male	All sites	15	0.4**	35	0.5	31	0.9	19	0.9
	All sites except initial sites	15	0.4**	39	0.6	31	0.9	19	1.0
	Stomach	5	0.4*	16	0.7	7	0.6	4	0.6
	Lung	2	0.3	7	0.6	5	0.8	3	0.8
Female	All sites	9	0.7	15	0.6*	15	1.1	11	1.0
	All sites except initial sites	9	0.7	15	0.6	15	1.1	11	1.1
	Stomach	0	0.0	3	0.4	1	0.3	4	1.4
	Lung	1	0.9	1	0.4	2	1.6	0	0.0

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

in the old-age group, and 2) as the average follow-up period for the old-age group was shorter than those for the younger groups (Table II), the reliability of O/E ratios for the old-age group would be less than those for the younger groups.

A significantly elevated risk for total second primary cancers was observed for both sexes in the younger-age group (O/E=3.1, 3.4). In the younger-age group, the risks of developing second primary cancers were significantly elevated for cancers of the stomach (O/E=4.7), colon (O/E=5.7) and lung (O/E=3.7) for males, and the stomach (O/E=4.0) rectum (O/E=13.1), corpus uteri (O/E=15.8) and ovary (O/E=8.8) for females.

The O/E ratio for total second primary cancers in the male elder-aged colon cancer group was 1.0. The risk of developing rectal cancer in this group was significantly higher than unity (O/E=2.9). Statistically increased risk for total second primary cancers was seen in the female elder-aged rectal cancer group (O/E=1.4). In this group, elevated risks of developing cancers of the corpus uteri (O/E=5.9) and ovary (O/E=4.2) were observed (Table VII).

Table VII. Observed (O) Numbers and O/E Ratios of Second Primary Cancers by Age at Diagnosis of Colon Cancer

Second primary cancer sites	Male				Female			
	Age ≤50 yr		51–69 yr		Age ≤50 yr		51–69 yr	
	O	O/E	O	O/E	O	O/E	O	O/E
All sites	33	3.1**	87	1.0	28	3.4**	58	1.4*
All sites except initial sites	30	2.9**	83	1.0	26	3.3**	55	1.4*
Stomach	17	4.7**	38	1.4	7	4.0**	15	1.4
Colon	3	5.7*	4	1.0	2	5.1	3	1.2
Rectum	2	3.7	10	2.9*	4	13.1**	5	2.9
Liver	3	1.5	10	1.0	1	3.6	4	1.4
Gall bladder, bile ducts	1	6.0	2	1.2	0	0.0	2	1.3
Pancreas	1	3.1	0	0.0	0	0.0	2	1.3
Lung, bronchus	4	3.7*	9	0.6	3	2.8	7	1.9
Breast	—	—	—	—	0	0.0	5	1.4
Cervix uteri	—	—	—	—	1	0.6	2	0.5
Corpus uteri	—	—	—	—	3	15.8**	3	5.9*
Ovary	—	—	—	—	3	8.8*	4	4.2*
Prostate gland	0	0.0	1	0.5	—	—	—	—
Bladder	1	3.8	2	0.7	0	0.0	2	2.9
Thyroid gland	0	0.0	0	0.0	2	12.7	2	3.3
Malignant lymphoma	1	3.5	1	0.7	0	0.0	0	0.0

*; $P<0.05$ **; $P<0.01$

Table VIII. Observed (O) Numbers and O/E Ratios of Second Primary Cancers by Age at Diagnosis of Rectal Cancer

Second primary cancer sites	Male				Female			
	Age ≤50 yr		51–69 yr		Age ≤50 yr		51–69 yr	
	O	O/E	O	O/E	O	O/E	O	O/E
All sites	19	1.7*	59	0.7**	9	1.3	31	0.9
All sites except initial sites	19	1.8*	59	0.7**	9	1.3	31	0.9
Stomach	5	1.4	18	0.6**	0	0.0	7	0.7
Colon	3	5.6*	1	0.2	2	6.3	4	1.8
Liver	3	1.5	8	0.7	1	4.0	3	1.2
Gall bladder, bile ducts	0	0.0	2	1.1	0	0.0	0	0.0
Pancreas	0	0.0	2	0.7	0	0.0	1	0.8
Lung, bronchus	3	2.8	11	0.7	0	0.0	2	0.6
Breast	—	—	—	—	1	0.7	3	1.0
Cervix uteri	—	—	—	—	2	1.4	2	0.6
Ovary	—	—	—	—	0	0.0	1	1.3
Prostate gland	0	0.0	2	1.0	—	—	—	—
Leukemia	0	0.0	2	2.0	1	7.8	2	4.7

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

The risk of contracting total second primary cancers following rectal cancer in males was significantly high in the younger-age group (O/E=1.7), though it was low in the elder-age group (O/E=0.7)(Table VIII). Observing the risks according to the site of second primary cancers, younger-aged rectal cancer patients were more likely to develop colon cancer than expected (O/E=5.6). In the male elder-aged rectal cancer group, the risk for stomach cancer was statistically significantly lower than expected (O/E=0.6).

Table IX. Summary of Population-based Studies of Second Primary Cancers among Colon Cancer Patients

	Sex	Connecticut[3]		Denmark[4]		Finland[5]		Osaka	
Number of subjects	M	12,324		15,442		4,461		3,862	
	F	14,480		11,155		5,252		3,450	
Person-years at risk	M	50,832		58,436		not shown		14,096	
	F	70,476		48,759		not shown		12,593	
Second primary sites	Sex	O	O/E	O	O/E	O	O/E	O	O/E
All sites	M	1,190	1.3*	584	0.9*	87	1.00	156	1.0
	F	1,078	1.3*	705	1.0	173	1.15	106	1.4**
All sites except initial sites	M	946	1.2*	541	0.9*	86	0.87	148	1.0
	F	816	1.2*	638	1.0	118	1.18	101	1.4**
Stomach	M	61	1.2	56	0.7*	11	0.77*	67	1.3
	F	27	0.8	41	0.7*	18	1.21	26	1.3
Colon	M	244	2.2	43	0.7*	—	—	8	1.0
	F	262	2.0*	67	0.8	—	—	5	1.1
Rectum	M	115	2.0*	66	1.2	8	2.07	14	2.0*
	F	89	1.8*	49	1.1	14	2.70**	14	4.3**
Lung, bronchus	M	134	0.9	94	0.8	17	0.58*	17	0.6*
	F	38	0.9	35	1.1	3	0.76	11	1.6
Breast	F	232	1.2*	131	0.9	17	0.96	5	0.8
Corpus uteri	F	80	1.7*	60	1.8*	21	3.75***	7	8.2**
Ovary	F	77	2.4*	93	2.6*	—	—	7	4.3**
Prostate gland	M	244	1.3*	93	0.9	15	1.01	6	1.3
Thyroid gland	M	6	2.9*	2	1.1	—	—	0	0.0
	F	3	0.6	5	1.0	—	—	5	4.7**

*; $P<0.05$. **; $P<0.01$. ***; $P<0.001$.

The O/E ratios of total second primary cancers following rectal cancer in females were 1.3 for the younger-age group, and 0.9 for the elder-age group.

DISCUSSION

In this study, colon and rectal cancer patients were passively followed up by collation of cancer reports and death certificates of Osaka residents accumulated in the Osaka Cancer Registry. Using this method, if we had no information on their death, or on the occurrence of second primary cancers, patients were assumed to be alive without any second primary cancer at the closing date (December 31, 1986). In this regard, the person-years at risk tend to be over-estimated. Moreover, information on those who moved out of Osaka Prefecture and developed second primary cancers at another location was not obtained using this system. These methodological biases would influence the O/E ratio, causing them to be lower than the actual figures.

Although the Osaka Cancer Registry has been trying to differentiate multiple cancers carefully, the possibility of misclassifying recurrent or metastatic cancers as independent primary cancers cannot be entirely excluded (classification bias). Another bias is that cancer patients who are under more extensive medical care have a higher chance of having latent second cancers detected than the general population (detection bias). These two biases would occur in a relatively short period after the date of initial cancer diagnosis, and the effects of the biases would become less with the passage of time. We therefore excluded the cases whose follow-up period was less than three months. Furthermore, the O/E ratios were calculated according to the length of follow-up.

We calculated the risks of simultaneous cancers in colon and rectal cancer patients. They were extremely high (O/E=22.0 (36/1.64) and O/E=27.8 (31/1.12) repectively). These risks include the detection and classification biases, whose magnitudes cannot be estimated now. Simultaneous cancers are therefore not presented.

Consistently elevated risks for rectal cancer were demonstrated after one year from the date of diagnosis of colon cancer among both sexes. Risks for endometrial cancer were also high in the 3 periods longer than 1 year. The risks for cancers of the ovary and thyroid gland in females were significantly elevated in the 1–4 year period after colon cancer. Of the 6 ovarian cancer patients diagnosed in this period, 5 were diagnosed histologically,

Table X. Summary of Population-based Studies of Second Primary Cancers among Rectal Cancer Patients

	Sex	Connecticut[3]		Denmark[4]		Finland[5]		Osaka	
Number of subjects	M	8,557		15,442		4,461		4,045	
	F	6,903		11,155		5,252		2,878	
Person-years at risk	M	35,008		58,436		not shown		14,764	
	F	33,650		48,759		not shown		11,023	
Second primary sites	Sex	O	O/E	O	O/E	O	O/E	O	O/E
All sites	M	582	1.0	581	0.7*	99	1.01	104	0.6**
	F	370	1.0	387	0.7*	140	1.26*	50	0.8
All sites except initial sites	M	568	1.1	581	0.8*	58	0.53***	104	0.7**
	F	363	1.1	387	0.8*	67	0.70**	50	0.8
Stomach	M	17	0.5*	54	0.5*	8	0.49*	32	0.6*
	F	17	1.1	22	0.5*	8	0.55	8	0.5*
Colon	M	129	1.8*	79	1.0	4	1.05	8	1.0
	F	93	1.6*	53	0.9	6	0.87	6	1.5
Rectum	M	14	0.4*	0	0.0	—	—	0	0.0
	F	7	0.3*	0	0.0	—	—	0	0.0
Lung, bronchus	M	83	0.8	109	0.8*	9	0.27***	17	0.6*
	F	24	1.2	18	0.8	1	0.27	4	0.7
Breast	F	91	1.0	103	1.0	14	0.86	6	0.7
Corpus uteri	F	22	1.0	28	1.1	0	0.0	0	0.0
Ovary	F	22	1.5	30	1.1	0	0.0	1	0.7
Prostate gland	M	148	1.3*	107	0.8	8	0.48*	4	0.9
Thyroid gland	M	1	0.7	3	1.3	—	—	1	0.9
	F	1	0.4	0	0.0	—	—	0	0.0

*; $P<0.05$. **; $P<0.01$. ***; $P<0.001$.

and 4 had different histological types from those of their colon cancer. Colon cancer seldom metastasizes to the thyroid gland. For these reasons, we concluded that the influence of the misclassification of metastasis on these risks would have been negligible.

There have been three reports of second primary cancers following colon and rectal cancer using the data of population-based cancer registries. These three findings and our results are summarized in Tables IX and X. Though there would exist some differences of registration methods among the four registries, the methods used to estimate the risks of multiple cancers are technically the same.

The elevated risks which were observed in our study are substantially consistent with those of the three other population-based studies (Table IX). The Connecticut[3] and the Finnish[5] Cancer Registries reported that significantly elevated risks following colon cancer were found for cancer of the rectum. Statistically significantly increased risk of developing endometrial cancer following colon cancer was demonstrated at all 4 registries (Connecticut,[3] Danish,[4] Finnish[5] and Osaka). The Connecticut[3] and the Danish[4] Cancer Resistries also observed increased risks of developing ovarian cancer following colon cancer. The risk of developing thyroid gland cancer among male colon cancer patients was statistically significantly higher in the Connecticut[3] study.

In this study, female colon cancer patients developed cancer of the endometrium and ovary more frequently than expected. Previous studies suggest that nulliparity is associated with an increased risk of endometrial cancer[10-14] and ovarian cancer.[10, 15-19] On the other hand, nulliparity was reported to be associated with an increased risk of colon cancer in a number of studies using a variety of epidemiological designs.[20, 22-26] Several of these studies have shown that the risk decreased with an increase in the number of live births[20, 25, 26] or the number of pregnancies.[22] These findings indicate that nulliparity is likely to be a common risk factor for these three cancers. Potter and McMichael suggested that the high risk of contracting colon cancer among nulliparous women was associated with endogenous estrogen which would increase bile acid production.[20, 21]

Contrary to our expectation, elevated risk of breast cancer following female colon cancer was not demonstrated in this study. Several studies carried out in western countries have indicated that nulliparity and fewer live

births were associated with risk of breast cancer.[10] We assume the reason for this discrepancy is that the etiological factors of breast cancer are different between Japanese women and western women. It has been reported that the proportion of estrogen-receptor-positive breast cancers among Japanese patients was lower than that among western patients.[27,28] The age distribution of breast cancer patients in Japan tends to be younger than that in western countries,[29] while postmenopausal breast cancer patients are more likely to have estrogen-positive cancers than premenopausal patients.[30-32] If endogenous estrogen is supposed to be associated with a particular etiology of colon cancer, and if postmenopausal breast cancer patients are more likely to have estrogen-positive cancers than premenopausal breast cancer patients, the risk of contracting breast cancer following colon cancer will be higher for elder-aged cases than younger-aged cases. Indeed, the risk of contracting subsequent breast cancer in female colon cancer patients was higher among the elder-age group (O/E=1.4) than the younger-age group (O/E=0.0) (Table II).

The risk of developing thyroid gland cancer following female colon cancer was statistically significantly higher than expected. The etiological factors relating these two cancers are unknown.

A significantly increased risk of developing rectal cancer was observed among colon cancer patients of both genders. One plausible explanation for this elevated risk is that the epithelium of the colon and rectum have a similar susceptibility to the same carcinogens, and that both of them are in contact with feces containing carcinogens.

The risk of contracting lung cancer following colon and rectal cancers in males was lower than unity. Similar findings were seen in other population-based studies (Tables IX and X). We compared the obseved (O) numbers of current smokers among the male colon and rectal cancer patients admitted to the Center for Adult Diseases, Osaka, in 1981–1987, with the expected (E) numbers calculated using the 10-year age-specific current smoking rates for Japanese males in 1983.[33] The proportion of current smokers among colon cancer patients was 52.8% (169/320) and the O/E was 0.87 ($P<0.1$). That of rectal cancer patients was 51.7% (135/261) and the O/E was 0.84 ($P<0.05$). These results might suggest that the low risk of developing lung cancer following male colon and rectal cancer was partly due to a lower prevalence of smoking among these patients than among the general population.

The risks for subsequent new primary cancers among younger colon and rectal cancer patients were higher than expected. Two explanations for this might be considered: 1) younger cancer patients may have a higher susceptibility to the carcinogens which cause second primary cancers as compared with other people of the same generation, and 2) an excessive exposure (either heavy exposure or exposure at an early age) may be responsible for development of the first cancer, and the patient may continue to be exposed to the same factors, resulting in the second primary cancer.

Ushio[34] compared the characteristics of hereditary nonpolyposis colon cancer (HNPCC) with sporadic colon cancer in his hospital: the average age at the onset of cancer was younger among HNPCC cases than that among sporadic cases (53.3 years vs. 58.2 years), and the average incidence of a multiple primary colorectal cancer among HNPCC cases was higher than that among sporadic cancer cases (31.0% vs. 6.1%). These findings suggest that younger colorectal patients are more likely to develop second primary cancers owing to hereditary factors.

ACKNOWLEDGMENTS

This study was supported in part by a Grant-in-Aid for Cancer Research from the Japanese Ministry of Health and Welfare (2-5). The authors wish to express their gratitude to the Osaka Medical Association for providing access to registry data. We also wish to thank Ms. Noriko Kinoshita, Ms. Mikiko Kiwata and the staff of the Osaka Cancer Registry for their technical assistance.

(Received May 29, 1991/Accepted September 3, 1991)

REFERENCES

1) Fujimoto, I., Hanai, A., Tominaga, S. and Kuroishi, T. Prediction of the incidence of cancer in Japan in the year 2000. *Jpn. J. Cancer Clin.*, **34**, 1911–1916 (1988).
2) Hanai, A. and Fujimoto, I. Population-based cancer registries in Japan. *In* "Epidemiology and Prevention of Cancer," ed. R. Sasaki and K. Aoki, pp. 199–210 (1990). University of Nagoya, Nagoya.
3) Hoar, S. K., Wilson, J., Blot, W. J., McLaughlin, J. K., Winn, D. M. and Kantor, A. F. Second cancer following cancer of the digestive system in Connecticut, 1935–82. *Natl. Cancer Inst. Monogr.*, **68**, 48–86 (1985).
4) Linge, E., Jensen, O. M. and Carstensen, B. Second cancer following cancer of the digestive system in Denmark, 1943–80. *Natl. Cancer Inst. Monogr.*, **68**, 277–308 (1985).
5) Teppo, L., Pukkala, E. and Saxen, E. Multiple cancer – an epidemiologic exercise in Finland. *J. Natl. Cancer Inst.*, **75**, 207–217 (1985).

6) Schottenfeld, D., Berg, J. W. and Vitsky, B. Incidence of multiple primary cancers. II. Index cancers arising in the stomach and lower digestive system. *J. Natl. Cancer Inst.*, **43**, 77–86 (1969).
7) Cancer incidence and medical care in Osaka in 1987. Annual Report of Osaka Cancer Registry No 48. Osaka Cancer Registry (1990) (in Japanese).
8) "International Classification of Diseases, Volume 1" (1977). World Health Organization, Geneva.
9) Monson, R. R. Analysis of relative survival and proportional mortality. *Comput. Biomed. Res.*, **7**, 325–332 (1984).
10) Franceschi, S. Reproductive factors and cancers of the breast, ovary and endometrium. *Eur. J. Cancer Clin. Oncol.*, **25**, 1933–1943 (1989).
11) Kvale, G., Heuch, I. and Ursin, G. Reproductive factors and risk of cancer of the uterine corpus: a prospective study. *Cancer Res.*, **48**, 6217–6221 (1988).
12) Vecchia, C. L., Franceschi, S., Decarli, A., Gallus, G. and Tognoni, G. Risk factors for endometrial cancer at different ages. *J. Natl. Cancer Inst.*, **73**, 667–671 (1984).
13) Henderson, B. E., Casagrande, J. T., Pike, M. C., Mack, T., Rosario, I. and Duke, A. The epidemiology of endometrial cancer in young women. *Br. J. Cancer*, **47**, 749–756 (1983).
14) Kelsey, J. L., Livolsi, V. A., Holford, T. R., Fischer, O. B., Mostow, E. D., Schwartz, P. E., O'Connor, T. and White, C. A case-control study of cancer of the endometrium. *Am. J. Epidemiol.*, **116**, 333–342 (1982).
15) Mori, M., Harabuchi, I., Miyake, H., Casagrande, J. T., Henderson, B. E. and Ross, R. K. Reproductive, genetic, and dietary risk factors for ovarian cancer. *Am. J. Epidemiol.*, **128**, 771–777 (1988).
16) Voigt, L. F., Harlow, B. L. and Weiss, N. S. The influence of age at first birth and parity on ovarian cancer risk. *Am. J. Epidemiol.*, **124**, 490–491 (1986).
17) Kvale, G., Heuch, I., Nissen, S. and Beral, V. Reproductive factors and risk of ovarian cancer; a prospective study. *Int. J. Cancer*, **42**, 246–251 (1988).
18) Winder, E. L., Dodo, H. and Barber, H. R. K. Epidemiology of cancer of the ovary. *Cancer*, **23**, 352–370 (1969).
19) Cramer, D. W., Hutchinson, G. B., Welch, W. R., Scully, R. E. and Ryan, K. J. Determinants of ovarian cancer risk. 1. Reproductive experiences and family history. *J. Natl. Cancer Inst.*, **71**, 711–716 (1983).
20) Potter J. D. and McMichael, A. J. Large bowel cancer in women in relation to reproductive and hormonal factors: a case-control study. *J. Natl. Cancer Inst.*, **71**, 703–709 (1983).
21) McMichael, A. J. and Potter, J. D. Host factors in carcinogenesis: certain bile-acid metabolic profiles that selectively increase the risk of proximal colon cancer. *J. Natl. Cancer Inst.*, **75**, 185–191 (1985).
22) Peters, R. K., Pike, M. C., Chang, W. W. L. and Mack, T. M. Reproductive factors and colon cancers. *Br. J. Cancer*, **61**, 741–748 (1990).
23) Davis, F. G., Furner, S. E., Persky, V. and Koch, M. The influence of parity and exogenous female hormones on the risk of colorectal cancer. *Int. J. Cancer*, **43**, 587–590 (1989).
24) Kune, G. A., Kune, S. and Watoson, L. F. Children, age at first birth, and colorectal cancer risk. *Am. J. Epidemiol.*, **129**, 533–542 (1989).
25) McMichael, A. J. and Potter, J. D. Do intrinsic sex differences in lower alimentary tract physiology influence the sex-specific risks of bowel cancer and other biliary and intestinal diseases? *Am. J. Epidemiol.*, **118**, 620–627 (1984).
26) Weiss, N. S., Daling, J. R. and Chow, W. H. Incidence of cancer of the large bowel in women in relation to reproductive and hormonal factors. *J. Natl. Cancer Inst.*, **67**, 57–60 (1981).
27) Nomura, Y., Kobayashi, S., Takatani, O., Sugano, H., Matsumoto, K. and McGuire, W. L. Estrogen receptor and endocrine responsiveness in Japanese versus American breast cancer patients. *Cancer Res.*, **37**, 106–110 (1977).
28) McGuire, W. L. Steroid hormone receptors in breast cancer treatment strategy. *Recent Progr. Hormone Res.*, **36**, 135–156 (1980).
29) Whelan, S. L., Parkin, D. M. and Masuyer, E. (ed.). "Patterns of Cancer in Five Continents" IARC Scientific Publications No. 102 (1990). International Agency for Research on Cancer, Lyon.
30) Lesser, M. L., Rosen, P. P., Senie, R. T., Duthie, K., Menendezbotet, C. and Schwartz, M. K. Estrogen and progesterone receptors in breast carcinoma. *Cancer*, **48**, 299–309 (1981).
31) Hulka, B. S., Chambless, L. E., Wilkinson, D. C., Deubner, D. C., McCarty, K. S., Sr. and McCarty, K. S., Jr. Hormonal and personal effects on estrogen receptors in breast cancer. *Am. J. Epidemiol.*, **119**, 692–704 (1984).
32) Stanford, J. L., Szklo, M., Boring, C. C., Brinton, L. A., Diamond, E. A., Greenberg, R. S. and Hoover, R. N. A case-control study of breast cancer stratified by estrogen receptor status. *Am. J. Epidemiol.*, **125**, 184–194 (1987).
33) Senbaitoukeiyouran: Nihonsenbaikousya (1983). Senbaikousaikai (in Japanese).
34) Ushio, K. Multiple tumors in polyposis syndrome and nonpolyposis colorectal cancer. *In* "Fundamental and Clinical Research in Multiple Primary Cancer," pp. 38–39 (1990). Foundation for Promotion of Cancer Research, Tokyo.