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Second Primary Cancer after Diagnosis of Stomach Cancer in Osaka, Japan

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The risk of developing a second primary cancer following stomach cancer was estimated from data accumulated in the Osaka Cancer Registry. Of the 38,777 male patients and 22,391 female patients newly diagnosed in the period 1966–1986 who were followed up until the end of 1986, 778 and 267 developed a second cancer other than stomach cancer, respectively, whereas the expected numbers had been 928.8 (RR=0.84, 95%CI=0.78–0.90) and 297.7 (RR=0.90, 95%CI=0.79–1.01). The risks were higher among younger patients (aged 30–54 at the diagnosis of stomach cancer) than among older patients (aged 55–69 at the diagnosis of stomach cancer). Significantly elevated risks were observed for cancers of the oral cavity & pharynx (RR=1.56), colon (RR=1.61) and rectum (RR=1.56) for males, and oral cavity & pharynx (RR=2.59) for females as second cancers. Results were substantially similar among the localized stomach cancer patients. Among younger male patients with gastrectomy, the risk of developing pancreatic cancer was elevated 10 or more years after stomach cancer diagnosis. The present study suggests the necessity of following up stomach cancer patients in order to enable the early diagnosis of digestive tract cancer.

Key words: Second primary cancer — Stomach cancer — Population-based cancer registry

Along with improvements in the prognosis of cancer patients, the risk of developing a second primary cancer may have increased. Stomach cancer is still the most common cancer in Japan, though its incidence rates have been steadily declining since the late 1960s for both sexes.[1-3] The prognosis of stomach cancer has been improved to 70% 5-year survival after diagnosis of localized cases.[4] This improvement in prognosis would provide ample opportunities for second primary cancers to develop over time.

Several hospital-based studies on second primary cancer after stomach cancer have been reported,[5-8] but the observed numbers were rather small, leading to unstable risk estimates. Population-based cancer registries, which register many cancer patients and follow them up over a long period, might provide a better opportunity to determine the risks. Two population-based studies were carried out in Connecticut[9] and in Denmark,[10] where stomach cancer is less prevalent.[3] Japan is one of the high-risk areas for stomach cancer, and the intestinal type under Lauren's classification,[11] which is supposed to be closely associated with environmental factors, is dominant.[12-14] Consequently, the risk of developing a second primary cancer in Japan may be different from that in low risk areas of stomach cancer.

This is the first population-based study designed to estimate the risks of developing second primary cancers after stomach cancer in Japan, and it could provide clues for understanding the etiologic factors for stomach cancer by comparing the results with those of studies carried out in low risk areas of stomach cancer, or by revealing adverse effects of treatment for stomach cancer.

SUBJECTS AND METHODS

The risks of developing second primary cancers were estimated for those who developed stomach cancer between 1966 and 1986. Those who were registered based on death certificate only were excluded. Patients with other malignancies recorded either before the diagnosis of stomach cancer or on the same day were also exclude. The period of observation used in calculating the risks for second primary cancers begins at the date of diagnosis of stomach cancer and ends at the date of diagnosis of the second primary cancer, the date of death or December 31st 1986, whichever occurred first.

Site-specific sex, 5-year age, and the 5-year calendar period incidence rates for each cancer among Osaka residents were applied to the appropriate person-years under observation to obtain the numbers of second primary cancers to be expected had these patients experienced the same rates as were prevailing in the corresponding general population.

To reduce errors due to the misclassification of a primary cancer from a metastatic growth, analysis was also carried out for those who were reported to have stomach cancer in a localized stage. Besides this, risks were estimated from among those who had had surgical operation for stomach cancer. The risks of developing second primary cancers were also estimated by age (aged 30–54 and aged 55–69) at diagnosis of stomach cancer.

The statistical methods used were based on the assumption that the observed number of cancers in any specific category follows a Poisson distribution.

RESULTS

In the Osaka Cancer Registry, 38,777 male and 22,391 female stomach cancer patients with a cancer report were registered between 1966 and 1986. The average length of follow-up was 3.3 years for males and 3.2 years for females (Table I). The average length of follow-up was slightly longer for younger male patients (4.4 years for aged 30–54 and 3.3 years for aged 55–69). For female patients, it was similar by age category, 3.3 years for both age groups. In Table I, the age-sex distribution and the average length of follow-up for localized cases and operated cases are also shown.

Overall, 778 male stomach cancer patients developed second primary cancers other than stomach cancer during the observation period (Table II), which was statistically lower than expected (observed/expected (O/E) = 0.84, 95% confidence interval (CI) = 0.78–0.90). Among females, 267 second primary cancers other than stomach cancer developed, which was lower than the expected number (O/E = 0.90 95% CI = 0.79–1.01), though the difference was not significant. The O/E ratios were significantly elevated for the sites of oral cavity & pharynx (O/E = 1.56), colon (O/E = 1.61) and rectum (O/E = 1.28) for males and of oral cavity & pharynx (O/E = 2.59) for females. The O/E ratios were significantly lower than unity for the sites of liver (O/E = 0.70) and lung (O/E = 0.71) for males and uterus (O/E = 0.68) for females.

Table III shows the O/E ratios of second primary cancers among localized stomach cancer patients. They had almost the same risks of developing all malignant neoplasms other than stomach as those of the general population (O/E = 1.01 for males and 0.97 for females). By site, the O/E ratios were elevated for oral cavity & pharynx, rectum and urinary bladder for both sexes, colon among males and lung and non-Hodgkin lymphoma among females, though the differences were significant only for male colon and rectal cancers.

Table IV shows the results for stomach cancer patients with surgical operation. The results were substantially similar to those for all stomach cancer cases.

Table V sets out the results according to age category at the diagnosis of stomach cancer, for groups 30–54 years of age and 55–69 years of age. The risks of developing second primary cancers other than stomach were higher than 1.0 for the younger age group for both sexes and lower than unity for the older age group. In most sites, the O/E ratios were higher among the younger age group than the older age group, except for the sites of non-Hodgkin lymphoma among males and oral cavity & pharynx, lung and urinary bladder among females. The O/E ratios for colon cancer, rectal cancer and pancreatic cancer among the younger male group were elevated significantly.

In order to clarify the risks over time after diagnosis of the initial stomach cancer, the observation period was divided into four categories: within 1 year, 1–4 years, 5–9 years and 10 or more years after diagnosis. Table VI shows the risks according to the length of follow-up for sites which show significantly increased risks. The O/E ratios for cancers of colon, rectum and pancreas were the highest within 1 year after the diagnosis of stomach cancer. The risks were higher than unity during 5–9 years after stomach cancer diagnosis for the sites of oral cavity & pharynx, colon and rectum, and the difference was significant for colon cancer. Among stomach cancer patients with gastrectomy, the risks of developing second primary cancers of the rectum and pancreas were increased 10 or more years after the diagnosis of stomach cancer.

Table I. Age-Sex Distribution of Study Subjects

Age	All cases		Localized cases		Operated cases	
	Male	Female	Male	Female	Male	Female
–29	383	395	74	63	289	289
30–54	11,229	7,510	3,099	1,685	9,178	5,946
55–69	17,242	8,710	3,848	1,853	12,942	6,340
70–	9,923	5,776	2,006	1,186	5,289	2,735
Total	38,777	22,391	9,027	4,787	27,698	15,310
Average follow-up period (yr)	3.3	3.2	4.8	4.8	3.6	3.6

Table II. Observed (O) and Expected (E) Numbers of Second Primary Cancers after Diagnosis of Stomach Cancer in Osaka, 1966–1986

Site		Obs. (O)	Exp. (E)	O/E (95%CI)
All sites	M	791	1402.9	0.56* (0.53–0.63)
	F	273	409.4	0.67* (0.59–0.75)
All sites except stomach	M	778	928.8	0.84* (0.78–0.90)
	F	267	297.7	0.90 (0.79–1.01)
Oral cavity & pharynx	M	39	25.1	1.56* (1.11–2.13)
	F	12	4.6	2.59* (1.34–4.52)
Esophagus	M	42	52.6	0.80 (0.58–1.08)
	F	3	8.1	0.37 (0.07–1.08)
Stomach	M	13	474.1	0.03* (0.01–0.05)
	F	6	111.6	0.05* (0.02–0.12)
Colon	M	105	65.1	1.61* (1.31–1.95)
	F	26	24.1	1.08 (0.70–1.58)
Rectum	M	75	58.6	1.28* (1.01–1.61)
	F	24	17.2	1.40 (0.90–2.08)
Liver	M	110	157.2	0.70* (0.58–0.84)
	F	22	26.4	0.83 (0.52–1.26)
Pancreas	M	35	44.1	0.79 (0.55–1.10)
	F	11	14.0	0.79 (0.39–1.41)
Larynx	M	23	27.0	0.85 (0.54–1.28)
	F	0	1.5	0.00 (0.00–2.42)
Lung	M	166	237.7	0.70* (0.60–0.81)
	F	30	35.6	0.84 (0.57–1.20)
Breast	F	39	33.7	1.16 (0.82–1.58)
Uterus	F	37	54.2	0.68* (0.48–0.94)
Ovary	F	7	8.6	0.81 (0.33–1.67)
Urinary bladder	M	39	48.0	0.81 (0.58–1.11)
	F	10	7.1	1.41 (0.67–2.59)
Non-Hodgkin lymphoma	M	15	22.4	0.67 (0.37–1.10)
	F	8	5.8	1.37 (0.59–2.71)
Leukemia	M	13	14.7	0.88 (0.47–1.51)
	F	4	4.7	0.86 (0.23–2.19)

* $P<0.05$.

DISCUSSION

The Osaka Cancer Registry has been operating since 1963 with the cooperation of the Osaka Medical Association, the Osaka Prefectural Health Department and the Center for Adult Diseases, Osaka. More than 700,000 cases were registered by the end of 1986, and all registered cases are followed up until death by collating them with all death certificates of Osaka residents.

In our study, around 24% of observed second primary cancer cases were registered by death certificate only. However, we assume that the diagnosis of these cases is highly reliable.[15] In the analysis, we assumed that patients were alive at the end of 1986 if we had no information on their death or on the occurrence of a second primary cancer. The person-years at risk were overestimated and this leads to a larger number of expected second primary cancer cases. On the other hand, information on those who moved out of Osaka Prefecture and developed a second primary cancer at another location was not obtained (it is estimated that around 1% of the stomach cancer patients moved out of Osaka Prefecture within 5 years after the diagnosis of stomach cancer). As a result, O/E ratios were underestimated when compared with actual figures.

The results of our study are consistent with those of two other population-based studies, evaluated at the Connecticut Cancer Registry[9] and the Denmark Cancer Registry,[10] except for the elevated risks for cancers of the oral cavity & pharynx, colon and rectum, observed in

Table III. Observed (O) and Expected (E) Numbers of Second Primary Cancers after Diagnosis of Stomach Cancer in Osaka, 1966–1986, Localized

Site		Obs. (O)	Exp. (E)	O/E (95%CI)
All sites	M	324	469.1	0.69* (0.62–0.77)
	F	93	128.4	0.73* (0.59–0.89)
All sites except stomach	M	317	314.3	1.01 (0.90–2.76)
	F	92	94.4	0.97 (0.79–1.20)
Oral cavity & pharynx	M	14	8.5	1.65 (0.90–2.76)
	F	4	1.5	2.71 (0.73–6.94)
Esophagus	M	8	17.1	0.47* (0.20–0.92)
	F	0	2.4	0.00 (0.00–1.50)
Stomach	M	7	154.7	0.05* (0.02–0.09)
	F	1	33.9	0.03* (0.00–0.16)
Colon	M	57	22.3	2.55* (1.93–3.31)
	F	7	7.8	0.90 (0.36–1.86)
Rectum	M	31	19.9	1.56* (1.06–2.22)
	F	9	5.4	1.67 (0.76–3.10)
Liver	M	52	55.2	0.94 (0.70–1.24)
	F	8	8.3	0.96 (0.41–1.90)
Pancreas	M	7	14.9	0.47* (0.19–0.97)
	F	4	4.5	0.90 (0.24–2.30)
Larynx	M	7	8.9	0.79 (0.32–1.62)
	F	0	0.5	0.00 (0.00–8.05)
Lung	M	63	79.7	0.79 (0.61–1.01)
	F	14	11.2	1.25 (0.68–2.10)
Breast	F	11	11.3	0.98 (0.49–1.75)
Uterus	F	16	16.9	0.94 (0.54–1.53)
Ovary	F	0	2.9	0.00 (0.00–1.27)
Urinary bladder	M	20	16.0	1.25 (0.76–1.93)
	F	4	2.2	1.83 (0.49–4.69)
Non-Hodgkin lymphoma	M	7	7.7	0.91 (0.37–1.88)
	F	3	1.9	1.58 (0.32–4.60)
Leukemia	M	2	5.1	0.39 (0.04–1.42)
	F	0	1.5	0.00 (0.00–2.41)

* $P<0.05$.

our study (Table VII). Watanabe *et al.*[7] found significantly higher risks of developing second primary cancers of the oro-pharynx, colon and rectum in their hospital-based study, O/E=2.6, 2.4 and 2.2, respectively (Table VIII). Ichikawa *et al.*[8] also revealed increased risks for head and neck cancer (O/E=1.7) and colorectal cancer (O/E=2.0) among stomach cancer patients with surgical operation. In two other hospital-based studies carried out in the USA,[5,6] the risks of second primary cancer by site were not analyzed because of the small numbers of second primary cancers.

As cancer patients are under closer scrutiny than the general population, especially shortly after the diagnosis of the first primary cancer, the observed increased risks of developing the second primary cancers for oral cavity & pharynx, colon, rectum and pancreas within 1 year after diagnosis of stomach cancer might be partly due to detection bias and misclassification from a metastatic growth besides the increase which is attributed to the effect of common risk factors. Actually, the proportions of cancer in an early stage among the observed cancer cases of the oral cavity & pharynx, colon and rectum ranged between 45% and 50%, and were higher than those among the primary cancer cases of the same sites in Osaka, whose levels are between 25–30%.

With the passage of time after the diagnosis of stomach cancer, the emigration rate of stomach cancer patients would increase, which leads to underestimated O/E ratios. On the other hand, the possibility of either detection bias or misclassification from a metastatic growth

Table IV. Observed (O) and Expected (E) Numbers of Second Primary Cancers after Diagnosis of Stomach Cancer in Osaka, 1966–1986, Treated with Surgical Operation

Site		Obs. (O)	Exp. (E)	O/E (95%CI)
All sites	M	674	1065.2	0.63* (0.59–0.68)
	F	222	304.3	0.73* (0.64–0.83)
All sites except stomach	M	661	708.2	0.93 (0.86–1.01)
	F	220	223.2	0.99 (0.86–1.13)
Oral cavity & pharynx	M	33	19.4	1.70* (1.17–2.39)
	F	9	3.5	2.58* (1.18–4.90)
Esophagus	M	34	39.4	0.86 (0.60–1.21)
	F	2	5.8	0.35 (0.04–1.25)
Stomach	M	13	356.9	0.04* (0.02–0.06)
	F	2	81.1	0.02* (0.00–0.09)
Colon	M	95	49.7	1.91* (1.55–2.34)
	F	24	18.0	1.33 (0.85–1.98)
Rectum	M	71	44.6	1.59* (1.24–2.01)
	F	23	12.6	1.83 (1.16–2.74)
Liver	M	84	123.1	0.68* (0.54–0.84)
	F	14	19.5	0.72 (0.39–1.21)
Pancreas	M	33	33.9	0.97 (0.67–1.37)
	F	9	10.5	0.86 (0.39–1.63)
Larynx	M	19	20.5	0.93 (0.56–1.45)
	F	0	1.1	0.00 (0.00–3.28)
Lung	M	135	180.2	0.75* (0.63–0.89)
	F	24	26.2	0.92 (0.59–1.36)
Breast	F	34	26.6	1.28 (0.89–1.79)
Uterus	F	26	41.4	0.63* (0.41–0.92)
Ovary	F	6	6.8	0.89 (0.32–1.93)
Urinary bladder	M	35	35.9	0.97 (0.68–1.36)
	F	10	5.1	1.97 (0.94–3.62)
Non-Hodgkin lymphoma	M	13	17.3	0.75 (0.40–1.29)
	F	7	4.4	1.58 (0.63–3.25)
Leukemia	M	11	11.5	0.96 (0.48–1.72)
	F	3	3.6	0.83 (0.17–2.43)

* $P<0.05$.

would decrease. Along with this, the observed increased risks for second primary cancers of the oral cavity & pharynx, colon and rectum during 5–9 years or 10 or more years after stomach cancer diagnosis, and the elevated risk for pancreatic cancer observed 10 or more years after diagnosis among operated stomach cancer patients, may suggest the possible existence of common risk factors, or adverse effects of therapy for stomach cancer.

Elevated risks for cancer of the oral cavity & pharynx were observed except among younger female stomach cancer patients, in which Lauren's diffuse-type stomach cancer is dominant.[14] Smoking habits are strongly connected with cancer of the oral cavity & pharynx.[16] Several studies have revealed the positive association between smoking habits and stomach cancer.[17–22] These results suggest that smoking habits may be one of the common risk factors between stomach cancer and cancer of the oral cavity & pharynx, though the risks of developing second laryngeal cancer or lung cancer after stomach cancer were not elevated. Dental conditions such as poor oral hygiene and jagged teeth, which are reported as risk factors for cancer of the oral cavity, might also be risk factors for stomach cancer through biochemical alteration.[23, 24]

The risks of developing second colon and rectal cancer after stomach cancer were not elevated in Connecticut and Denmark, where stomach cancer is less prevalent. The results of the two hospital-based studies and the present study carried out in Japan, where stomach cancer

Table V. Observed (O)/Expected (E) Ratio of Second Primary Cancers Following Stomach Cancer by Age at the Diagnosis of Stomach Cancer in Osaka, 1966–1986

Site	Male		Female	
	Age 30–54	Age 55–69	Age 30–54	Age 55–69
All sites except stomach	1.5* (207)	0.8* (399)	1.2 (73)	0.8 (129)
Oral cavity & pharynx	1.7 (9)	1.5 (22)	1.1 (1)	4.0 (10)
Esophagus	1.3 (9)	0.7 (21)	1.2 (1)	0.2 (1)
Colon	3.6* (36)	1.1 (40)	1.8 (7)	1.0 (13)
Rectum	3.1* (30)	1.0 (32)	1.6 (5)	1.5 (13)
Liver	1.0 (36)	0.6 (52)	1.4 (5)	0.7 (10)
Pancreas	2.1* (14)	0.5* (13)	0.0 (0)	0.6 (5)
Larynx	1.8 (7)	0.9 (14)	0.0 (0)	0.0 (0)
Lung	0.8 (21)	0.8* (109)	0.7 (3)	1.1 (21)
Breast	—	—	1.5 (20)	0.9 (13)
Ovary	—	—	1.7 (5)	0.2 (1)
Uterus	—	—	0.7 (13)	0.7 (17)
Urinary bladder	1.4 (8)	0.9 (23)	1.4 (1)	2.2 (8)
Non-Hodgkin lymphoma	0.5 (2)	0.6 (8)	1.7 (2)	0.8 (2)
Leukemia	1.2 (4)	1.0 (8)	2.3 (3)	0.4 (1)

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

Table VI. Observed/Expected Ratio of Second Primary Cancers by Number of Years after Diagnosis of Stomach Cancer

Second primary	Category	Obs./Exp. ratio				
		<1 yr	1–4 yr	5–9 yr	10+ yr	Total
Oral cavity and pharynx	all cases	1.7 (10)	2.3 (25)	1.4 (10)	1.0 (6)	1.7* (51)
	localized	1.9 (3)	2.4* (10)	1.6 (4)	0.6 (1)	1.8* (18)
	operation(+)	1.4 (6)	2.7** (24)	1.2 (7)	1.2 (5)	1.8** (42)
	aged 30–54, operation(+)	0.0 (0)	2.5 (4)	2.8 (4)	0.7 (1)	1.8 (9)
Colon	all cases	2.7** (42)	1.2 (35)	1.7** (37)	0.8 (17)	1.5** (131)
	localized	4.2** (19)	1.6 (19)	2.3** (18)	1.3 (8)	2.1** (64)
	operation(+)	3.4** (39)	1.3 (31)	2.1** (35)	1.0 (14)	1.8** (119)
	aged 30–54, operation(+)	5.2** (6)	4.1 (13)	3.9** (12)	1.9 (7)	3.4** (38)
Rectum	all cases	1.9** (26)	1.3 (34)	1.1 (21)	1.1 (18)	1.3* (99)
	localized	2.6* (10)	1.5 (15)	1.4 (9)	1.3 (6)	1.3 (40)
	operation(+)	2.4** (24)	1.6* (34)	1.4 (20)	1.4 (15)	1.6** (94)
	aged 30–54, operation(+)	8.6** (10)	2.9 (9)	1.8 (5)	2.6* (8)	3.1** (32)
Pancreas	all cases	1.5 (16)	0.3 (6)	0.7 (9)	1.2 (15)	0.8 (46)
	localized	1.3 (4)	0.3 (2)	0.4 (2)	0.8 (3)	0.6 (11)
	operation(+)	1.8 (14)	0.4 (6)	0.7 (8)	1.6 (14)	0.9 (42)
	aged 30–54, operation(+)	2.9 (2)	0.5 (1)	1.6 (3)	2.1 (7)	1.9 (13)

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

Table VII. Observed and Expected Numbers of Second Primary Cancers after Diagnosis of Stomach Cancer in Two Population-based Studies

Site	Connecticut[a]		Denmark[b]	
	M	F	M	F
All sites except stomach	1.1 (173)	1.0 (76)	0.8 (320)	0.9 (201)
Oral cavity & pharynx	0.8 (7)	0.0 (0)	0.5 (8)	0.8 (3)
Esophagus	1.1 (4)	1.7 (1)	0.5 (4)	0.6 (2)
Colon	0.9 (19)	0.9 (13)	1.1 (48)	1.0 (29)
Rectum	0.6 (7)	0.6 (3)	0.7* (29)	0.8 (14)
Liver	1.7 (5)	1.0 (2)	0.9 (9)	0.5 (4)
Pancreas	1.2 (7)	0.7 (2)	1.4 (27)	1.3 (12)
Larynx	0.8 (3)	0.0 (0)	0.5 (2)	0.0 (0)
Lung	1.1 (31)	0.8 (3)	0.6* (48)	0.8 (8)
Breast		1.3 (25)		0.8 (37)
Uterus		0.4 (3)		1.5 (31)
Ovary		1.2 (4)		1.9* (23)
Urinary system	1.9* (32)	0.8 (3)	0.8 (40)	1.0 (14)
Non-Hodgkin lymphoma	0.0 (0)	2.0 (4)	0.8 (6)	0.5 (10)
Leukemia	0.9 (5)	2.6 (6)	0.8 (12)	1.0 (6)

a) 1935–1982. *b*) 1943–1980. * $P<0.05$.
Numbers in parentheses are the observed numbers.

Table VIII. Studies of Multiple Primary Cancer Following Stomach Cancer

Authors (ref. no.); Study design	Country; Period	No. of subjects	Average follow-up	Findings
Schottenfeld *et al.* (5); Hospital base	USA; 1949–62	1,204	1.2 yr	lower risks for genitourinary system. (O/E ratios were not mentioned)
Newell and Krementz (6); Hospital base	USA; 1948–70	W 485 B 1,397	1.4 1.5	white males had elevated risks of second malignant tumors. The O/E ratios were not shown for detailed sites.
Watanabe *et al.* (7) Hospital base	Japan; 1962–81	M 3,346 F 1,718	3.4 3.7	elevated risks for oropharynx (2.6), esophagus (2.1), colon (2.4) rectum (2.2), urinary bladder (2.3). lower risk for liver (0.4).
Ichikawa *et al.* (8); Hospital base	Japan; 1961–79	2,447	5.8	elevated risks for oropharynx (1.7), colo-rectal (2.0).
Hoar *et al.* (9); Population base	USA; 1935–82	M 6,478 F 3,770	1.7 2.0	elevated risks for male urinary system (1.9), female acute lymphocitic leukemia (5.5).
Lynge *et al.* (10); Population base	Denmark 1943–80	M 18,442 F 12,401	1.9 1.8	elevated risk for ovary (1.9). lower risks for male rectum (0.7), lung (0.6).
Hiyama *et al.* (this paper); Population base	Japan; 1966–86	M 38,777 F 22,391	3.3 3.2	elevated risks for male oro-pharynx (1.6), colon (1.6), rectum (1.3), female oro-pharynx (2.6). lower risks for male liver (0.7), lung (0.7), female uterus (0.7).

W, white; B, black; M, male; F, female; O, observed number; E, expected number.
Numbers in parentheses are the O/E ratios.

is prevalent, showed increased risks for colo-rectal cancer among stomach cancer patients. These results raise the possibility that some risk factors affect the development of both intestinal-type stomach cancer and colo-rectal cancer, though no confirmed common risk factors have been identified thus far. Further investigation in this area is necessary.

Several studies have reported that the mortality or incidence rates of colon cancer increased among those who had gastrectomy for benign gastro-duodenal diseases,[25-27] though the mechanism remains unclear. These findings may suggest that the elevation in the risk of developing second primary colon cancer 5 or more years after stomach cancer diagnosis observed among the stomach cancer patients with gastrectomy is partly due to gastrectomy. Inokuchi *et al.*[27] revealed that those who had Billroth II gastrectomy had an increased risk of developing colon cancer, though the risk was not elevated among those who had Billroth I gastrectomy. Unfortunately, more detailed information on gastrectomy was not available in our series. Hospital-based studies, which have the advantage of obtaining more detailed information concerning therapy, and of following the patients individually, could provide useful information for revealing the effects of gastrectomy on the risks of developing colon cancer.

Elevated risk of developing second primary cancer of the pancreas was observed among stomach cancer patients with gastrectomy 10 or more years after stomach cancer diagnosis (O/E=1.6), though the difference was not significant. Several cohort studies of those who had gastrectomy for benign gastroduodenal diseases revealed increased risk of developing pancreatic cancer.[25, 28, 29] Mack *et al.* found a positive association between pancreatic cancer and previous gastrectomy in their case-control study for pancreatic cancer.[30] These findings suggest that gastrectomy might result in the increased risk of developing pancreatic cancer, though the mechanisms are not yet clear.

Slightly, though not significantly, increased risks were observed for the sites of urinary bladder for both sexes and non-Hodgkin lymphoma among female stomach cancer patients. Analysis limited to those who had been treated with anti-cancer drugs also revealed elevated risks, though the differences were not significant. Further investigation into this area may be necessary.

In general, younger stomach cancer patients had higher risks of developing second primary cancers. Better prognosis of stomach cancer among younger patients than older patients might be one of the reasons. There exists the possibility that younger patients were more closely followed up than older patients. Another plausible explanation is that those who suffered from stomach cancer at a younger age were heavily and continuously exposed to risk factors, or that they are genetically predisposed.

A study of second primary cancers helps to identify various groups of cancer patients in whom increased surveillance aimed at early detection is desirable, as well as to provide clues with which to further understand various etiologic factors. In this respect, our study suggests that it is necessary to follow up stomach cancer patients, especially those diagnosed at younger ages, in order to enable the early detection of second digestive tract cancers.

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REFERENCES

1) Waterhouse, J., Muir, C., Correa, P. and Powell, J. "Cancer Incidence in Five Continents. Vol. III," IARC Scientific Publications No. 15 (1976). IARC, Lyon.
2) Waterhouse, J., Muir, C., Shanmugaratnam, K. and Powell, J. "Cancer Incidence in Five Continents. Vol. IV," IARC Scientific Publications No. 42 (1982). IARC, Lyon.
3) Muir, C., Waterhouse, J., Mack, T., Powell, J. and Whelan, S. "Cancer Incidence in Five Continents. Vol. V," IARC Scientific Publications No. 88 (1987). IARC, Lyon.
4) Hanai, A. and Fujimoto, I. Survival rate as an index in evaluating cancer control. *In* "The Role of the Registry in Cancer Control," IARC Scientific Publications No. 66, pp. 87-107 (1985). IARC, Lyon.
5) 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).
6) Newell, G. R. and Krementz, E. T. Multiple malignant neoplasms in the Charity Hospital of Louisiana Tumor Registry. *Cancer*, **40**, 1812–1820 (1977).
7) Watanabe, S., Kodama, T., Shimosato, Y., Arimoto, H. and Suemasu, K. Second primary cancers with gastrointestinal cancers. *Jpn. J. Clin. Oncol.*, **15** (Suppl. 1), 171–182 (1985).
8) Ichikawa, T., Iwanaga, T., Taniguchi, K., Koyama, H., Imaoka, S., Fukuda, I., Furukawa, H. and Kabuto, T. Double malignancies in the stomach and other organs. *J. Jpn. Soc. Cancer Ther.*, **19**, 2157–2167 (1984) (in

Japanese).
9) Hoar, S. K., Wilson, J., Blot, W., McLaughlin, J. K., Winn, D. H. and Kantor, A. F. Second cancer following cancer at the digestive system in Connecticut, 1935–82. *Natl. Cancer Inst. Monogr.*, **68**, 49–82 (1985).
10) Lynge, 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).
11) Lauren, P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal type carcinoma. An attempt at a histo-clinical classification. *Acta Pathol. Microbiol. Scand.*, **64**, 31–49 (1965).
12) Correa, P., Sasano, N., Stenmmermann, N. and Haenszel, W. Pathology of gastric carcinoma in Japanese population: comparisons between Miyagi prefecture, Japan and Hawaii. *J. Natl. Cancer Inst.*, **51**, 1449–1459 (1973).
13) Munoz, N., Correa, P., Cuello, C. and Duque, E. Histologic types of gastric carcinoma in high- and low- risk areas. *Int. J. Cancer*, **3**, 809–818 (1968).
14) Hanai, A. and Fujimoto, I. Trends of stomach cancer incidence and histological types in Osaka. *In* "Trends in Cancer Incidence," ed. K. Magnus pp. 143–154 (1982). Hemisphere Publ. Co.,Washington.
15) Muir, C. and Waterhouse, J. Compatability and quality of data: reliability of registration. *In* "Cancer Incidence in Five Continents. Vol. V," ed. C. Muir, J. Waterhouse, T. Mack, J. Powell and S. Whelan, IARC Scientific Publications No. 88, pp. 45–54 (1987). IARC, Lyon.
16) U.S. Public Health Service. The health consequences of smoking — cancer. A report of the Surgeon General. DHHS publication No. PHS 82–50179, pp. 78–90 (1982). Rockville, MD.
17) Hu, J., Zhang, S., Jia, E., Wang, Q., Liu, S., Liu, Y., Wu, Y. and Cheng, Y. Diet and cancer of the stomach: a case-control study of dietary factors and stomach cancer risk. *Int. J. Cancer*, **37**, 827–842 (1986).
18) You, W. C., Blot, W. J., Chang, Y. S., Ershow, A. G., Yang, Z. T., An, Q., Henderson, B., Xu, G. W., Fraumeni, J. F. and Wang, J.G. Diet and high risk of stomach cancer in Shandong, China. *Cancer Res.*, **48**, 3518–3522 (1988).
19) Hirayama, T. Epidemiology of stomach cancer in Japan with special reference to the strategy for the primary prevention. *Jpn. J. Clin. Oncol.*, **14**, 159–168 (1984).
20) Ubukata, T., Nakao, M., Oshima, A., Sobue, T. and Fujimoto, I. Drinking and smoking in the etiology of stomach cancer. *Jpn. J. Public Health*, **35**, 286–292 (1988) (in Japanese).
21) Risch, H. A., Jain, M., Choi, N. M., Fodor, G., Pfeiffer, C. J., Howe, G. R., Harrison, L. W., Craib, K. J. P. and Miller, A. B. Dietary factors and the incidence of cancer of the stomach. *Am. J. Epidemiol.*, **122**, 947–959 (1985).
22) Nomura, A., Grove, J. S., Stenmmermann, G. N. and Severson, R. K. A prospective study of stomach cancer and in relation to diet, cigarettes and alcohol consumption. *Cancer Res.*, **50**, 627–631 (1990).
23) Graham, S., Dayal, H., Rohrer, T., Swanson, M., Sultz, H., Shedd, D. and Fisherman, S. Dentition, diet, tobacco and alcohol in the epidemiology of oral cancer. *J. Natl. Cancer Inst.*, **59**, 1611–1617 (1977).
24) Wynder, E. J., Bross, I. J. and Feldman, R. M. A study of the etiologic factors in cancer of the mouth. *Cancer*, **10**, 1300–1323 (1957).
25) Ross, A. H. M., Smith, M. A., Anderson, J. R. and Small, W. P. Late mortality after gastrectomy for peptic ulcer. *N. Engl. J. Med.*, **307**, 519–512 (1982).
26) Watt, P. C., Patterson, C. C. and Kennedy, T. L. Late mortality after vagotomy and drainage for duodenal ulcer. *Br. Med. J.*, **288**, 1335–1338 (1984).
27) Inokuchi, K., Tokudome, S., Ikeda, M., Kuratsune, M., Ichiyama, H., Kaibara, N., Ikejiri, T. and Oka, N. Mortality from carcinoma after partial gastrectomy. *Gann*, **75**, 588–594 (1984).
28) Caygill, C. P. J., Hill, M. J., Hall, C. N., Kirkham, J. S. and Northfield, T. C. Increased risk of cancer at multiple sites after gastric surgery for peptic ulcer. *Gut*, **28**, 924–928 (1987).
29) Tersmette, A. C., Offerhaus, J. A., Giardiello, F. M., Tersmette, K. W. F., Vandenbrouck, J. P. and Tytgat, G. N. J. Occurrence of non-gastric cancer in the digestive tract after remote partial gastrectomy: analysis of an Amsterdam cohort. *Int. J. Cancer*, **46**, 792–795 (1990).
30) Mack, T. M., Yu, M. C., Hanisch, R. and Henderson, B. E. Pancreatic cancer and smoking, beverage consumption, and past medical history. *J. Natl. Cancer Inst.*, **76**, 49–60 (1986).