ACTA ONCOLOGICA

Vol. 30
No. 1

1991

THE RISK OF GASTROINTESTINAL AND OTHER PRIMARY MALIGNANT DISEASES FOLLOWING GASTRIC CANCER

G. LUNDEGÅRDH, L.-E. HANSSON, O. NYRÉN, H.-O. ADAMI and U. B. KRUSEMO

Abstract

The risk of developing a second primary cancer was studied among 34 506 gastric cancer patients identified through the Swedish Cancer Registry. A second cancer was reported in 962 patients compared to an expected number of 826 (relative risk = 1.16, 95% confidence limits = 1.09–1.24). The slightly but significantly elevated risk was largely confined to the first year after the gastric cancer diagnosis, and to patients under 70 years old at the time of diagnosis. The risk was significantly increased for cancer in the small intestine, colon, rectum, kidney, breast and prostate. A closer look at the data, however, revealed that a substantial proportion of the second cancers were diagnosed within one month after the gastric cancer diagnosis, or at autopsy. We recalculated the relative risk estimates under the assumption that only 75% of the cancers incidentally detected in connection with diagnosis/treatment of the gastric cancer would have become clinically manifest during the relatively short observation time, and that 20% of the cancers revealed at autopsy in the gastric cancer patients would have been detected if the death and autopsy rates in this group had been equal to those in the general population (matched for age and gender). Under those assumptions the risk of having a second primary cancer among gastric cancer patients was close to what would be expected. The increased risk reported in some previous studies could be the result of closer patient surveillance.

Key words: Gastric cancer, secondary malignancies, cohort study.

Associations between different malignant diseases may indicate that the same etiologic factors – whether environmental or genetic – are operating in their causation. Such associations might also influence routines for follow-up and stimulate efforts aimed at early diagnosis of second cancers.

In regard to gastric cancer, the risk of developing a second primary cancer at other sites has been reported as being increased (1, 2) unchanged (3, 4) and decreased (5, 6). An increased risk of thyroid (1) oesophageal (1) liver/pancreatic (1) ovarial (6) and bladder cancers (3) has been observed following gastric cancer. A negative association has been demonstrated for cancers of the lung (5, 6) breast (5) and prostate (5). Data on the association between gastric and colorectal cancers (1, 5, 6) and between gastric and renal cancers (1, 3) are conflicting.

These equivocal results indicate a need for further investigation about second primary cancers after gastric cancer. Such studies are hampered by the short mean survival time in gastric cancer (7) which means that few patients remain at risk for a sufficiently long period of time. This problem can be overcome – at least to some extent – by taking advantage of the favourable opportunity offered by the Swedish nationwide Cancer Registry for creating large cohorts. With its nearly complete follow-up and its valid incidence figures for the population under study, it allows analyses of gender, age at diagnosis, and time after diagnosis as possible determinants of an increased risk of a second primary cancer.

Material and Methods

The cohort

The Swedish Cancer Registry at the National Board of Health and Welfare was started in 1958. All newly diagnosed malignant tumours must be reported to the Registry both by the physician/surgeon and by the pathologist or cytologist who confirms the diagnosis on biopsied or surgically removed tissues, cytologic specimens, or at autopsy.

From the Departments of Surgery, Central Hospital, Boden, and University Hospital, Uppsala, and Uppsala University Data Center, Uppsala, Sweden.

Submitted 11 October 1989.
Accepted for publication 19 May 1990.

As a result, most cases included in the Registry are reported from two sources (8). The Registry does not include any information on stage of disease or treatment.

During the first few years after the establishment of the Registry the frequency of underreporting decreased to a level of about 5% (9). This small percentage permits a follow-up of cohorts with respect to newly diagnosed cancers which is almost complete (95%), and this was considered adequate for the purpose of the present study.

Information on all 35 052 persons diagnosed as having gastric cancer from 1960 through 1981, and who were alive at the time of diagnosis was extracted from the Registry. Each person's national registration number (which includes the date of birth and also permits positive identification) and date of diagnosis were included in a computerized register that allowed follow-up through linkage to other registers. The person-years at risk were calculated, starting from the date of gastric cancer diagnosis, by linkage of the cohort to the Causes of Death Registry (date of death), the Swedish Emigration Registry (date of emigration) and the Registry of Living Persons, which includes the total Swedish population (followed until the closing date). People who were not identified in any of the latter three registries—a total of 556 persons (1.6%)—were most probably entered the Cancer Registry with erroneous national registration numbers and therefore lost to follow-up. As a result, 34 506 individuals, 21 492 men and 13 014 women, were available for follow-up and comprised the study cohort. The distribution by age and gender is shown in Table 1. At the time of this study the register was complete up to December 31, 1981, which was the closing date. Thus, the follow-up period ranged from 0 to 21 completed years. At the closing data 2 111 men and 1 459 women in the cohort were alive.

Expected and observed incidence of second cancers

Official statistics (8) from the Swedish Cancer Registry included age-specific incidence rates for all cancer sites according to the ICD-7 (10) for each year under study. By multiplication of person-years at risk in different 5-year age groups by the corresponding age-specific incidences for each successive year under study, the expected number of second (or more) primary cancers in the cohort was obtained. No separate analysis for a third and subsequent primary cancers was done due to the small number that was found (30 males and 15 females).

The observed incidence of second cancers was obtained by again linking the register for the cohort to the Swedish Cancer Registry. Since metastatic or recurrent disease is not normally re-reported and since checks are made at the Registry to assure that such cases are not included as new cancers, all cancers reported subsequent to gastric cancer were regarded as second primary cancers.

Validity check

We performed a validity check by scrutinizing the original report forms, kept by the National Board of Health and Welfare, for every case with one of the following combinations: gastric-oesophageal, gastric-small intestinal, gastric-colonic, gastric-rectal, gastric-renal or gastric-breast carcinomas. Coding errors were rare, and we could confirm the occurrence of the two cancers in over 99% of the cases.

Statistical methods

The relative risk (RR) was defined as the ratio of observed cases of a second carcinoma to expected cases. The 95% confidence limits (CL) of the relative risk were calculated under the assumption that the observed number of cases in each class followed a Poisson distribution (11).

Results

In the whole cohort a second cancer was reported in 962 (2.8%) patients as compared with 826.2, which was the expected number. The overall relative risk was slightly but significantly elevated (RR = 1.16, 95% CL = 1.09–1.24).

Table 1

Distribution of the cohort by gender, age at diagnosis and person-years at risk

Age at diagnosis (years)	Males			Females		
	No.	%	Person-years	No.	%	Person-years
<40	212	1	578	226	2	545
40–49	850	4	2 385	580	4	1 507
50–59	2 789	13	7 057	1 451	11	3 613
60–69	6 438	30	12 547	3 202	25	7 016
70–79	7 812	36	11 603	4 926	38	9 001
>80	3 391	16	3 491	2 629	20	3 331
Total	21 492	100	37 661	13 014	100	25 013

Table 2

The risk of a second cancer after gastric cancer by age and time after diagnosis

Age at diagnosis (years)	Time since diagnosis											
	<1 year				1–21 years				0–21 years			
	OBS	EXP	RR	95% CI	OBS	EXP	RR	95% CI	OBS	EXP	RR	95% CI
<50	3	2.4	1.2	0.4–1.8	21	12.4	1.7	1.1–2.3	24	14.9	1.6	1.1–2.4
50–59	33	12.5	2.7	1.9–3.7	81	57.6	1.4	1.1–1.8	114	70.1	1.6	1.4–2.0
60–69	111	57.7	1.9	1.6–2.3	194	171.5	1.1	1.0–1.3	305	229.2	1.3	1.2–1.5
70–79	168	132.0	1.3	1.1–1.5	218	232.2	0.9	0.8–1.1	386	364.2	1.1	1.0–1.2
>80	76	78.6	1.0	0.8–1.2	57	69.4	0.8	0.6–1.1	133	148.0	0.9	0.8–1.1
All ages	391	283.1	1.4	1.3–1.5	571	543.1	1.1	1.0–1.1	962	826.2	1.2	1.1–1.2

Abbreviations: Observed cases = OBS; Expected cases = EXP; Relative risk = RR; 95% confidence limits = 95% CI.

Table 3

The risk of developing a second cancer after gastric cancer by gender and site

Site	Male				Female				Males and females			
	OBS	EXP	RR	95% CI	OBS	EXP	RR	95% CI	OBS	EXP	RR	95% CI
All	626	550.5	1.1	1.1–1.2	336	275.8	1.2	1.1–1.4	962	826.2	1.2	1.1–1.2
Oesophagus	11	8.0	1.4	0.7–2.5	4	2.6	1.5	0.4–3.9	15	10.6	1.4	0.8–2.3
Small intestine	6	2.6	2.3	0.9–5.1	3	1.4	2.1	0.5–6.2	9	4.0	2.3	1.0–4.3
Colon	71	48.1	1.5	1.2–1.9	46	30.5	1.5	1.1–2.0	117	78.6	1.5	1.2–1.8
Rectum	48	31.5	1.5	1.2–2.0	26	13.4	1.9	1.3–2.8	74	44.9	1.7	1.3–2.1
Liver	17	18.1	0.9	0.6–1.5	10	15.2	0.7	0.3–1.2	27	33.2	0.8	0.5–1.2
Pancreas	31	24.3	1.3	0.9–1.8	11	13.2	0.8	0.4–1.5	42	37.5	1.1	0.8–1.5
Lung	50	55.4	0.9	0.7–1.2	9	8.8	1.0	0.5–2.0	59	64.2	0.9	0.7–1.2
Breast					83	63.1	1.3	1.1–1.6				
Ovary					22	14.2	1.6	1.0–2.4				
Prostate	196	161.1	1.2	1.1–1.4								
Kidney	33	22.4	1.5	1.1–2.1	18	9.9	1.8	1.2–2.9	51	32.4	1.6	1.2–2.1
Bladder	37	35.1	1.1	0.7–1.5	11	8.2	1.4	0.7–2.4	48	43.2	1.1	0.8–1.5

Abbreviations: Observed cases = OBS; Expected cases = EXP; Relative risk = RR; 95% confidence limits = 95% CI.

A second cancer was reported in 626 men (RR = 1.14, 95% CL = 1.05–1.23) and 336 women (RR = 1.22, 95% CL = 1.10–1.36).

During the first year after diagnosis the risk of a second cancer was increased (RR = 1.38, 95% CL = 1.25–1.52), while during the period from 1–21 years after diagnosis the overall relative risk was close to unity (RR = 1.05, 95% CL = 0.97–1.14). This risk pattern was observed among men as well as among women.

In both genders, age at diagnosis was a determinant of the risk of having a second cancer reported to the Registry (data not shown). The increased overall risk was confined to patients younger than 70 years at diagnosis (Table 2). During the first year after diagnosis the risk was increased in all age-groups except >80 years. After that the risk remained elevated only in age-groups <60 years.

The sites of second cancers are shown in Table 3. Only sites with a sufficient number of observed cases have been included. The risk of having a second cancer in the colon, rectum, of kidney was significantly increased in both men and women. There was a significantly increased risk of breast cancer in women and of prostate cancer in men. When both genders were analysed together, the risk of a second cancer in the small intestine also became statistically significant. Site is stratified by time after diagnosis in Table 4. The risk was increased at all sites during the first year, while it was close to what would be expected after that.

In order to explore the possibility of closer medical surveillance in connection with the diagnosis and treatment of gastric cancer being responsible for the observed risk increase, we calculated the exact time period that elapsed between the two cancer diagnoses for each patient with a second cancer in the oesophagus, small intestine, colon, rectum, kidney or breast. If the second cancer was diagnosed within one month after the diagnosis of the

Table 4

The risk of developing a second cancer after gastric cancer by site and time after diagnosis

Site	<1 year				1–21 years			
	OBS	EXP	RR	95% CI	OBS	EXP	RR	95% CI
Colon	58	26.8	2.2	1.7–1.8	59	51.8	1.1	0.9–1.5
Rectum	37	15.7	2.4	1.7–3.2	37	29.2	1.3	0.9–1.8
Breast	37	20.7	1.8	1.3–2.5	46	42.4	1.1	0.8–1.5
Prostate	97	56.3	1.7	1.4–2.0	99	104.8	0.9	0.8–1.2
Kidney	26	11.2	2.3	1.6–3.4	25	21.4	1.2	0.8–1.8

Abbreviations: Observed cases = OBS; Expected cases = EXP; Relative risk = RR; 95% confidence limits = 95% CI.

Table 5

The proportion of second primary cancers diagnosed intra vitam within one month and more than one month after the gastric cancer diagnosis, and the proportion diagnosed post mortem

Site	Diagnosis within 1 month	Diagnosis after >1 month	Post mortem diagnosis (corresponding proportions in the general population)	Diagnosis either within one month or post mortem
Oesophagus	9/15 (60%)	4/15 (27%)	2/15 (13%) [8%]	11/15 (73%)
Small intestine	4/9 (44%)	1/9 (11%)	4/9 (44%) [18%]	8/9 (89%)
Colon	44/115 (38%)	45/115 (39%)	26/115 (23%) [7%]	70/115 (61%)
Rectum	32/74 (43%)	37/74 (50%)	5/74 (7%) [3%]	37/74 (50%)
Breast	29/83 (35%)	52/83 (63%)	2/83 (2%) [.4%]	31/83 (37%)
Kidney	7/51 (14%)	12/15 (24%)	32/51 (63%) [21%]	39/51 (76%)
Total	125/347 (36%)	151/347 (44%)	71/347 (20%)	196/347 (56%)

gastric cancer, it is reasonable to believe that it was an incidental finding precipitated by the diagnostic/therapeutic measures in connection with the first cancer. Table 5 shows the proportion diagnosed within one month, and after more than one month following diagnosis of the index cancer. That table also shows the proportion of registered second cancers that were found incidentally at autopsy. The proportion of incidentally discovered second cancers (either in direct connection with diagnosis/treatment of the index cancer or at autopsy) varied from 37% (breast cancer) to 89% (small intestinal cancer).

Discussion

This study has shown that the risk of a subsequent primary cancer was seemingly increased for both men and women. The risk increase was largely confined to the first year after diagnosis, and it was absent in the oldest age groups. There was a significantly increased risk of colorectal, small intestinal, breast, prostatic, and renal cancer, but only during the first year after the gastric cancer diagnosis.

A closer look at this material revealed that most of the observed second cancers were either diagnosed within one month after diagnosis of the index gastric cancer, or at autopsy. A majority of the cases in the cohort died within a few years, while the expected death rate in the age-matched background population is only a small fraction of that observed in the cohort. Moreover, the autopsy rate among deceased individuals who have had a cancer diagnosis may be higher than average. Therefore a higher rate of detection of subclinical malignancies would be expected among the gastric cancer cases as compared with the background population. This seemed, in fact, to be true, since the proportion of cancers diagnosed at autopsy was considerably higher than average for all sites in the gastric cancer cohort—despite the fact that the cohort was scrutinized and cleared from clinical and subclinical cancers in connection with the diagnostic work-up and/or treatment of the index gastric cancer. Thus our supposition that the general risk increase observed by us and by others (1, 3, 6) is an artifact due to an increased detection rate (ascertainment bias) derives further support from this study.

We recalculated the relative risk estimates under the assumption that only 75% of the cancers incidentally detected in connection with the diagnosis/treatment of the initial gastric cancer would have become clinically manifest during the short mean observation time in the cohort (21.8 months) had not the gastric cancer precipitated their diagnosis, and that 20% of the post mortem detected cancers

Table 6

The relative risk of developing a second primary cancer after gastric cancer. This analysis was made under the assumption that only 75% of the cancers incidentally detected in connection with diagnosis/treatment of the initial gastric cancer would have become clinically manifest during the short mean observation time in the cohort (21.8 months) had not the gastric cancer precipitated their diagnosis, and that 20% of the post mortem detected cancers in the cohort would have been diagnoses if the autopsy rate had been equal to that in the general population

Site	Observed cases (modified)	Expected cases	Relative risk	95% confidence limits
Oesophagus	11.2	10.6	1.1	0.5–2.4
Small intestine	4.8	4.0	1.2	0.3–4.5
Colon	83.2	78.6	1.1	0.8–1.4
Rectum	62.0	44.9	1.4	0.9–2.0
Breast	74.2	63.1	1.2	0.8–1.6
Kidney	23.7	32.4	0.7	0.4–1.2
All sites above	259.0	233.6	1.1	0.9–1.3

in the cohort would have been diagnosed if the death and autopsy rates had been equal to those in the backgroud population (Table 6). Under these arbitrary but probably conservative assumptions, all increased relative risk estimates disappeared.

In this study we have used the Swedish Cancer Registry for compilation of the gastric cancer cohort, identification of all incident cases with a second primary cancer in that cohort, and for calculation of the expected incidence rates. The registry covers the whole Swedish population (7.9 million in 1980) and its completeness is about 95%. The risk of selection bias is thus eliminated. The small amount of underreporting will influence observed and expected number of cases to the same extent. As a result, the quotient between them will remain virtually unchanged.

The possibility of bias exists due to misclassification, since metastatic disease may be mistaken for an independent primary malignancy. This problem is likely to be greater when a gastric cancer metastatis occurs in an atypical site. On the other hand, primary cancers in locations typical for gastric cancer metastatis are liable to be erroneously classified as being secondary to gastric cancer. This might be one explanation for the divergent pattern observed for hepatic and lung cancers. As opposed to many other sites, there was a tendency towards a decreased risk in those locations. A negative association between gastric cancer and subsequent primary lung cancer has also been reported by others (5, 6).

The relative risk estimates showed an age-related gradient; the risk was highest among the youngest and lowest—below unity—among the oldest (Table 2). It is conceivable that the younger patients receive more medical attention than very old patients with a previous cancer diagnosis. This would explain the data presented by Teppo et al. (5), who also found low age at diagnosis to be a determinant for a second cancer. Regardless of the probable ascertainment bias, however, our data do not permit us to categorically rule out the possibility that young cancer patients do in fact have a genuinely—but slightly—increased risk of multiple cancers. Factors common to young cancer patients, such as a possible general susceptibility to a carcinogenesis and stronger than average exposure to carcinogenic agents, may conceivably contribute to a tendency to develop cancers, not necessarily specific for certain sites. The fact that the relative risk estimates in the youngest age groups did not reach unity even in the second period lends some support to this assumption.

It should be pointed out that this analysis assumes that the induction time for an associated cancer after exposure to a common etiologic factor is approximately the same as in gastric cancer. However, it seems highly unlikely that latency periods for solid tumours would differ to such an extent that an association would not be reflected by an increased incidence during the—admittedly short—survival time after gastric cancer. The mean survival time is too short, however, to allow for types of cancer induced by the treatment of the gastric cancer, if any, to be pinpointed.

It is concluded that a seemingly increased risk of developing second primary cancers after a gastric cancer diagnosis, as demonstrated by us and by others, is probably due to ascertainment bias—a result of the closer medical surveillance given to these cases. Although the perspective is somewhat narrow, covering only a mean survival time of 21.7 months after gastric cancer diagnosis, we have found no strong indication of any associations between gastric cancer and primary cancers at other sites.

ACKNOWLEDGEMENT

This work was supported by grants from the Swedish Cancer Society.

Corresponding author: Dr Lars-Erik Hansson, Department of Surgery, Akademiska sjukhuset, S-751 85 Uppsala, Sweden.

REFERENCES

1. Yoshino K, Asanuma F, Hanatani Y, Otani Y, Kumai K, Ishibiki K. Multiple primary cancer in the stomach and other organs: Frequency and the effects on prognosis. Jpn J Clin Oncol 1985; 15 (Suppl 1): 183–90.
2. Koga S, Kaibara N, Tamura H, Nishidoi H, Kimura O. Cause of late postoperative death in patients with early gastric cancer with special reference to recurrence and the incidence of metachronous primary cancer in other organs. Surgery 1984; 94: 511–6.
3. Hoar SK, Wilson J, Blot WJ, McLaughlin JK, Winn DM, Kantor AF. Second cancer following cancer of the digestive system in Connecticut, 1935–82. Washington: NCI Monograph No. 68. 1985: 49–64.

4. Schottenfeld D, Berg JW, Vitsky B. Incidence of multiple primary cancers. II. Index cancers arising in the stomach and lower digestive system. JNCI 1969; 43: 77–86.
5. Teppo L, Pukkala E, Saxén E. Multiple cancer—an epidemiologic exercise in Finland. JNCI 1985; 75: 207–17.
6. Lynge E, Jensen OM, Carstensen B. Second cancer following cancer of the digestive system in Denmark, 1943–80. Washington: NCI Monograph No. 68. 1985: 277–90.
7. Lundegårdh G, Adami HO, Malker B. Gastric cancer survival in Sweden: lack of improvement during 19 years. Ann Surg 1986; 204: 546–51.
8. The Cancer Registry. Cancer incidence in Sweden 1964–1980 (Annual publications). Stockholm: Swedish Board of Health and Welfare 1969–1983.
9. Mattson B. The completeness of registration in the Swedish Cancer Registry. Stockholm: Swedish Board of Health and Welfare, Statistical Reports, 1977: 15.
10. World Health Organization. Manual of international statistical classification of diseases, injuries and causes of death. Seventh Revision. Geneva: WHO, 1957: 1–393.
11. Bailar JC III, Ederer F. Significant factors for the ratio of a Poisson variable to its expectation. Biometrics 1964; 20: 639–43.