

Malignant Neoplasms after Radiation Therapy for Peptic Ulcer

Zhanat A. Carr,^{a,1} Ruth A. Kleinerman,^a Marilyn Stovall,^b Robert M. Weinstock,^a Melvin L. Griem^c and Charles E. Land^a

^a Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Bethesda, Maryland; ^b Department of Radiation Physics, The University of Texas M. D. Anderson Cancer Center, Houston, Texas; and ^c Professor Emeritus, Department of Radiation and Cellular Oncology, University of Chicago Medical Center, Chicago, Illinois

Carr, Z. A., Kleinerman, R. A., Stovall, M., Weinstock, R. M., Griem, M. L. and Land, C. E. Malignant Neoplasms after Radiation Therapy for Peptic Ulcer. *Radiat. Res.* 157, 668–677 (2002).

Most information on radiation-related cancer risk comes from the Life Span Study (LSS) of the Japanese atomic bomb survivors. Stomach cancer mortality rates are much higher in Japan than in the U.S., making the applicability of LSS findings to the U.S. population uncertain. A unique cohort of U.S. patients who were irradiated for peptic ulcer to control gastric secretion provides a different perspective on risk. Cancer mortality data were analyzed and relative risks estimated for 3719 subjects treated by radiotherapy (mean stomach dose 14.8 Gy) and/or by surgery and medication during the period 1936–1965 and followed through 1997 (average 25 years). Compared to the U.S. rates, stomach cancer mortality was significantly increased for irradiated and nonirradiated patients (observed/expected = 3.20 and 1.52, respectively). We observed strong evidence of exposure-related excess mortality from cancer of the stomach (RR 2.6, 95% CI 1.3, 5.1), pancreas (RR 2.7, 95% CI 1.5, 5.1), and lung (RR 1.5, 95% CI 1.1, 2.1), with commensurate radiation dose responses in analyses that included nonexposed patients. However, the dose responses for these cancers were not significant when restricted to exposed patients. Our excess relative risk per gray estimate of 0.20 at doses ≤ 10 Gy (95% CI 0, 0.73) is consistent with the estimate of 0.24 (95% CI 0.10, 0.40) obtained from the LSS study with the linear model. © 2002 by Radiation Research Society

INTRODUCTION

Most information on radiation-related stomach cancer risk comes from the Life Span Study (LSS) of the Japanese atomic bomb survivors (1–3). However, stomach cancer incidence and mortality rates are much higher in Japan than in the United States, which makes the applicability of LSS findings to the U.S. population uncertain. A unique cohort of U.S. patients with peptic ulcer who were irradiated to

control gastric acid secretion provides a different perspective on radiation-related stomach cancer risk. Radiation therapy for treatment of peptic ulcer was widely used from the 1940s through the 1960s at the University of Chicago (4, 5). Previous follow-up studies (until January 1, 1985) of the peptic ulcer cohort treated at the University of Chicago have been reported (6–8). Radiotherapy, given as a treatment for peptic ulcer, was associated with a significantly increased risk for cancer, and particularly for stomach, lung and pancreatic cancers.

The purpose of the current follow-up study, through December 31, 1997, is to determine the lifetime risk of cancer, to evaluate the relative risk pattern of specific cancers by radiation dose during long-term follow-up (up to 60 years), and to evaluate the interaction of radiation exposure with other risk factors such as type of ulcer and treatment by means other than radiotherapy.

MATERIALS AND METHODS

Study Population and Follow-up

A total of 3997 patients treated for peptic ulcer at the University of Chicago between 1937 and 1965 were identified. Of these, 1941 patients were treated with radiotherapy to decrease the acidity of gastric secretion and 2056 patients were not. A total of 278 subjects were excluded from the analysis because of unknown radiotherapy status ($n = 3$), death within 1 year after treatment ($n = 16$), treatment after 1965 ($n = 41$), loss to follow-up within 1 year ($n = 213$), or other reasons ($n = 5$). After all exclusions were applied, the follow-up data were analyzed on 3719 patients (1859 exposed and 1860 not exposed to radiotherapy). Compared to the cohort of 3609 peptic ulcer patients evaluated in the previous follow-up study (8), this study included an additional 110 newly located patients (28 irradiated and 82 nonirradiated) who previously had been lost to follow-up (8).

The analysis considered mortality from 1 year after treatment until December 31, 1997. Follow-up methods for assessing vital status and cause of death information included searches of the National Death Index (NDI) Plus, Social Security Administration Mortality Files and Presumed Living Files, and Pension Benefit Information records. By December 31, 1997, 83.6% of irradiated and 81.1% of nonirradiated patients were deceased. In both groups, 2.5% of patients were confirmed alive; 13.9% of irradiated and 16.5% of nonirradiated patients were lost to follow-up.

The Office of Human Subjects Research, National Institutes of Health, determined that the current follow-up study of peptic ulcer patients was exempt from Institutional Review Board approval due to the nature of

¹ Author to whom correspondence should be addressed at REB/DCEG, NCI, 6120 Executive Blvd., Executive Plaza South, Suite 7091, Rockville, MD 20852-7238; e-mail: abykasz@mail.nih.gov.

the research activity, i.e. determination of vital status and collection of publicly available mortality data. The study was conducted within the Intramural Research Program at the National Cancer Institute and was supported by a contract with Westat Inc. (N01-CP-81121) for data collection and management.

Exposure

Radiation treatment for peptic ulcer at the University of Chicago has been described in detail elsewhere (5, 7, 8). Radiation therapy (250 kVp X rays) was given in one or two 6- to 14-day courses of treatment. More than one treatment course was received by 182 (9.8%) of 1859 irradiated patients. Individual radiotherapy records were available for 1852 patients. Organ-specific doses were assessed experimentally using an anthropomorphic phantom and were reconstructed from individual radiotherapy records (8). The organ dose averaged over the entire stomach ranged from 1.0 to 42.0 Gy, with a mean of 14.8 ± 5.6 Gy. Stomach doses of 1–10 Gy were received by 19.7% of all irradiated patients, while 63.8% received 11–20 Gy and 16.5% received more than 20 Gy.

Statistical Analysis

For irradiated patients, the date of entry into the cohort was the date of first treatment, and for nonirradiated patients it was the date of first ulcer diagnosis or the date of the first visit to the University of Chicago Hospital, whichever occurred later. The date of exit was the date of death for deceased patients; for patients known to be alive and patients lost to follow-up after 1979 (the start of the NDI) but not reported as deceased, the exit date was December 31, 1997. Person-years (PY) were computed beginning 1 year after the date of treatment. Expected numbers of deaths were estimated by summing the products of age-, sex-, race- and calendar year-specific PY of observation times the corresponding mortality rates for the general population of the U.S. for each cause of interest. The observed number of deaths was compared with the expected number of deaths (O/E), and 95% confidence intervals (CI) were computed.

The main statistical analysis was by time-dependent proportional hazards analysis (9, 10), as implemented in the SAS PHREG software package (11). In this analysis, the hazard function for an individual at age t after study entry, and with covariates z_1, \dots, z_k , is modeled as

$$\lambda(t; z_1, \dots, z_k) = \lambda_0(t) \exp\{\beta_1 z_1 + \dots + \beta_k z_k\},$$

where $\lambda_0(t)$ is the baseline or background rate (hazard) as a function of time t since entry into the cohort and $\exp\{\beta_1 z_1 + \dots + \beta_k z_k\}$ is the relative risk (RR) function with unknown parameters β_1, \dots, β_k . Covariates z_1, \dots, z_k represented such factors as radiation exposure, radiation dose, sex, age at exposure, smoking status, indicator variables for different types of surgery and types of ulcer, and interaction terms. The minimum latent period for radiation-related increase in RR was assumed to be 10 years for solid cancers and 2 years for leukemia; thus the relative risks associated with radiation exposure and with dose were calculated only for $t > 10$ for solid cancers and $t > 2$ for leukemia.

Inasmuch as significant differences between exposed and nonexposed subjects were observed with respect to their distribution by a number of factors (year of birth, year of treatment, age at treatment, sex, race, cigarette habits, and type of surgery), in all analyses, the estimated RR, with 95% CI, was adjusted for calendar year, age at first treatment for irradiated patients or at diagnosis for nonirradiated patients, sex, and smoking history (12–14). The relative risk for stomach cancer was also adjusted for type of ulcer and type of surgery (partial gastrectomy, vagotomy or none) as potential confounders (15–17). Possible interactions of radiotherapy with surgery, ulcer type (for RR of stomach cancer), and partial gastrectomy (for RR of pancreatic cancer) were analyzed using the same statistical model. The interaction between radiotherapy and cigarette smoking as lung cancer risk factors was examined, excluding subjects with unknown smoking status. More generally, exposure-related RRs for those cancer sites which showed statistically significant excesses in mortality among irradiated patients were also computed separately for age

groups <35 , $35\text{--}54$ and ≥ 55 , since age at exposure is considered as an effect-modifying factor for radiation (1, 3).

For dose–response analyses and trend tests for stomach, lung and pancreatic cancers, we used individual organ-specific doses and the number of radiotherapy treatments. For some organs, such as lung, liver, kidney or colon, three dose estimates (minimal, maximal and average) were estimated in consideration of the nonuniform dose distribution within the organ; the average estimated organ doses were used for analyses. The average dose for the left lung, which was somewhat higher than that for the right lung, was used for lung cancer analyses. Organ-specific doses were stratified into quartiles, and linear model estimates of excess relative risk (ERR = RR – 1) per gray, with 95% CI, were computed for related quartiles by dividing the ERR and its CI limits by the mean organ-specific dose for each quartile. For more detailed dose–response analyses, relative risks were calculated for shorter dose intervals, corresponding dose deciles, and an isotonic regression approach (18) was applied to obtain the best-fitting monotonic, nondecreasing dose–response function at that level of resolution.

RESULTS

Over 15,000 additional PY of follow-up were accrued since the previous follow-up, for a total of 92,979 PY in 3,719 patients [41,779 PY in 1,859 irradiated patients and 51,200 PY in 1,860 nonirradiated patients (Table 1)]. The average period of observation after treatment was 25.0 ± 15.0 years (maximum 62 years): 22.5 years for irradiated patients and 27.5 years for nonirradiated patients. The two groups of patients were statistically significantly different by year and age at treatment, sex, race, cigarette smoking, and surgical treatment. No difference between the two groups was observed with respect to vital status by the end of follow-up. Radiation therapy was used for treatment of peptic ulcer from 1937 to 1965 (mean year of treatment 1949). Treatment for peptic ulcer by means other than radiotherapy occurred earlier, from 1929 to 1959 (mean 1944). The average age at the time of treatment was 49 years for irradiated patients and 45 years for nonirradiated patients. The majority of the study subjects were white male patients. More than half of the patients in each group smoked cigarettes (58.9% and 53.3%, respectively), and the number of cigarettes smoked per day was higher for irradiated patients: 29.7% of irradiated patients compared to 23.3% of nonirradiated patients reported smoking more than a pack of cigarettes per day. Slightly less than half of the patients in both groups drank alcohol (47.2% and 42.7%, respectively). Ulcer type was distributed similarly in both groups: The duodenal type significantly dominated over the gastric type (85.6% compared to 8.6% among irradiated, and 83.9% compared to 9.0% among nonirradiated). About one-quarter of irradiated patients and one-third of nonirradiated patients had a history of stomach surgery: partial gastrectomy (8.9% and 16.2%, respectively), vagotomy (10.9% and 19.5%), and other surgery types (11.8% and 14.4%).

There was a 19% excess for all causes of death combined in the irradiated group (O/E = 1.19, 95% CI 1.13, 1.25), while in the nonirradiated group a deficit of 8% of all deaths was observed (O/E = 0.92, 95% CI 0.87, 0.96) (data

TABLE 1
Characteristics of Patients with Peptic Ulcer by Radiotherapy Status

Characteristics	Total	Radiotherapy		No. of patients	Percentage	<i>P</i> value ^a
		Yes	No			
		No. of patients	No. of patients			
All patients	3,719	1,859	100	1,860	100	
Person-years	92,979	41,779		51,200		
Vital status (12/31/1997)						
Alive	93	47	2.5	46	2.5	
Deceased	3,062	1,554	83.6	1,508	81.1	
Lost to follow-up	564	258	13.9	306	16.5	0.091
Year of birth						
<1890	720	320	17.2	400	21.5	
1890–1899	1,003	506	27.2	497	26.7	
1900–1909	1,139	577	31.0	562	30.2	
≥1910	857	456	24.5	401	21.6	0.005
Year of treatment						
<1940	760	226	12.2	534	28.7	
1940–1944	862	403	21.7	459	24.7	
1945–1949	817	313	16.8	504	27.1	
1950–1959	1,124	761	40.9	363	19.5	
≥1960	156	156	8.4	0	0	<0.001
Age at treatment, years						
<35	709	272	14.6	437	23.5	
35–44	1,039	490	26.4	549	29.5	
45–54	1,046	549	29.5	497	26.7	
≥55	925	548	29.5	377	20.3	<0.001
Sex						
Male	2,914	1,491	80.2	1,423	76.5	
Female	805	368	19.8	437	23.5	0.006
Race						
White	3,581	1,747	94.0	1,834	98.6	
Black	69	60	3.2	9	0.5	
Other or unknown	69	52	2.8	17	0.9	<0.001
Cigarette habits ^b						
Never smoked	941	442	23.8	499	26.8	
Smoked	2,087	1,095	58.9	992	53.3	
Unknown	691	322	17.3	369	19.8	0.003
Quantity of cigarettes smoked ^b						
≤1 pack a day	1,462	736	67.2	726	73.2	
>1 pack a day	556	325	29.7	231	23.3	
Unknown	69	34	3.1	35	3.5	0.001
Alcohol habits ^b						
Never drank	1,257	615	33.1	642	34.5	
Drank	1,672	878	47.2	794	42.7	
Unknown	790	366	19.7	424	22.8	0.055
Quantity of alcohol ^b						
≤5 drinks per week	812	433	49.3	379	47.7	
6–15 drinks per week	274	151	17.2	123	15.5	
>15 drinks per week	325	181	20.6	144	18.1	
Unknown	261	113	12.9	148	18.7	0.729
Type of ulcer						
Duodenal	3,151	1,591	85.6	1,560	83.9	
Gastric	328	160	8.6	168	9.0	
Duodenal and gastric	53	24	1.3	29	1.6	
Other	124	71	3.8	53	2.8	
Unknown stomach subsite	63	13	0.7	50	2.7	0.357

TABLE 1
Continued

Characteristics	Total	Radiotherapy				P value ^a
		Yes		No		
		No. of patients	Percentage	No. of patients	Percentage	
Type of surgery ^c						
None	2,694	1,412	76.0	1,282	68.9	
Partial gastrectomy:	468	166	8.9	302	16.2	
Billroth I	166	79	4.2	87	4.7	
Billroth II	250	63	3.4	187	10.1	
Other	52	24	1.3	28	1.5	
Total gastrectomy	17	8	0.4	9	0.5	
Gastrostomy	423	197	10.6	226	12.2	
Vagotomy	566	203	10.9	363	19.5	
Other	65	33	1.8	32	1.7	<0.001

^a Test for independence.

^b At the time of ulcer treatment at University of Chicago.

^c Totals more than 100% because some patients had more than one surgery or the same surgery more than once.

not shown). Cancer mortality by radiotherapy status and follow-up period is shown in Table 2. Statistically significant increases in mortality were observed among irradiated patients for all cancers combined (O/E = 1.65), for cancers of stomach (O/E = 3.20), pancreas (O/E = 2.76), and lung (O/E = 1.99), and for non-Hodgkin's lymphoma (NHL) (O/E = 1.98); we did not find a statistically significant increase in mortality from cancers of esophagus (O/E = 0.77), liver (O/E = 1.80), or kidney (O/E = 1.31), which received relatively high doses of radiation, and for non-CLL leukemia (O/E = 1.41). Nonirradiated patients showed a statistically significant elevation in mortality from all cancers combined (O/E = 1.12) and for cancers of the stomach (O/E = 1.52) and prostate (O/E = 1.47).

Comparing irradiated and nonirradiated patients, we did not observe statistically significantly elevated relative risks for any cancer or leukemia within 10 years after treatment, but such excesses were observed after 10 years of follow-up for all cancers combined, RR = 1.41 (95% CI 1.18, 1.67), stomach, 2.60 (95% CI 1.33, 5.09), lung, 1.50 (95% CI 1.08, 2.08), and pancreatic cancer, 2.73 (95% CI 1.46, 5.13). For pancreatic cancer, we additionally calculated relative risks separately for two periods of follow-up (<1970 and 1970+) to investigate the possibility that poorer specificity of pancreatic cancer diagnosis before 1970 might be a source of bias. RR estimates for radiotherapy-associated pancreatic cancer mortality before and after 1970 were similar: 2.59 (95% CI 0.93, 7.26) and 2.47, (95% CI 1.03, 5.91), respectively (data not shown). The increases in RR for NHL (2.04, 95% CI 0.66, 6.24) observed 10 years after the exposure and for non-CLL leukemia (2.46, 95% CI 0.75, 8.01) observed 2 years after the exposure were not statistically significant.

Dose-response analyses were based on observations more than 10 years after entry into the study. Statistically significant trends with radiation dose and with number of

radiotherapy treatments were observed for stomach, pancreas and lung (Table 3). However, dose-response analyses limited only to irradiated patients gave no statistical evidence for these sites of a trend with increasing total organ-specific dose, nor was there a trend with the number of radiotherapy treatments. Individual organ doses for the irradiated patients were stratified into quartiles and quartile-specific relative risks were computed, compared to the non-exposed, for these three cancer sites (Table 4). However, there was no clear evidence of dose response by dose quartile. Linear model estimates of excess relative risk per gray based on comparison between nonexposed patients and patients with estimated dose in the first quartile were 0.20 (95% CI 0, 0.73), 0.34 (95% CI 0.09, 0.89), and 0.43 (95% CI -0.12, 1.35) for stomach, pancreatic and lung cancer, respectively, whereas the corresponding estimates for the higher quartiles tended to be lower. Table 5 shows the results of isotonic, nondecreasing function, regression analyses of dose response for the risks of stomach, pancreatic and lung cancer. Only for pancreas is there a suggestion that the dose-specific RR fails to increase above 10 Gy, as might be the case in the presence of a competing cell-killing effect at high doses (19-21). For stomach cancer, RR increased from 2.11 at 1-17 Gy to 5.69 at 18-42 Gy. For lung cancer, we also observed an increase, from 0.85 at 0.1-1.1 Gy to 2.26 at 2.5-5.1 Gy.

Age at exposure is an important modifier of radiation-associated risk for some cancer sites (1-3). The RRs among the irradiated patients younger than 35, 35-54 and older than 55 years decreased with increasing age at exposure for all cancers combined and for pancreatic cancer, although most of these changes were not statistically significant (Table 6). For stomach and lung cancers, however, there was no suggestion of a trend.

In addition to radiation exposure, stomach cancer risk was also analyzed for type of ulcer (gastric or duodenal)

TABLE 2
Cancer Mortality According to Treatment for Peptic Ulcer

Cause of death (ICD-8 code)	Radiotherapy				Average organ dose (Gy)	Relative risk (RR) for radiotherapy by follow-up period			
	Yes		No			0–10 years		11–62 years	
	<i>n</i> = 1859 PY ^a = 41,779	O/E	<i>n</i> = 1860 PY ^a = 51,200	O/E		RR ^d	95% CI	RR ^d	95% CI
All cancers (140–209)	414	1.65 ^b	336	1.12 ^b	N/A	0.91	0.51, 1.63	1.41	1.18, 1.67
Buccal and pharynx (140–149)	1	0.16	3	0.42	0.03	0	0	0.38	0.04, 3.85
Esophagus (150)	4	0.77	4	0.67	2.3	0	0	0.97	0.17, 5.45
Stomach (151)	47	3.20 ^b	28	1.52 ^b	14.8	1.11	0.28, 4.49	2.60	1.33, 5.09
Large intestine (153)	36	1.34	33	0.99	10	2.60	0.28, 24.20	0.95	0.54, 1.67
Rectum (154)	2	0.24	10	0.99	0.1	0	0	0.49	0.10, 2.38
Liver (155–156)	11	1.80	11	1.42	4.8	0	0	0.84	0.29, 2.48
Pancreas (157)	37	2.76 ^b	22	1.38	13.5	1.26	0.15, 10.52	2.73	1.46, 5.13
Larynx (161)	5	1.71	5	1.51	0.1	0	0	1.18	0.31, 4.59
Lung (162)	125	1.99 ^b	84	1.20	1.8 ^e	0.84	0.28, 2.56	1.50	1.08, 2.08
Bone (170)	0	0	2	1.58	1.6	0	0	0	0
Breast female (174)	14	1.81	13	1.15	0.2	0	0	1.02	0.34, 3.08
All female genital (180–184)	2	0.33	4	0.65	0.4	0	0	1.66	0.24, 11.76
Prostate (185)	30	1.24	42	1.47 ^b	0.1	0.29	0.04, 2.09	0.84	0.49, 1.45
Bladder (188)	13	1.47	8	0.75	0.2	0	0	1.49	0.50, 4.44
Kidney (189)	7	1.31	2	0.32	14.2 ^e	0	0	2.68	0.49, 14.76
Brain (191–192)	6	1.34	9	1.78	0.03	0	0	1.08	0.31, 3.78
Thyroid (193)	2	3.31	1	1.29	0.2	0	0	2.41	0.21, 27.14
Non-Hodgkin's lymphoma (200, 202)	14	1.98 ^b	12	1.40	1.6 ^f	3.20	0.45–22.70	2.04	0.66–6.24
Hodgkin's disease (201)	0	0	2	1.08	1.6	0	0	0	0
Multiple myeloma (203)	4	1.15	3	0.73	1.6	0	0	0.03	0–3.2
Leukemia (204–207, without CLL)	10	1.41	5	0.57	1.6	0 ^c	0	2.46	0.75, 8.01

^a PY = person-years at risk.

^b $P < 0.05$.

^c 0–2 years and 3–62 years of follow-up for leukemia.

^d RR estimated by Cox proportional hazards model and adjusted for age, sex, calendar year, time since entry into cohort (year of first exposure for irradiated, and year of first visit/ulcer diagnosed for nonirradiated), and quantity of cigarettes smoked, comparing irradiated and nonirradiated groups. Stomach cancer RR was also adjusted for partial gastrectomy, vagotomy, and gastric type of ulcer.

^e Average dose for left organ.

^f Active bone marrow average dose applied for all hematopoietic tissue.

and type of surgery (partial gastrectomy, vagotomy or none) and for interaction of these risk factors with radiation (Table 7). Gastric ulcer was associated with higher stomach cancer mortality risk among both irradiated and nonirradiated patients, with no significant departure from a simple multiplicative interaction model. Conversely, duodenal ulcer was associated with reduced risk among both irradiated and nonirradiated patients, again with no evidence of interaction with radiotherapy on a multiplicative scale. Both partial gastrectomy and vagotomy were associated with increased risk of gastric cancer. On the multiplicative scale, there was no evidence of interaction between vagotomy and radiotherapy ($P = 0.482$). The interaction between partial gastrectomy and radiotherapy, on the other hand, was suggestively greater than multiplicative ($P = 0.107$).

Partial gastrectomy was also considered as a possible pancreatic cancer risk factor (22, 23). In our data, partial gastrectomy was not significantly associated with risk (RR = 2.01,

95% CI 0.88, 4.59), and there was no evidence of deviation from a multiplicative interaction model with respect to radiation exposure (RR for interaction = 0.72, 95% CI 0.14, 3.77) (data not shown). Adjustment for partial gastrectomy did not alter the radiation-related RR of pancreatic cancer.

To evaluate possible selection bias for those patients who underwent radiotherapy treatment, we estimated stomach cancer risk by the length of time ulcer symptoms persisted prior to treatment. Patients with a longer disease history, who may have been resistant to other types of treatment (surgery or medications), may have had more opportunities to be treated with radiotherapy. Compared to patients with less than 3 years since disease onset, the relative risks for stomach cancer for 3–6 years, 7–14 years, and 15–32 years of persistence of peptic ulcer symptoms were 2.07 (95% CI 0.92, 4.58), 1.59 (95% CI 0.71, 3.80), and 1.82 (95% CI 0.67, 4.45), respectively (data not shown). Because risks for stomach cancer did not rise with increasing duration of

TABLE 3
Trend Tests for Organ-Specific Mean Dose and Number of Radiotherapy Treatments Applied for Selected Cancer Sites among Peptic Ulcer Patients with more than 10 Years of Follow-up

Cancer site	Irradiated and nonirradiated patients ^a		Irradiated patients only	
	RR ^b per Gy (95% CI)	P trend	RR ^b per Gy (95% CI)	P trend
Stomach	1.06 (1.02, 1.10)	0.002	1.05 (0.97, 1.13)	0.231
Pancreas	1.04 (1.0, 1.08)	0.033	0.97 (0.90, 1.05)	0.453
Lung ^c	1.24 (1.07, 1.44)	0.005	1.24 (0.92, 1.68)	0.166
Cancer site	RR per treatment ^d (95% CI)	P trend	RR per treatment ^d (95% CI)	P trend
All cancers combined	1.32 (1.16, 1.52)	<0.001	1.15 (0.81, 1.62)	0.445
Stomach	2.17 (1.35, 3.50)	0.002	1.87 (0.60, 5.82)	0.279
Pancreas	1.84 (1.18, 2.85)	0.007	0.74 (0.21, 2.60)	0.638
Lung	1.41 (1.09, 1.81)	0.008	1.33 (0.69, 2.53)	0.394

^a Both irradiated and nonirradiated groups of patients were included in the analyses and zero dose was assigned for nonirradiated patients.
^b Relative risk (RR) adjusted for sex, age at treatment, person-years, and number of cigarettes smoked; for stomach cancer the RR was additionally adjusted for gastric ulcer, partial gastrectomy, and vagotomy.
^c Average left lung dose applied for trend test computation.
^d Radiotherapy treatment was conducted in one or two 2-week courses. Zero number of treatments was applied to nonirradiated patients in the analyses.

persistence of ulcer symptoms, the study findings are unlikely to have been biased by this factor.

Lung cancer risk was significantly higher among smokers regardless of radiation exposure status (Table 8). There was no departure from a multiplicative model of interaction ($P = 0.945$) between radiotherapy and smoking as risk factors. In particular, when we compared irradiated and nonirradiated patients according to smoking category (never smoked, smoked ≤ 1 pack/day, and > 1 pack/day), we did

not observe a dramatic or consistent difference in radiation-related lung cancer RRs: 1.31 (95% CI 0.28, 6.09), 1.63 (95% CI 1.0, 2.65), and 1.18 (95% CI 0.64, 2.16), respectively (data not shown).

DISCUSSION

The results of our study strengthen the previously reported association between radiotherapy for peptic ulcer

TABLE 4
Relative Risk (RR) and Excess Relative Risk (ERR) of Selected Cancer Sites Stratified by Organ-Specific Dose for Peptic Ulcer Patients with more than 10 Years of Follow-up

Dose strata	Mean dose (Gy)	No. of patients ^a	No. of deaths	RR ^b	95% CI	ERR/Gy ^c	95% CI
Stomach							
1–10 Gy	8.9	309	11	2.79	1.04, 7.53	0.20	0, 0.73
11–13 Gy	12.2	426	11	2.07	0.85, 5.01	0.09	–0.01, 0.33
14–16 Gy	15.0	356	4	1.35	0.33, 5.53	0.02	–0.05, 0.30
≥ 17 Gy	21.7	384	11	4.55	1.63, 12.69	0.16	0.03, 0.54
Pancreas							
0.9–9 Gy	8.2	370	14	3.80	1.74, 8.30	0.34	0.09, 0.89
10–12 Gy	11.4	378	9	2.45	1.02, 5.91	0.13	0.01, 0.37
13–15 Gy	14.0	345	7	2.92	1.07, 8.0	0.14	0.01, 0.50
≥ 16 Gy	19.8	382	4	1.12	0.33, 3.79	0.01	–0.03, 0.14
Lung^d							
0.1–1.3 Gy	1.1	382	21	1.47	0.87, 2.48	0.43	–0.12, 1.35
1.4–1.6 Gy	1.5	364	30	1.54	0.98, 2.42	0.36	–0.01, 0.95
1.7–2 Gy	1.8	347	21	1.14	0.64, 1.93	0.08	–0.20, 0.52
≥ 2.1 Gy	2.6	382	34	1.84	1.15, 2.94	0.32	0.06, 0.75

^a Dose estimates not available for eight patients.
^b RR adjusted for age at treatment, sex, person-years, and number of cigarettes smoked. RR for stomach cancer additionally adjusted for gastric ulcer, partial gastrectomy, and vagotomy.
^c $(RR - 1)/\text{Mean dose}$.
^d Average left lung dose.

TABLE 5
Isotonic Regression Analyses of Dose Response, by Cancer Site, for 10-Year Survivors: Stomach, Pancreas and Lung

Stomach cancer			Pancreatic cancer			Lung cancer		
Dose group (Gy)	No. of subjects/ no. of deaths	RR ^a (95% CI)	Dose group (Gy)	No. of subjects/ no. of deaths	RR ^a (95% CI)	Dose group (Gy)	No. of subjects/ no. of deaths	RR ^a (95% CI)
1-9	150/5	4.55 (1.19, 17.34)	0.9-9.0	162/5	2.05 (0.70, 6.05)	0.1-1.1	116/4	0.84 (0.29, 2.39)
10	167/6	2.0 (0.56, 7.16)	9.1-9.4	154/4	3.79 (1.06, 13.54)	1.2	188/13	1.88 (0.97, 3.65)
11	129/4	1.27 (0.33, 4.85)	9.5-10.0	130/6	8.78 (2.87, 26.85)	1.3	86/6	1.62 (0.64, 4.10)
12	87/2	4.65 (0.75, 28.97)	11.0	104/2	2.09 (0.43, 10.25)	1.4-1.5	190/19	1.83 (1.06, 3.17)
13	210/5	2.41 (0.72, 8.10)	12.0	206/6	2.68 (0.97, 7.4)	1.6	174/11	1.22 (0.63, 2.38)
14	126/0	0	13.0	117/4	6.92 (2.0, 23.97)	1.7	115/8	1.15 (0.52, 2.54)
15	116/2	1.87 (0.20, 17.70)	14.0	120/2	1.99 (0.40, 9.81)	1.8-1.9	125/4	0.61 (0.21, 1.78)
16-17	198/3	1.67 (0.32, 8.68)	15.0	108/1	0.96 (0.11, 8.82)	2.0-2.1	198/17	1.46 (0.79, 2.72)
18-20	143/2	6.01 (0.92, 39.05)	16.0-18.0	225/1	0.36 (0.04, 3.26)	2.2-2.4	114/10	1.60 (0.75, 3.40)
21-42	157/8	5.42 (1.80, 16.34)	19.0-38.0	157/3	2.17 (0.59, 7.98)	2.5-5.1	177/16	2.15 (1.2, 3.83)

^aRR adjusted for age at treatment, sex, person-years, and number of cigarettes smoked. RR for stomach cancer additionally adjusted for gastric ulcer, partial gastrectomy, and vagotomy.

and subsequent cancer risk (8). Significant excess mortality from cancer in general and cancers of the stomach, pancreas and lung in particular were associated with radiotherapy. Relative risk estimates for cancer of stomach and lung were consistent with estimates reported previously, whereas the estimate for pancreatic cancer was higher in the current analysis (8), although the previously published relative risk estimates were calculated for entire follow-up period rather than being restricted to 10-year survivors as in the present analyses. We observed strong evidence of exposure-related excess mortality from cancer of the stomach, pancreas and

lung, with commensurate radiation dose responses in analyses including nonexposed patients. However, perhaps because the middle 80% of the doses to the stomach, pancreas and affected parts of the lung were between 10 and 20 Gy, no significant dose response was seen in analyses restricted to the exposed patients. Isotonic regression analyses produced monotonic increasing dose responses, but with few steps. The results did not correspond closely to a classical curve in which a competing cell-killing effect predominates at the highest doses (19-21).

Our estimate, ERR per Gy = 0.20 for stomach cancer,

TABLE 6
Relative Risk (RR) for Selected Cancer Sites by Age at Treatment among Peptic Ulcer Patients with more than 10 Years of Follow-up

Cause of death	Age group (years)						Trend for exposure by age group, <i>P</i> value
	<35 <i>n</i> = 680, mean age 28.8		35-54 <i>n</i> = 1792, mean age 44.6		55+ <i>n</i> = 579, mean age 61.2		
	RR ^a	95% CI	RR ^a	95% CI	RR ^a	95% CI	
All cancers combined	1.35	0.99, 1.86	1.18	0.96, 1.44	0.94	0.63, 1.41	0.075
Stomach cancer	4.33	1.47, 12.75	1.56	0.72, 3.36	3.89	0.43, 35.48	0.701
Pancreatic cancer	2.99	1.15, 7.79	1.69	0.74, 3.87	1.19	0.32, 4.39	0.125
Lung cancer	0.79	0.40, 1.56	1.67	1.02, 2.75	1.27	0.80, 2.03	0.190

Note. Reference group is nonirradiated patients.

^aRR adjusted for sex and number of smoked cigarettes; RR of stomach cancer additionally adjusted for gastric ulcer, partial gastrectomy, and vagotomy.

TABLE 7
Relative Risk (RR) for Stomach Cancer According to Type of Ulcer, Type of Surgery and Radiotherapy Status among Peptic Ulcer Patients with more than 10 Years of Follow-up

Risk factor	Radiotherapy	Stomach cancer				RR	95% CI	Interaction <i>P</i> value
		Yes	No	RR ^a	95% CI			
Ulcer type ^b								
Gastric ulcer								
No	No	24	1,668	1.0	reference			
No	Yes	39	1,660	2.17	1.27, 3.71			
Yes	No	4	164	2.56	0.82, 7.93			
Yes	Yes	8	152	6.12	2.57, 14.56	2.22 ^d	1.02, 4.82	0.437 ^f
Duodenal ulcer								
No	No	9	291	1.0	reference			
No	Yes	11	257	1.92	0.73, 5.01			
Yes	No	19	1,541	0.30	0.13, 0.69			
Yes	Yes	36	1,555	0.79	0.36, 1.73	0.41 ^d	0.21, 0.80	0.770 ^f
Surgery type ^c								
Partial gastrectomy								
No	No	22	1,558	1.0	reference			
No	Yes	36	1,667	2.00	1.13, 3.53			
Yes	No	6	274	1.59	0.62, 4.08			
Yes	Yes	11	145	6.90	3.18, 14.94	2.73 ^e	1.49, 5.0	0.107 ^g
Vagotomy								
No	No	17	1,480	1.0	reference			
No	Yes	36	1,620	2.69	1.44, 5.01			
Yes	No	11	352	2.89	1.24, 6.71			
Yes	Yes	11	192	6.01	2.64, 13.66	2.72 ^e	1.51, 4.88	0.482 ^g

^a RR adjusted for age at treatment, sex, person-years, and number of cigarettes smoked.

^b Number of patients with non-gastric type of ulcer does not correspond to the number of patients with duodenal type of ulcer, because there were 240 patients with other types of ulcer.

^c Number of patients without gastrectomy does not correspond to the number of patients with vagotomy, because there were 505 patients with other types of surgeries.

^d RR for ulcer type adjusted for radiotherapy, partial gastrectomy and vagotomy.

^e RR for surgery type adjusted for radiotherapy and gastric ulcer.

^f Interaction between ulcer type and radiotherapy.

^g Interaction between ulcer type and radiotherapy.

for the lowest dose quartile (≤ 10 Gy) compared to the non-exposed is consistent with the estimate of 0.54 based on excess stomach cancer incidence for 5-year survivors after radiotherapy for cervix cancer (24), with the estimate of 0.27 based on mortality data for 60-year follow-up after radium treatment for uterine bleeding (25), and with the linear model estimate of 0.24 from the LSS study (3). Our findings suggest that, for stomach cancer, the dose-specific ERR estimated from A-bomb survivor data may be appropriate for the U.S. population. Because baseline stomach cancer rates are an order of magnitude higher in Japan than in the U.S., the finding also suggests that the LSS-based estimate of excess absolute risk would greatly overestimate radiation-related stomach cancer risk for a U.S. population (26).

It is well documented that the gastric type of peptic ulcer is positively associated and the duodenal type is negatively associated with stomach cancer risk (15, 16, 27, 28), and our findings confirm these relationships. The duodenal and pyloric types of peptic ulcer were thought to respond well to radiotherapy, since ulcers at these anatomical sites re-

curred frequently and were resistant to other methods of treatment employed at that time (4). The majority of our cohort patients had duodenal ulcer. Our findings of a multiplicative interaction between radiation exposure and ulcer type as a risk factor for stomach cancer suggest that ulcer type is not an important confounder for estimating radiation-related relative risk.

Partial gastrectomy and vagotomy have been convincingly associated with increased risk of stomach cancer (17, 29–32). Our estimated stomach cancer RR values for partial gastrectomy, vagotomy and radiotherapy were 2.7, 2.7 and 2.6, respectively; the combinations of radiation and partial gastrectomy (RR = 6.9) and radiation and vagotomy (RR = 6.0) were statistically consistent with a multiplicative interaction model (roughly, RR = $2.6 \times 2.7 = 7.0$).

Because the study cohort was formed prior to the discovery of *H. pylori* as an etiological agent of peptic ulcer and stomach cancer (34–36), no information on *H. pylori* infection status was available.

The literature on radiation-associated pancreatic cancer is inconsistent, with no clear evidence of a radiation asso-

TABLE 8
Relative Risk (RR) of Lung Cancer According to Smoking and Radiotherapy Status among Peptic Ulcer Patients with more than 10 Years of Follow-up

Smoking	Radiotherapy	Lung cancer ^a				RR ^b	95% CI	Interaction P value ^c
		Yes	No	RR	95% CI			
No	No	5	494	1.0	reference			
No	Yes	5	437	1.57	0.42, 5.94			
Yes	No	66	926	6.62	2.38, 18.42			
Yes	Yes	100	995	9.89	3.54, 27.66	6.44	3.24, 12.81	0.945

^a 322 nonirradiated and 361 irradiated patients with unknown smoking status were excluded from the analyses.

^b RR adjusted for radiotherapy.

^c Interaction between smoking and radiotherapy.

ciation (37, 38). We found a significantly increased RR for irradiated compared to nonirradiated patients but no evidence of a dose response when analysis was restricted to the exposed patients. The two findings are not necessarily incompatible, because pancreatic doses among the exposed patients were very high and consistent with a competing cell-killing effect, as hypothesized for stomach cancer. Recent reports also suggest an increased risk of pancreatic cancer after partial gastrectomy (22, 23, 39), possibly related to decreased acid production and *N*-nitroso compound mutagens in the hypochlorhydric gastric remnant, excretion of carcinogens, such as cholecystokinin, by the liver into the bile and subsequent reflux of carcinogens into the pancreatic duct, and secretory dysfunction of pancreatic gland (31, 40). However, this hypothesis does not explain our results, because adjustment for partial gastrectomy did not alter our findings of an association between radiotherapy and pancreatic cancer.

One of the weaknesses of the previous follow-up data analysis (8) was possible misclassification of cause of death, which may have contributed to the excess of pancreatic cancer deaths. Indeed, death certificate diagnosis of pancreatic cancer must be considered cautiously, because at the advanced stage, cancer of the stomach or liver may sometimes be misdiagnosed as pancreatic cancer. For the subjects who died from pancreatic cancer, this diagnosis was indicated as an immediate cause of death on 62% of death certificates and the remaining 38% indicated another immediate cause of death (carcinomatosis, kidney failure, etc) due to pancreatic cancer as an underlying disease. Percy *et al.* (41), using data from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) Program, reported that the specificity of death certificates for pancreatic cancer was 91% for more than 2000 pancreatic cancer cases diagnosed in 1974–1975. It is possible that death certificate accuracy was substantially worse in earlier years (before 1970). However, we obtained very similar RR estimates for exposure-related pancreatic cancer deaths that occurred before and after 1970. This finding does not suggest a time-dependent association of pancreatic cancer risk with death certificate accuracy.

Radiation exposure has been shown to be a lung carcin-

ogen in numerous epidemiological studies (2). Our findings are very close to the results of the previous analysis [RR = 1.7, 95% CI 1.2–2.4 (8)]. There were clear differences between exposed and nonexposed patients, but we did not observe a dose response by dose quartile when the analysis was limited to irradiated patients only, contrary to findings for atomic bomb survivors (2, 3). Average lung doses for our patients were too small to suggest a cell-killing effect. However, lung dose was highly nonhomogeneous within the organ, with mean minimum, average and maximum estimated doses of 0.2, 1.8 and 17.4 Gy for the left lung, and a mean average estimated dose of 0.6 Gy for the right lung. Thus a cell-killing effect could still be a contributing factor in a high-dose region of the lung.

The findings of our radiotherapy and smoking interaction analysis are consistent with the findings of a Netherlands case-control study of Hodgkin's disease patients treated with radiotherapy that reported a multiplicative interaction of radiotherapy and smoking and a sixfold increase of lung cancer RR for those who smoked more than 10 pack-years (42).

Our study did not produce evidence of radiation-related cancer for a number of organ sites generally accepted as radiation-sensitive, with mean organ doses in excess of 1 Gy. These included esophagus (2.3 Gy), liver (4.8 Gy), and bone marrow (1.6 Gy). For all of these organs, it seems clear that the organ dose was highly nonuniform, and that radiation-related cell killing at high doses might have acted to minimize evidence of radiation-related risk.

ACKNOWLEDGMENTS

The authors are grateful for Dr. Martha Linet's meticulous editing of the manuscript and thoughtful and valuable comments. The authors also thank Ms. Shanell Whitney of Westat, Inc. for data management and Mr. Henry Chen of IMS for programming support.

Received: December 12, 2001; accepted: February 25, 2002

REFERENCES

1. D. E. Thompson, K. Mabuchi, E. Ron, M. Soda, M. Tokunaga, S. Ohikubo, S. Sugimoto, T. Ikeda, M. Terasaki and D. L. Preston,

- Cancer incidence in atomic bomb survivors. Part II: Solid tumors, 1958–1987. *Radiat. Res.* **137** (Suppl.), S17–S67 (1994).
2. UNSCEAR, *Sources and Effects of Ionizing Radiation*, Vol. II, *Effects*, pp. 297–450. United Nations, New York, 2000.
 3. D. A. Pierce, Y. Shimizu, D. L. Preston, M. Vaeth and K. Mabuchi, Studies of the mortality of atomic bomb survivors. Report 12, Part I. Cancer: 1950–1990. *Radiat. Res.* **146**, 1–27 (1996).
 4. W. L. Palmer, Ed., *Gastric Irradiation in Peptic Ulcer*. University of Chicago Press, Chicago 1974.
 5. M. L. Griem, External irradiation at the University of Chicago. In *Gastric Irradiation in Peptic Ulcer* (W. Palmer, Ed.), pp. 39–44. University of Chicago Press, Chicago, 1974.
 6. C. B. Clayman, W. H. Kruskal, J. W. Culpender and W. L. Palmer, The neoplastic potential of gastric irradiation. In *Gastric Irradiation in Peptic Ulcer* (W. L. Palmer, Ed.), pp. 95–138. University of Chicago Press, Chicago, 1974.
 7. M. Griem, J. Justman and L. Weiss, The neoplastic potential of gastric irradiation. IV. Risk estimates. *Am. J. Clin. Oncol.* **7**, 675–677 (1984).
 8. M. L. Griem, R. A. Kleinerman, J. D. Boice, Jr., M. Stovall, D. Shefner and J. H. Lubin, Cancer following radiotherapy for peptic ulcer. *J. Natl. Cancer Inst.* **86**, 842–849 (1994).
 9. D. R. Cox, *Analysis of Binary Data*. Methuen, London, 1970.
 10. N. E. Breslow and N. E. Day, *The Design and Analysis of Cohort Studies. Statistical Methods in Cancer Research*, Vol. 2. IARC Scientific Publication No. 82, International Agency for Research on Cancer, Lyon, 1987.
 11. SAS/STAT® Software: Changes and Enhancements through Release 6.12, pp. 873–948. SAS Institute Inc., Cary, NC, 1997.
 12. R. L. Prentice, Y. Yoshimoto and M. W. Mason, Relationship of cigarette smoking and radiation exposure to cancer mortality in Hiroshima and Nagasaki. *J. Natl. Cancer Inst.* **70**, 611–622 (1983).
 13. W. Ye, A. M. Ekstrom, L-E. Hansoon, R. Bergstrom and O. Nyren, Tobacco, alcohol and the risk of gastric cancer by sub-site and histologic type. *Int. J. Cancer* **83**, 223–229 (1999).
 14. D. Zaridze, E. Borisova, D. Maximovitch and V. Chkhikvadze, Alcohol consumption, smoking and risk of gastric cancer: Case-control study from Moscow, Russia. *Cancer Causes Control* **11**, 363–371 (2000).
 15. L. E. Hansson, O. Nyren, A. W. Hsing, R. Bergstrom, S. Josefsson, W. H. Chow, J. F. Fraumeni, Jr. and H. O. Adami, The risk of stomach cancer in patients with gastric or duodenal ulcer disease. *N. Engl. J. Med.* **335**, 242–249 (1996).
 16. L. Hansson, Risk of stomach cancer in patients with peptic ulcer disease. *World J. Surg.* **24**, 15–20 (2000).
 17. C. S. Von Holstein, Long-term prognosis after partial gastrectomy for gastroduodenal ulcer. *World J. Surg.* **24**, 307–314 (2000).
 18. R. E. Barlow, D. J. Bartholomew, J. M. Bremner and H. D. Brunk, *Statistical Interference under Order Restrictions*. Wiley, London, 1972.
 19. L. H. Gray, Radiation biology and cancer. In *Cellular Radiation Biology. Eighteenth Symposium on Fundamental Cancer Research*, pp. 7–25. Williams & Wilkins, Baltimore, 1965.
 20. M. M. Elkind, A. Han and C. K. Hill, Error-free and error-prone repair in radiation-induced neoplastic cell transformation. In *Radiation Carcinogenesis: Epidemiology and Biological Significance* (J. D. Boice, Jr. and J. F. Fraumeni, Jr., Eds.), pp. 304–318. Raven Press, New York, 1984.
 21. P. G. Smith, Radiation. In *Cancer Risks and Prevention* (M. P. Vessey and M. Gray, Eds.), pp. 119–148. Oxford University Press, Oxford, 1985.
 22. P. Watanapa, B. Flaks, H. Oztas, P. H. Deprez, J. Calam and R. C. Williamson, Enhancing effect of partial gastrectomy on pancreatic carcinogenesis. *Br. J. Cancer* **65**, 383–387 (1992).
 23. B. P. Van Rees, M. Tascilar, R. H. Hruban, F. M. Giardiello, A. C. Tersmette and G. J. Offerhaus, Remote partial gastrectomy as a risk factor for pancreatic cancer: Potential for preventive strategies. *Ann. Oncol.* **10** (Suppl.), S204–S207 (1999).
 24. J. D. Boice, Jr., G. Engholm, R. A. Kleinerman, M. Blettner, M. Stovall, H. Lisco, W. C. Moloney, D. F. Austin, A. Bosh and B. MacMahon, Radiation dose and second cancer risk in patients treated for cancer of the cervix. *Radiat. Res.* **116**, 3–55 (1988).
 25. P. D. Inskip, R. R. Monson, J. K. Wagoner and J. D. Boice, Jr., Cancer mortality following radium treatment for uterine bleeding. *Radiat. Res.* **123**, 331–344 (1990).
 26. C. E. Land and W. K. Sinclair, The relative contribution of different cancer sites to the overall detriment associated with low-dose radiation exposure. *Ann. ICRP* **22**, 31–57 (1991).
 27. P. Correa and B. A. Schmidt, The relationship between gastric cancer frequency and the ratio of gastric to duodenal ulcer. *Aliment. Pharmacol. Ther.* **9**, 13–19 (1995).
 28. C. La Vecchia, C. Braga, E. Negri and S. Franceschi, Risk of stomach cancer in patients with gastric or duodenal ulcer. *Eur. J. Cancer Prev.* **6**, 20–23 (1997).
 29. S. Meisner, C. Slim and J. Kjaergaard, The outcome of vagotomy for peptic ulcer disease. *Acta Chir. Scand.* **547** (Suppl), 59–64 (1988).
 30. H. Moller and C. Toftgaard, Cancer occurrence in a cohort of patients surgically treated for peptic ulcer. *Gut* **32**, 740–744 (1991).
 31. A. C. Tersmette, F. M. Giardiello, G. N. Tytgat and G. J. Offerhaus, Carcinogenesis after remote peptic ulcer surgery: The long-term prognosis of partial gastrectomy. *Scan. J. Gastroenterol.* **212** (Suppl), 96–99 (1995).
 32. V. K. Zuev, K. N. Movchan and S. V. Komarov, Malignant stomach tumors in patients who have had a vagotomy for duodenal ulcers. *Vestn. Khir. Im. Grek.* **155**, 97–100 (1996).
 33. P. C. Watt, C. C. Patterson and T. L. Kennedy, Late mortality after vagotomy and drainage for duodenal ulcer. *Br. Med. J.* **288**, 1335–1338 (1984).
 34. A. Covacci, J. L. Telford, G. D. Giudice, J. Parsonnet and R. Rappuoli, *Helicobacter pylori* virulence and genetic geography. *Science* **284**, 1328–1333 (1999).
 35. M. J. Blaser, Linking *Helicobacter pylori* to gastric cancer. *Nat. Med.* **6**, 376–377 (2000).
 36. D. T. Smoot, M. F. Go and B. Cryer, Peptic ulcer disease. *Prim. Care* **28**, 487–503 (2001).
 37. C. E. Land, Carcinogenic effect of radiation on the human digestive tract and other organs. In *Radiation Carcinogenesis* (A. C. Upton, R. E. Albert, F. Burns and R. E. Shore, Eds.), pp. 347–378. Elsevier/North Holland, New York, 1986.
 38. J. D. Boice, Jr., C. E. Land and D. Preston, Ionizing radiation. In *Cancer Epidemiology and Prevention* (D. Schottenfeld and J. F. Fraumeni, Jr., Eds.), pp. 319–354. Oxford University Press, New York and Oxford, 1996.
 39. A. C. Tersmette, G. J. Offerhaus, F. M. Giardiello, K. W. Tersmette, J. P. Vandenbroucke and G. N. Tytgat, 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).
 40. M. Hedberg, L. Janzon, J. F. Rehfeld and A. Borgstrom, Long-term effects on the regulation of pancreatic secretion after gastric surgery. *Dig. Surg.* **16**, 111–116 (1999).
 41. C. L. Percy, B. A. Miller and L. A. Ries, Effect of changes in cancer classification and the accuracy of cancer death certificates on trends in cancer mortality. In *Trends in Cancer Mortality in Industrial Countries* (D. Lee and D. Hoel, Eds.), pp. 87–99. New York Academy of Sciences, New York, 1990.
 42. F. E. van Leeuwen, W. J. Klokman, M. Stovall, A. Hagenbeck, A. W. van den Belt-Dusebout, R. Noyon, J. D. Boice Jr., J. M. Burgers and R. Somers, Roles of radiotherapy and smoking in lung cancer following Hodgkin's disease. *J. Natl. Cancer Inst.* **18**, 1530–1537 (1995).