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Incidence of Benign Gastrointestinal Tumors among Atomic Bomb Survivors

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Using the Hiroshima and Nagasaki tumor and tissue registries, benign tumors of the stomach, colon, and rectum were identified among members of the Life Span Study cohort of atomic bomb survivors. During the period 1958–1989, a total of 470 cases with histologically confirmed benign gastrointestinal tumors (163 stomach, 215 colon, and 92 rectum) were identified among approximately 80,000 Life Span Study members with known radiation doses, who were alive in 1958. Restricting the analysis to adenomatous tumors not detected at autopsy, a dose-response relation was observed for stomach tumors (excess relative risk at 1 sievert (ERR_{1Sv}) = 0.53; 95% confidence interval (CI) –0.01 to 1.43). However, there was little evidence of a dose response for colon tumors (ERR_{1Sv} = 0.14; 95% CI –0.20 to 0.76), and no evidence was present for rectal tumors (ERR_{1Sv} = –0.25; 95% CI undetermined to 0.80). The excess relative risk (ERR) for benign tumors of the stomach is consistent with the excess found for stomach cancer. For cancer of the rectum, the dose response was not significant, but the point estimate of the excess relative risk was positive. The excess relative risk for benign colon tumors is less than that reported for colon cancer (ERR_{1Sv} = 0.72). The authors observed a dramatic increase in colon tumors detected after 1985, suggesting that the relatively recent introduction of colonoscopy may be influencing these results. *Am J Epidemiol* 1995;142:68–75.

neoplasms; neoplasms, radiation-induced; prospective studies; radiation

A large body of evidence demonstrates that an excess of cancers of the gastrointestinal tract occurs following radiation exposure (l–4). Both incidence and mortality data clearly show an increased risk of cancers of the stomach and colon associated with exposure from the atomic bombings in Hiroshima and Nagasaki, Japan, but little association between radiation exposure and cancer of the rectum (4, 5). Epidemiologic and pathologic data have demonstrated a close link between adenomatous colorectal polyps and colorectal carcinomas. Results from recent research have suggested that most colorectal tumors progress through an adenoma-to-carcinoma sequence (6, 7). The role of gastric polyps in the etiology of stomach carcinoma is less clear. There is growing evidence that gastric dysplasia, not polyps, increases the risk of stomach cancer (8), but gastric polyps and cancers often occur simultaneously (9). Despite the known association between some types of gastrointestinal adenomas and cancer and the fact that many benign tumors are induced by radiation, the relation between the incidence of benign gastrointestinal tumors and radiation is not well documented. We examined the effect of ionizing radiation on the risk of developing benign tumors of the stomach, colon, and rectum among members of the Life Span Study of atomic bomb survivors.

MATERIALS AND METHODS

Study population

The Atomic Bomb Casualty Commission and later the Radiation Effects Research Foundation have been following a fixed cohort of atomic bomb survivors. The Life Span Study cohort includes about 120,000 people: approximately 93,000 survivors and 27,000 nonexposed individuals who were not living in Hiroshima or Nagasaki at the time of the bombings in 1945 (10, 11). This cohort has been followed extensively for several decades in terms of mortality (5) and, more recently, cancer incidence (4). Almost 70 percent of the cohort were exposed to the bomb in Hiroshima, and nearly 60 percent are female. At the time of the bombings, the mean age of the cohort was slightly less than 30 years.

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Abbreviations: CI, confidence interval; ERR_{1Sv}, excess relative risk at 1 sievert.

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As in most Life Span Study reports published during the last 15 years, only persons in Hiroshima or Nagasaki at the time of the bombings and those with known Dosimetry System 1986 radiation dose estimates were included in this analysis (4, 5, 11). Follow-up for this study began in 1958, the year the Hiroshima and Nagasaki tumor registries and the Atomic Bomb Casualty Commission/Radiation Effects Research Foundation Adult Health Study clinical examination program were established. The study population was limited to persons who were alive on January 1, 1958, leaving 80,311 people in the present study population.

Tumor ascertainment

Information on benign tumors among Life Span Study cohort members is available from several sources: the Hiroshima and Nagasaki tumor registries, the Hiroshima and Nagasaki tissue registries, the Adult Health Study, and the Atomic Bomb Casualty Commission/Radiation Effects Research Foundation autopsy program. Each of these resources provides partial coverage of benign tumors for different time periods. The majority of cases are identified by actively searching hospital records for mention of cancer or cancer-related diagnoses, but several other sources are used to supplement case ascertainment (12). Between 1958 and 1980, information on benign tumors of the brain, salivary gland, digestive system, bladder, kidney, and bone was collected by the tumor registries. However, at the present time, data are obtained routinely only for benign tumors of the brain and central nervous system, pineal glands, and pituitary. The tissue registries were established in 1973 to collect and store pathologic specimens and reports. All diagnoses of benign tumors are reportable and, for each biopsied or surgical case identified, pathology reports and tissue specimens are collected. The Adult Health Study cohort is a 20 percent subsample of the Life Span Study. It was constructed to oversample individuals in high-dose categories. Since 1958, Adult Health Study subjects have been invited for biennial comprehensive health examinations at the Atomic Bomb Casualty Commission/Radiation Effects Research Foundation, and the level of participation has been between 70 and 85 percent among persons living in the Hiroshima or Nagasaki areas (13). The Adult Health Study database was also used to ascertain cases of benign gastrointestinal tumors. For this report, we used each of the data sources to identify benign tumors of the stomach, colon, and rectum *(International Classification of Diseases for Oncology* (14), topography codes 151, 153, and 154 and behavior code 0).

Radiation dose estimation

Since 1987, the Dosimetry System 1986 has been used for dose estimation at the Radiation Effects Research Foundation (15). This system takes into account the detailed shielding histories of survivors and provides individual estimates of the absorbed dose to various organs. To be consistent with the most recent analyses of cancer incidence in the Life Span Study (14), we used Dosimetry System 1986 organ dose equivalents in sieverts with an assumed constant relative biologic effectiveness of neutrons of 10. Stomach dose estimates were used for the stomach analyses, and intestinal dose estimates were used for the analyses of colon and rectal tumors. We excluded subjects with organ dose estimates greater than 4 sieverts. Dose estimates based on Dosimetry System 1986 are available for 92 percent of the Life Span Study cohort members.

Statistical methods

Poisson regression methods for longitudinal analysis of grouped cohort data using a stratified background model were used. Data on case counts and person-years were tabulated by strata formed by city (Hiroshima, Nagasaki), sex, Adult Health Study cohort membership (yes, no), attained age (0–19, 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, >=80 years), calendar year period (1958–1964, 1965–1969, 1970–1974, 1975–1979, 1980–1984, 1985–1989), and organ dose in sieverts (0, 0.001–0.09, 0.10–0.49, 0.50–0.99, 1.00–1.49, 1.50–1.99, 2.00–2.99, 3.00–4.00).

The analyses were based on modeling the incidence rate in a stratum ij by the product of the background rate using an excess relative risk model with a linear dose-response relation multiplied by 1 plus the excess risk per sievert averaged over all strata. That is,

$$RR_{ij} = 1 + \beta\, d_{ij} \exp\left[\, \alpha_k(Z_k) \,\right]$$

where RR_{ij} is the relative risk due to radiation exposure at a level associated with stratum ij, d_{ij} is the organ dose equivalent in sieverts (computed as the γ-ray dose plus 10 times the neutron dose), β is the excess risk per sievert averaged over all strata, and exp $[\, \alpha_k(Z_k) \,]$ describes dose-effect modification by covariate Z_k. Background rates (the incidence rate in the absence of radiation exposure) were estimated in each stratum defined by city, sex, Adult Health Study cohort membership, attained age, and calendar-year categories. The effect modifiers included the previously mentioned covariates, as well as age at the time of the bombings. Negative coefficients for effect modifiers were derived for each stratum in which the estimate of exp α_k was 0. Likelihood ratio tests were used to

evaluate the significance of the dose-response relation and modifying effects of the covariates, using the computer program AMFIT (16). The likelihood ratio method was used to compute the 95 percent confidence intervals.

Follow-up began on January 1, 1958, and continued until the date of diagnosis of a benign tumor of the stomach, colon, or rectum or until the date of diagnosis of a cancer of the same or other site, date of death, or the end of 1989, whichever occurred first.

RESULTS

Altogether 689 benign stomach tumors, 374 colon tumors, and 123 tumors of the rectum were identified. For this analysis, we excluded the following cases: 1) tumors detected only at autopsy; 2) patients who had a malignant gastrointestinal tumor; and 3) cases not histologically confirmed. Cases detected at autopsy were excluded because autopsy rates are correlated with dose, thus biasing the case ascertainment (17), and because the number of tumors detected at autopsy is highly correlated with the intensity of examination, and these tumors may not be representative of living patients (18). Cases with clinical diagnoses only were excluded, because an undetermined proportion of these cases actually has hypertrophic polyps, which are not truly neoplastic. Depending on the tumor site, between 16 and 37 percent of the cases were diagnosed only at autopsy (table 1). Almost half (45.9 percent) of the stomach tumors were detected by endoscopy or radiographic examination, mostly through the Adult Health Study examination program, and were not histologically verified, whereas less than 10 percent of the colorectal tumors had only a clinical diagnosis. The largest percentage of histologically confirmed tumors was of the rectum (76.4 percent). After the cases detected only at autopsy and those without histologic confirmation were excluded, 210 stomach, 226 colon, and 94 rectal tumors were available for analysis. Following a review of registry records, tumor morphology could be classified for 75, 94, and 64 percent of the stomach, colon, and rectal tumors, respectively. We excluded 47 stomach cases (24 hyperplastic polyps, 13 leiomyomas, and 10 other nonadenomatous polyps), one colon lipoma, 10 persons with familial polyposis syndrome, one hyperplastic rectal polyp, and one rectal papilloma. This left 163 stomach, 215 colon, and 92 rectal tumor cases for the final analysis.

As seen in table 2, the percentage of males and females differed for the three tumor sites. More stomach tumors occurred among females, but more colorectal tumors occurred among males. Persons developing stomach tumors tended to be slightly older at diagnosis and at the age at the time of the bombings and had higher radiation doses than did patients diagnosed with colorectal tumors. The distribution by type of benign tumor also is shown in table 2.

The crude incidence rates (table 3) suggest a dose response for tumors of the stomach and colon. For tumors of the rectum, no dose response was discernible. Analyzing the data using the linear excess relative risk model described in Materials and Methods, we found that the results confirmed the patterns seen in the crude rate table for tumors of the stomach and rectum. However, there was little evidence of a dose response for colon tumors. This difference mainly was due to the finding that Adult Health Study membership influenced colorectal tumor detection and, therefore, the crude rates do not characterize adequately the

TABLE 1. Distribution of benign tumors by site, method of detection, and morphology: atomic bomb survivors, 1958-1989

Identified cases	Tumor site		
	Stomach	Colon	Rectum
Total cases	689	374	123
Exclusions			
Detected at autopsy	163 (23.7)*	137 (36.6)	20 (16.3)
Clinical diagnosis only	316 (45.9)	11 (2.9)	9 (7.3)
Available for study (histologically confirmed)	210 (30.5)	226 (60.4)	94 (76.4)
Exclusions			
Nonadenomatous lesions	47	1	2
Familial polyposis syndrome	0	10	0
Final study cases	163	215	92

* Numbers in parentheses, percentage.

TABLE 2. Selected characteristics of atomic bomb survivors with benign gastrointestinal tumors diagnosed between 1958 and 1989

Tumor site	Sex		Mean radiation dose (Sv)		Mean age at the time of the bombing (years)	Mean age at diagnosis (years)	Morphology (no.)				
	Male (no.)	Female (no.)	Total cases	Exposed cases (>0 Sv)			Adenoma NOS* or adenomatous polyps	Tubular adenomas	Multiple adenomatous polyps	Other adenomas	Unknown morphology
Stomach (n = 163)	66 (40.5)†	97 (59.5)	0.19	0.31	30.7	65.2	80 (49.1)	40 (24.5)	0 (0.0)	0 (0.0)	43 (26.4)
Colon (n = 215)	132(61.4)	83 (38.6)	0.14	0.22	21.4	61.4	89 (41.4)	92 (42.8)	22 (10.2)	8 (3.7)	4 (1.9)
Rectum (n = 92)	48 (52.2)	44 (47.8)	0.11	0.17	26.4	60.2	40 (43.5)	15 (16.3)	0 (0.0)	4 (4.3)	33 (35.9)

* NOS, not otherwise specified.
† Numbers in parentheses, percentage.

underlying dose-response relation. The estimated excess relative risks at 1 sievert (ERR_{1Sv}) were 0.53, 0.14, and –0.25 for histologically confirmed benign tumors of the stomach, colon, and rectum, respectively (table 4). The relatively small number of tumors led to fairly wide confidence intervals around the point estimates and, although the point estimate was large for stomach tumors, the lower confidence limit was about zero. For the stomach, almost 75 percent of the cases were excluded from the analysis because the tumors were detected at autopsy, not histologically confirmed, or found to be nonadenomatous lesions during record review. We, therefore, also analyzed the data with all cases (n = 689) included and with all histologically confirmed cases (n = 210) included. The ERR_{1Sv} was virtually the same for all cases (ERR_{1Sv} = 0.48; 95 percent confidence interval (CI) 0.21 to 0.83) and for the histologically confirmed cases (ERR_{1Sv} = 0.49; 95 percent CI 0.02 to 1.25) as when the restricted series was studied, except that the width of the confidence interval increased as the number of cases decreased. For the colon, about 40 percent of the tumors were excluded. Again, the excess relative risk was similar when all cases (n = 374) were analyzed (ERR_{1Sv} = 0.08; 95 percent CI –0.17 to 0.50).

Analyses of effect modification did not show strong effects (table 4). No evidence of heterogeneity was noted in the excess relative risk by city, sex, Adult Health Study membership, age at the time of the bombings, attained age, or time since exposure for any of the three tumor sites. Among the people who had developed stomach tumors, the risk tended to decrease somewhat with increasing age at the time of the bombings; however, the trend was not strong, and the results differed depending on how the age categories were defined, because the risks differed within the 20- to 39-year category for age at the time of the bombings. Risks were low for the 20- to 29-year category for age at the time of the bombings but high for the 30- to 39-year category for age at the time of the bombings (data not shown).

The number of colon tumors detected before 1980 was small (13 tumors between 1958 and 1969 and 13 tumors between 1970 and 1979), began to increase after 1980 (30 tumors between 1980 and 1984), and increased dramatically after 1985 (159 tumors between 1985 and 1989). Furthermore, the proportion of tumors registered with nonspecific diagnoses (such as polyp or adenomatous polyp) was 34 percent before 1985 compared with 42 percent after 1985. These changes are correlated with the more frequent use of colonoscopy. Before 1985, the ERR_{1Sv} for colon tumors was 0.64 (95 percent CI –0.11 to 2.46) based on

TABLE 3. Crude rates* by radiation dose and site of benign tumor: atomic bomb survivors, 1958–1989

Dosimetry System 1986 estimated radiation dose (Sv)	Stomach		Colon		Rectum		No. of persons	Person-years at risk
	Crude rate	No. of tumor cases	Crude rate	No. of tumor cases	Crude rate	No. of tumor cases		
0	0.77	62	0.90	73	0.40	32	31,441	806,582
0.001–0.49	0.76	84	1.14	127	0.45	50	43,411	1,111,350
0.50–0.99	0.93	7	1.20	9	1.20	9	2,981	75,126
>=1.00	1.90	10	1.33	7	0.00	0	2,119	52,627

* Rates are cases per 10,000 person-years.

59 cases, whereas after 1985 the risk was –0.20 (95 percent CI undetermined to 0.47) based on 167 cases.

DISCUSSION

Persons with benign tumors or conditions of a variety of organs (e.g., esophagus, stomach, colon, cervix, breast, and thyroid) reportedly have a higher risk for developing malignant tumors of the same organ. Although the biologic basis for these associations has not been established, some benign conditions appear to be precursor lesions that progress into malignancies. By studying benign tumors, we may be able to improve our understanding of the etiology of specific cancers and possibly identify factors that could prevent the transformation from benign to malignant neoplasms.

Adenomatous polyps are rare neoplasms. They show malignant change in between 20 and 75 percent of the polyps examined and often occur in conjunction with stomach cancers. Gastric polyps have a high incidence of cellular dysplasia and atypia, but a clear adenoma-to-carcinoma sequence has not been demonstrated (9, 19, 20). On the other hand, progression from superficial gastritis, chronic atrophic gastritis, intestinal metaplasia, and dysplasia to carcinoma seems likely (21). Stomach cancer is the most common malignancy in Japan (22) and, although its incidence is decreasing, it is not doing so at the same rate as in the West (23, 24). Over 2,500 incident cases have been identified among the Life Span Study cohort members (4). A strong association between stomach cancer and radiation exposure was demonstrated (ERR_{1Sv} = 0.32; 95 percent CI 0.16 to 0.50), and the risk was higher among persons exposed to the bombings before the age of 30 years. In our study, we found the radiation risk for benign stomach tumors to be consistent (ERR_{1Sv} = 0.53; 95 percent CI –0.01 to 1.43) with that seen for malignant tumors. Furthermore, our data suggest that persons aged less than 40 years at the time of the bombings had higher risks than did those aged 40 or more years.

Given the known role of colorectal adenomas as precursor lesions for colorectal carcinoma (6, 7, 25), common risk factors would be expected. Indeed, many risk factors, including a positive association with fat intake, obesity, and family history of colorectal cancer and a negative association with fiber, coffee intake, and physical activity (26–28), have been reported for both benign and malignant colon tumors. Therefore, comparisons between the radiation risk estimates for benign and malignant gastrointestinal tumors are relevant in terms of radiation tumorigenesis. Radiation has been shown to increase the risk of colon cancer in some studies, whereas there has been little evidence for an association with cancer of the rectum, except possibly at very high doses (29). Based on 351 incident cases of rectal cancer in the latest Life Span Study follow-up (4), the estimated ERR_{1Sv} for cancer of the rectum was 0.21 (95 percent CI –0.17 to 0.75). The confidence interval around the negative risk estimate (ERR_{1Sv} = –0.25; 95 percent CI undetermined to 0.75) for benign rectal tumors does not differ statistically from that seen for malignant tumors. The ERR_{1Sv} (0.14; 95 percent CI –0.20 to 0.76) for benign colon tumors was considerably smaller than the high risk (ERR_{1Sv} = 0.72; 95 percent CI 0.29 to 1.28) seen for colon cancers among atomic bomb survivors (4). This finding was somewhat unexpected but may be related to the introduction of colonoscopy, which allows the identification of small, clinically unimportant tumors. Indeed, after 1985, the number of benign tumors ascertained increased greatly, as well as the proportion of tumors registered with nonspecific diagnoses (such as polyp or adenomatous polyp). An increase in the background rate of tumors makes it more difficult to detect a radiation effect. The difference in the point estimate of the excess relative risk before (ERR_{1Sv} = 0.64) and after (ERR_{1Sv} = –0.20) 1985 (p = 0.14) is consistent with a confounding effect of a new diagnostic test.

In the only other Life Span Study of benign tumors of the digestive tract, Yamamoto et al. (18) evaluated tumors detected at autopsy between 1961 and 1970.

TABLE 4. Excess relative risk estimates at 1 sievert (ERR_{1Sv}) for benign gastrointestinal tumors: atomic bomb survivors, 1958–1989

Effect modifier	Stomach			Colon			Rectum		
	No. of cases	ERR_{1Sv}	*p* value	No. of cases	ERR_{1Sv}	*p* value	No. of cases	ERR_{1Sv}	*p* value
None	163	0.53 (–0.01 to 1.43)*	0.05	215	0.14 (–0.20 to 0.76)	0.52	92	–0.25 (ND† to 0.80)	0.47
City									
Hiroshima	123	0.77	0.30‡	185	0.22	0.52‡	73	–0.25	0.75‡
Nagasaki	40	0.09		30	–0.25		21	–0.25	
Sex									
Male	66	0.10	0.20	132	0.14	0.79	48	–0.25	0.83
Female	97	0.98		83	0.19		44	0.18	
AHS†									
Yes	41	0.45	0.76	47	0.30	0.39	17	–0.25	0.56
No	122	0.68		168	–0.25		75	0.24	
Age ATB† (years)									
0–9	8	5.34	0.49	43	–0.28	0.30	10	0.10	0.95
10–19	24	0.35		61	0.73		25	–0.16	
20–39	89	0.81		91	0.13		36	–0.17	
>=40	42	0.13		20	–0.25		21	–0.25	
Attained age (years)									
0–49	22	0.54	0.18	41	0.36	0.82	24	1.0	0.78
50–59	44	–0.25		64	0.23		19	–0.25	
60–69	50	1.11		54	–0.25		28	–0.10	
>=70	61	0.73		57	0.02		23	–0.25	
Calendar year§									
1958–1969	29	–0.25	0.06	13	0.66	0.69	24	0.33	0.92
1970–1979	48	0.79		13	0.47		22	–0.22	
1980–1984	28	0.63		30	0.63		9	–0.25	
1985–1989	58	0.60		159	–0.15		37	–0.25	

* Numbers in parentheses, 95% confidence interval.
† ND, not determined; AHS, Adult Health Study; ATB, age at the time of the bombings.
‡ Significance level for a test of homogeneity.
§ Since this is a one-tme exposure, calendar-year categories correspond to the following time since exposure years: 13–24, 25–34, 35–39, and 40–44 years, respectively.

They found no association with radiation exposure for any of the individual gastrointestinal sites or total digestive tumors. However, as the authors point out, the prevalence rate of tumors detected at autopsy is highly correlated with how carefully the tissue is examined. In this autopsy series, 90 percent of the polyps were 4 mm or less. Thus, it is possible that these small polyps are etiologically different from larger polyps or those diagnosed during life.

Only two other studies of benign tumors and radiation exposure in the Life Span Study cohort have been undertaken. Using autopsy data, Yoshimoto et al. (30) found a significant association between thyroid adenoma and radiation dose, whereas among Adult Health Study participants an excess of uterine myoma was related to radiation exposure (13). In addition, there is evidence of a dose response associated with the prevalence of proliferative breast disease at autopsy (31).

While this study provides information about the relation between benign gastrointestinal tumors and radiation exposure, certain limitations regarding case ascertainment should be mentioned. Although benign tumors are numerous, they are generally not fatal and sometimes do not even require hospitalization. Therefore, it is considerably more difficult to identify benign tumors than malignant ones. Furthermore, case ascertainment may not be complete because the tumor registry has changed its policy on registering benign tumors over the years. To try to compensate for the problems in ascertainment, we identified tumors using multiple data sources that were suitable for different time periods. Although we restricted the analysis to histologically confirmed, nonautopsy cases in an attempt to reduce any ascertainment or radiation-dose bias, some unknown bias may still remain. However, there is no inherent reason to suspect that cases coming from the tumor or tissue registries are related to radiation dose.

The suggestion of a difference in colon adenoma risk before and after 1985 is intriguing. Additional years of follow-up with better information on the size and means of tumor detection will be needed to better understand whether the use of colonoscopy has confounded the relation between radiation and benign colon tumors.

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