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Colorectal Cancer Incidence among Atomic Bomb Survivors, 1950–80

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Abbreviations used: LSS, Life Span Study; NIC, Not In City; ICRP, International Commission on Radiological Protection; age ATB, age at the time of the bombing; AHS, Adult Health Study; PY-Sv, Person-Year Sv; DS86, Dosimetry System 1986, T65D, Tentative 1965 Dosimetry System

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Colorectal cancer incidence in the LSS sample during 1950–80 was investigated. A total of 730 incidence cases of colorectal cancer were confirmed from a variety of sources. Sixty-two percent of the cancers were microscopically verified and 12% were ascertained through death certificate only.

The risk of colon cancer increased significantly with intestinal dose, but no definite increase of risk was observed for rectal cancer. Relative risk at 1 Sv and excess risk per 10^4 PY-Sv for colon cancer are 1.80 (90% confidence internal 1.37–2.36) and 0.36 (90% confidence interval 0.06–0.77) respectively. City and sex did not significantly modify the dose-response of colon cancer, but the risk decreased with age at the time of bombings (ATB). The relative risk of colon cancer does not vary substantially over time following exposure. A non-linear dose response did not significantly improve the fit. Further, the anatomic location of the tumors indicate that the cecum and ascending, transverse and descending, and sigmoid colon seem equally sensitive to radiation. No difference in the distribution of tumor histological types could be observed by radiation dose.

INTRODUCTION

Cancers of the colon and rectum are often grouped together under the rubric of colorectal cancer in statistical abstracts of site-specific cancer risk, and they share certain epidemiological similarities[1]. Both organs are considered to be at risk for cancer induction by ionizing radiation, but the supporting epidemiological evidence comes from different types of exposed populations. In general, excess colon cancer is seen in populations with organ doses of a few Gy or less, while excess rectal cancer is found in therapeutically-irradiated populations with highly localized, partial-body exposures giving rectal doses of tens of Gy[2].

Probably the strongest evidence for radiation induction of colon cancer comes from the Life Span Study (LSS) mortality follow-up, based on death certificantes[3]. For rectal cancer, on the other hand, there has never been any indication of an increasing trend in mortality with increasing dose in the LSS sample. Analyses of the tumor registry data for 1959–1970 found significantly increasing trends for colon cancer in both the (then incomplete) Hiroshima registry and the Nagasaki registry, but no trends in either registry for rectal cancer[4]. A later report of Nagasaki registry data through 1978 found a statistically significant increasing trend for colon cancer[5].

Currently accepted estimates of radiation-related cancer risks for the colon and rectum depend strongly on the LSS sample data, and the death certificate data in particular. But comparisons of autopsy findings with death certificate diagnoses suggest detection and confirmation rates of only 52% and 65%, respectively, for the colon and about 70% each for rectal cancer[6]. Moreover, the published tumor registry data are somewhat ambiguous, raising the faint possibility that a radiation-related excess risk of rectal cancer might be emerging in this population. Accordingly, it seemed appropriate to conduct a new investigation at the level of incidence, utilizing diagnostic information from a variety of sources.

A second purpose of this investigation, not covered in the prsent report, was a study of prognosis with respect to cancer stage, site, and surgical procedure. Those findings have been reported elsewhere[7].

MATERIALS AND METHODS

Case ascertainment Subjects for this study were the 82,064 exposed and 26,675 non-exposed members of the (extended) LSS sample as of 1982[8]. Incident cases were included with diagnosis at any time between the reference data for inclusion of the subject in the LSS sample and 31 December, 1980; for exposed subjects the reference date is 1 October, 1950, whereas for the non-exposed subjects, who were selected on the basis of surveys conducted during 1951, 1952, and 1953, various dates are used.

Sources for initial case ascertainment included information from death certificates, which are routinely collected by RERF from the Japanese family registry (koseki) system for all sample members, the Hiroshima City Tumor Registry, the Nagasaki Prefecture Tumor Registry, the Hiroshima Prefecture Tissue Registry, the Nagasaki City Tissue Registry, and the RERF autopsy and surgical files. For each case thus identified, all availble information was collected for diagnostic review. Where possible, visits were made to the medical institution or institutions concerned and the clinical history of the case was collected from medical records or from the attending physician. For cases outside the two cites questionnaires were sent to the physicians who made the diagnoses. Where available, histological specimens from autopsy, surgery, or biopsy were reviewed microscopically.

All reviews of diagnostic materials were carried out without knowledge of radiation dose. Tissues specimens were reexamined by pathologists (T.Y, I.S) and the site and hitological classfication determined according to the General Rules for Clinical and Pathological Studies on Cancer of Colon, Rectum and Anus[9]. For the site, the colon begins with the cecum and is made up of the ascending, transverse, descending, and sigmoid colon, the sigmoid colon extending to the level of the promontory. The rectum, extending anally from the sigmoid colon, is further divided into three parts, but these have been treated collectively here as rectum. Cancer developing in the anus has been excluded from the study. The rectosigmoid junction, extending from the promontory to the level of the lower edge of the second sacral vertebra, has a mesentery and is anatomically included in sigmoid colon, but is classified in the General Rules as rectum because its vascular system is the same as that of the upper rectum. In the present study, all cancers developing in the rectosigmoid have been classified as rectal cancer. Multiple cancer cases which had developed two or more cancers in the large intestine were classified in heterochronous cases by the site of the primary cancer, and in synchronous cases by the site of the more advanced tumor. Cases with unsatisfactory information as to site of tumor, such as those with only death certificate information without adequate specification of site, or cases that already presented extensive infiltration of the tumor at the time of diagnosis, were classified as colorectal cancers of unknown site.

Statistical analysis The possible variation in cancer risk with increasing radiation dose from the atomic bombs is of course the main focus of cancer incidence studies based on the LSS sample. In the time since the current study was begun, however, the T65D dosimetric system in use for the past 20 years or so has been replaced by a new system, designated DS86[10], which is now the accepted basis of inference for dose-response analyses of LSS sample data. All analyses

were carried out using DS86 organ dose estimates. Dose-response analyses were in terms of tissue dose equivalent in Sv, calculated assuming a constant neutron RBE of 10, relative to gamma rays; this follows the precedent established in the Technical Report version of the most recent LSS mortality report (see Table 5 of that report)[3] and in ICRP documents[11,12] which used coefficients from that source. It is also consistent with recent ICRP recommendations for an RBE of 20 at low doses of 100 KeV to 2 MeV neutrons[11], given that (1) a decline in RBE with increasing neutron dose is commonly observed in experimental studies[13], (2) annual neutron doses consistent with radiation protection guidelines are on the order of 2.5 mGy or less, and (3) and LSS sample risk estimates are determined mainly by excess risks observed above 0.5 Gy total kerma. There, the average neutron kerma is over 40 mGy[3], and a lower RBE is appropriate.

Investigators have differed in their treatment of the non-exposed (not-in-city, or NIC) portion of the LSS sample. For example, the NIC group has not been included in the periodic LSS mortality reports because it was felt that demographic differences between the NIC and exposed portions of the sample might be a potential source of bias[14]. Other authors have felt that the NIC group provided a valuable strengthening of the sample in the lower dose range, especially in Nagasaki[15]. The approach of the present investigation is to present data separately for the NIC and zero-dose exposed sample components, and to exclude the NIC data in dose-response analyses.

Other information available for all LSS sample members includes age at the time of the bombings (age ATB), sex, and of course calendar time of observations for risk. Variation of both baseline and excess cancer risk with respect to these variables is important both for risk estimation and for its relevance to cancer etiology.

The most important analytic problem is the possibility of biased ascertainment. Underascertainment of colorectal cancer incidence is almost a certainty, given that death certificate detection rates are 70% or less[6] and given that cases occurring among sample members living outside Hiroshima and Nagasaki prefectures were unlikely to be detected by the methods of this study unless diagnosis was followed by death and the cancer was mentioned on the death certificate. The tumor registries did not begin operation until the late 1950s and the tissue registries did not begin until 1973; moreover, local coverage by the tumor registries, while high probably was incomplete at the time of the case ascertainment for the present study. But dose-response analyses in terms of *relative risk,* if they are specific to age ATB, sex, and city, are only minimally affected by such underascertainment as long as it does not vary by radiation dose[15], whereas estimates of excess additive risk are sensitive even to nondifferential underascertainment.

It is known that migration from Hiroshima and Nagasaki since 1950, while dependent upon age ATB, has not varied consistently by dose[15]. Three other methods are available to test for confounding of ascertainment level with dose. First, because death certificate notification is complete, the proportion of incident cases mentioned on death certificates can be compared by dose within age-ATB, sex, and city groups. Second, the case series can be examined for variations in level of diagnostic uncertainty by dose. Finally, the clinical subsample[16], which has been subject to closer surveillance at RERF than the remainder of the sample, can be contrasted

with the rest of the sample within dose and age classes.

In this study the AMFIT algorithm[17,18] for unconditional, Poisson model, maximum likelihood regression of grouped survival data has been used to test for the existence of dose-related ascertainment bias, to estimate the possible dependence of risk on radiation dose, and to evaluate the variation of the level of dose response with respect to city, age ATB, sex, time after exposure, and age at observation for risk. These analyses were based on numbers of cases and persn-years of observation for risk, the latter accumulated through the date of diagnosis of colorectal cancer for cases and to the date of death or 31 December, 1980 for non-cases, grouped by estimated tissue dose, averaged over the large intestine, city of exposure, sex, age ATB, and calendar year. Rates were analyzed with respect to average values for tissue dose equivalent, age ATB, attanied age, and time since exposure, computed for each cell in the above cross-classification.

Most dose-response analyses were carried out using stratified relative risk models, in which in effect a saturated loglinear model was used to estimate zero-dose risk in 384 strata defined by the two cities, two sexes, 12 age-ATB intervals (<5, 5–9, 10-14, ..., 45–49, 50–59, 60+), and eight calendar time periods (1950–54, 55–58, 59–62, 63–66, 67–70, 71–74, 75–78, 79–80). Only relative measures of excess risk could be calculated using this approach. Another approach, used for a few analyses, was to model the logarithm of zero-dose risk as a linear function of the city, sex, age at observation (log scale), and time since exposure (both log and arithmetic scales). With a modelled background, it was possible to estimate absolute as well as relative excess, e.g., excess cases per 10^4 persons per year per Sv, as well as excess as a percentage of the risk at zero dose. In general, estimates of excess relative risk made using the stratified and modelled background approaches were very similar.

Table 1. Number of Colorectal Cancer Cases by Method of Case Ascertainment

Method of Case Ascertainment*	Site							
	Total		Colon		Rectum		Unknown	
	No.	%	No.	%	No.	%	No.	%
Total	730	100.0	381	100.0	337	100.0	12	100.0
1	451	61.8	260	68.2	191	56.7		
2	86	11.8	50	13.1	35	10.4	1	8.3
3	75	10.3	30	7.9	45	13.4		
4	33	4.5	14	3.7	16	4.7	3	25.0
5	85	11.6	27	7.1	50	14.8	8	66.7

*: 1 Cases identified in microscopic examination by present investigators
2 Cases identified in microscopic examination, but specimens not available to present investigators
3 Cases identified by surgical operation
4 Cases identified clinically
5 Cases identified only by death certificate

RESULTS

In all, 963 possible cases were identified during the ascertainment period, including 29 that were previously unreported to the RERF tuor registry. The criteria for inclusion as a possible case were intentionally permissive, and 233 were determined by the investigators not to be colorectal cancers, or lacked sufficient information to support a positive finding. Of the 730 cases accepted as colorectal cancer, 381 were determined to be colon cancer, 337 to be rectal cancer, and 12 were classified as cases of unknown site. Frequencies are given in Table 1, by source of

Table 2. Histological Classification by Radiation Dose

	Histological Type	Total	NIC	DS86 large intestine dose (Gy)				
				0	0.01–0.09	0.10–0.99	1.0+	Unk.
Colorectal	Total	435	95	102	132	75	15	16
	Well differentiated adenocarcinoma	163	36	38	47	27	6	9
	Moderately differentiated adenocarcinoma	202	44	47	62	37	6	6
	Poorly differentiated adenocarcinoma	28	3	10	11	2	1	1
	Mucinous	31	8	7	8	7	1	—
	Signet ring cell	5	1	—	2	1	1	—
	Other	6	3	—	2	1	—	—
Colon	Total	248	60	56	67	45	12	8
	Well differentiated adenocarcinoma	94	23	17	29	16	5	4
	Moderately differentiated adenocarcinoma	110	30	27	23	22	5	3
	Poorly differentiated adenocarcinoma	18	2	7	6	1	1	1
	Mucinous	19	3	5	6	5	—	—
	Signet ring cell	5	1	—	2	1	1	—
	Other	2	1	—	1	—	—	—
Rectum	Total	187	35	46	65	30	3	8
	Well differentiated adenocarcinoma	69	13	21	18	11	1	5
	Moderately differentiated adenocarcinoma	92	14	20	39	15	1	3
	Poorly differentiated adenocarcinoma	10	1	3	5	1	—	—
	Mucinous	12	5	2	2	2	1	—
	Signet ring cell	—	—	—	—	—	—	—
	Other	4	2	—	1	1	—	—

diagnostic material in roughly increasing order of uncertainty, as follows:

1) Cases identified in the study by microscopic examination of histological specimens by the present investigators (T.Y, I.S);

2) Cases without review of histological specimens by the present investigators, but whose original diagnosis had been based on pathology review by other pathologists;

3) Cases whose original diagnosis was based on surgical operation without histological review;

4) Cases with clinical diagnosis but not 1), 2), or 3) above;

5) Cases with death certificate information only.

Histological classification Of the 451 cases for which hitological materials were available for review by the present investigators (Table 1), 435 had sufficiently informative material to permit further subclassification by histological type. These cases are shown in Table 2 by site, exposure group, and histological type. No statistically significant within-site differences in histological type were found by radiation dose or exposure class.

Bias analyses The data of Table 3 were analyzed for possible association between degree of diagnostic uncertainty and exposure class, and no statistically significant dose-related nonhomogeneity or trend was found for the colon and rectum separately as well as for the colorectal cancer as a whole. In Table 4, numbers of cases mentioned on death certificates and, in principle, ascertainable through that source alone are compared with total numbers of cases, by site and exposure class. No statistically significant evidence was found of nonhomogeneity among exposure classes, for combined sites or for colon or rectum separately.

Contrasts between incidence in the clinical subsample and in the remainder of the sample, stratified by city, sex, age ATB, follow-up interval and radiation dose (Table 5), found a 12% greater incidence of colorectal cancer generally, and 13% and 12% greater incidence of colon cancer and rectal cancer, specifically, in the Adult Health Study (AHS) subsample. These differences seemed to correspond mainly to the NIC and unknown dose groups; when those

Table 3. Bias Analysis: Distribution of Method of Case Ascertainment for colorectal cancer by Radiation Dose

Method of Case Ascertainment*	Total		NIC		DS86 Large Intestine Dose (Gy)									
					0		0.01–0.09		0.10–0.99		≥1.0		Unk.	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Total	730	100.0	166	100.0	170	100.0	211	100.0	118	100.0	22	100.0	43	100.0
1	451	61.8	101	60.8	104	61.2	136	64.5	77	65.3	16	72.7	17	29.5
2	86	11.8	26	15.7	17	10.0	21	10.0	8	6.8	3	13.6	11	25.6
3	75	10.3	18	10.8	16	9.4	16	7.6	14	11.9	3	13.6	8	18.6
4	33	4.5	6	3.6	10	5.9	11	5.2	4	3.4	—	—	2	4.7
5	85	11.6	15	9.0	23	13.5	27	12.8	15	12.7	—	—	5	11.6

*: 1. Cases identified in microscopic examination by present investigators
2. Cases identified in microscopic examination, but specimens not available to present investigators
3. Cases identified by surgical operation
4. Cases identified clinically
5. Cases identified only by death certificate

Table 4. Bias Analysis: Colorectal Cancer Cases Identified on Death Certificates as Compared to Total Incident Cases, 1950–1980

Site		Total	NIC	DS86 large intestine dose (Gy)					Homogeneity
				0	0.01–0.09	0.10–0.99	≥1.0	Unk.	
Colorectal	Observed death	408	91	101	115	62	10	29	
	Expected†	408	92.8	95.0	117.9	66.0	12.3	24.0	p=0.42
	Total incidence case	730	166	170	211	118	22	43	
Colon	Observed death	168	39	39	46	24	7	13	
	Expected†	168	40.1	37.0	47.2	28.2	7.5	7.9	p=0.20
	Total incidence case	381	91	84	107	64	17	18	
Rectum	Observed death	200	43	49	58	34	2	14	
	Expected†	200	43.9	47.5	58.8	32.0	3.0	14.8	p=0.93
	Total incidence case	337	74	80	99	54	5	25	

†: based on the percentage of cases identified on death certificates for all dose categories combined

groups were removed from the comparison, the AHS subcohort had radiation dose-adjusted rates 4% less than the remainder of the LSS sample for colorectal cancer and for rectal cancer considered separately, and a 6% excess for colon cancer. None of the above differences, with or without the NIC and unknown dose groups, approached statistical significance. Within the NIC group, however, the 40% greater rectal cancer rate among AHS subsample members was almost significant, whereas the 24% greater colon cancer rate was not.

Overall, the bias analysis is reassuring in that there is no reason to suspect a consistent relationship between case ascertainment efficiency and radiation dose that might affect estimation of dose-related excess relative risk. The analysis does, however, reinforce the reservations mentioned above about the suitability of the NIC group as a low-dose reference. The NIC group was excluded from all dose-response analyses presented in the remainder of this paper.

Table 5. Bias Analysis: Ratios of incidence rate for AHS to Non-AHS

	Total	NIC	DS86 Large Intestine Dose (Gy)				
			0	0.01–0.09	0.10–0.99	1.0+	Unk.
Colorectal	1.12	1.40[Sug.]	0.85	0.87	1.20	0.68	1.57
				0.97			
Colon	1.13	1.24	0.61	0.95	1.41	1.01	2.24[Sug.]
				1.01			
Rectum	1.12	1.65[Sug.]	1.14	0.72	1.00	0.10	1.22
				0.93			

[Sug.]: $0.05 \leq P < 0.10$

Table 6. Case Frequencies and Relative Risk (vs. 0 Gy), 1950–80, —all method of

Site		Total	NIC	DS86 Large Intestine Dose (Gy) 0	0.01–0.09	0.10–0.19	0.20–0.49	0.50–0.99
	Mean dose†		0	0	0.029	0.14	0.33	0.73
	Person-years at risk	2804980	700147	692028	779916	153854	163019	80711
Colorectal	No. of case	730	166	170	211	46	46	26
	RR		1.00	1.0	1.15	1.16	1.12	1.41
Colon	No. of case	381	91	84	107	27	23	14
	RR		1.11	1.0	1.20	1.38	1.13	1.53
Rectum	No. of case	337	74	80	99	19	23	12
	RR		0.94	1.0	1.12	1.01	1.19	1.39

†: Tissue dose equivalent (RBE=10) ( ): 90% confidence interval —: not estimable

Dose response Table 6 gives numbers of cases and relative risks by DS86 large intestine dose, using the zero-dose (<0.005 Gy) exposed group as the standard. Relative risks are adjusted for city, sex, age ATB, and time after exposure. These results are given for all colorectal cancers as a group, and for cancers of the colon and rectum separately. The same information is given in Table 7 for cases ascertained on the basis of pathology or surgical information, separately for each organ and for the following colon divisions: cecum and ascending colon, transverse and descending colon, and sigmoid colon. Colorectal cancers were about evenly divided between colon and rectum, and most of the colon cancers occurred in the sigmoid colon.

For each of the above sites and subsites, the following summary dose-response analyses are presented: (1) linear trend in DS86 tissue dose (more precisely, dose equivalent), (2) test for non-linearity, and (3) general test of nonhomogeneity of risk with dose. For colorectal cancers as a group, there was a strong and highly significant ($p=0.007$) increase in risk with increasing tissue dose (Table 6). When broken down by site, however, it is clear that all the evidence for a dose-related excess risk pertains to the colon ($p<0.001$), and none to the rectum (Figure 1). The same pattern holds, with similar risk estimates, whether the basis for inference was sources of case ascertainment or only those confirmed by pathology or surgery (Table 7). Within the latter class, there is a notable similarity in stratified risk estimates for the colon, whether for the organ as a whole or for the cecum and ascending colon, transverse and descending colon, and sigmoid

by DS86 Large Intestine Dose and Site

ascertainment—

1.0–1.99	2.0–2.99	3.0–3.99	4.0+	Unk.	TEST: Linear trend excess RR per Sv	TEST: Linear trend P	TEST: Non. linearity P	TEST: Homo geneity P
1.44	2.54	3.82	4.86					
40163	9177	3663	2098	180204				
16	3	1	2	43				
					0.395 (0.113, 0.725)	0.007	0.96	0.23
1.82	1.86	1.24	4.90	1.14				
11	3	1	2	18				
					0.798 (0.368, 1.36)	0.00024	0.56	0.024
2.59	3.63	2.53	11.41	1.01				
5	0	0	0	25				
					−0.084 (—, 0.360)	0.72	0.39	0.80
1.18	0.0	0.0	0.0	1.35				

sections considered separately.

For no site did a general quadratic dose-response function fit significantly better than a simple linear function, and for all except the sigmoid colon the linear model fit slightly better than the simple dose-squared model. On the other hand, there was no site for which the latter model could be rejected. Thus these data were rather uniformative about the shape of the dose-response relationship.

Modifying factors of radiation effect on colon cancer Table 8 presents colon cancer incidence rates, stratified by city, sex, exposure age, and time period, as appropriate, for the entire sample and by various subsets. Also presented are corresponding linear regression estimates of excess RR per Sv and excess risk per 10^4 PYSv for assumed expression period. Many of these coefficients have wide confidence limits.

It is notoriously difficult to estimate the minimum time between an exposure and the diagnosis of a cancer caused by that exposure, which, in the present data, is complicated by the possibility of more complete case ascertainment following the establishment in 1957 and 1958, respectively, of the Hiroshima and Nagasaki tumor registries. A more modest goal is to estimate when an excess risk first assumed substantial proportions or, alternatively, the best period on which to base lifetime risk estimates.

The present analysis proceeded by exploring the effect on residual deviance, and on

Table 7. Case frequencies and Relative Risk (vs. 0 Gy), 1950–80, —Cases ascertained by microscopic

Site		Total	NIC	DS86 Large Intestine Dose (Gy) 0	0.01–0.09	0.10–0.19	0.20–0.49	0.50–0.99
Colon	No. of case	340	85	76	88	22	22	13
	RR		1.14	1.0	1.10	1.25	1.20	1.57
Cecum. Ascending	No. of case	104	27	18	31	10	5	3
	RR		1.57	1.0	1.62	2.32	1.15	1.56
Transverse, Descending	No. of case	81	15	22	20	4	5	6
	RR		0.68	1.0	0.86	0.82	0.94	2.41
Sigmoid Colon	No. of case	155	43	36	37	8	12	4
	RR		1.21	1.0	0.99	0.97	1.39	1.03
Rectum	No. of case	271	60	61	84	14	19	9
	RR		1.00	1.0	1.27	0.99	1.29	1.35

( ): 90% confidence interval —: not estimable

estimated excess risk, of varying the minimum time following exposure, and minimum attained age, at which a dose-related excess was assumed to exist. A linear dose response was assumed, without modification of excess risk by other factors. Minimum residual deviance was obtained for expression periods beginning about 1959 or 1963 (based on 4-year time intervals), and not before about age 35 (analysis available on request). Estimates of excess relative and absolute risk were locally maximized for an expression period beginning in 1963, 17 years after exposure; however, the difference between 1959 and 1963 was very slight. Thus, we assumed an expression period beginning in 1959, but not before age 35.

City and Sex: In the present data, rectal cancer rates, after adjustment for sex, age ATB, dose interval, and time after exposure, are about the same in the two cities whereas colon cancer rates are between 70% and 75% as high in Nagasaki as in Hiroshima. Rates for both sites among women were about 60% as high as those among men. In terms of radiationassociated excess relative risk, however, neither city of exposure nor sex was an important modifier; estimates of

by DS86 Large Intestine Dose and Site
examination or surgical operation—

1.0–1.99	2.0–2.99	3.0–3.99	4.0+	Unk.	TEST			
					Linear trend		Non. linearity	Homo geneity
					excess RR per Sv	P	P	P
11	3	1	2	17				
					0.997 (0.499, 1.66)	0.00004	0.59	0.015
2.83	4.03	2.90	12.34	1.03				
3	2	0	0	5				
					0.901 (0.104, 2.26)	0.050	0.69	0.14
3.45	11.96	0.0	0.0	1.56				
2	0	1	0	6				
					0.927 (0.077, 2.38)	0.061	0.75	0.43
1.71	0.0	8.01	0.0	1.14				
6	1	0	2	6				
					1.093 (0.387, 2.16)	0.002	0.30	0.049
3.21	2.85	0.0	24.88	0.71				
5	0	0	0	19				
					−0.037 (—, 0.468)	0.88	0.39	0.69
1.50	0.0	0.0	0.0	1.30				

absolute risk differed somewhat more, but not significantly. Even though the estimated excess risk of colon cancer was similar in the two cities, the Nagasaki data were not sufficiently strong alone to support a statistically significant dose response.

Age at Exposure, Time Following Exposure, and Age at Observation for Risk: Some variation in dose response by age and time is suggested by the estimates in Table 8. In particular, no dose response was observed among subjects younger than age 10 ATB, possibly because there were too few cases at any dose level (6 exposed with DS86 dose), nor was there an increase among those over 50 ATB (65 exposed).

Table 9 is a summary of linear-model dose-response analyses incorporating age ATB, age at observation for risk, and time following exposure, in terms of relative and additive risk models; the expression period was restricted to 1959 and later, and to observation at (about) age 34 and older. Highly significant dose responses were obtained. Both age ATB and age at observation were significant ($p<0.05$) modifiers of excess relative risk, but no further improvement in fit was obtained by including both in the model, or (equivalently) by including time since exposure with

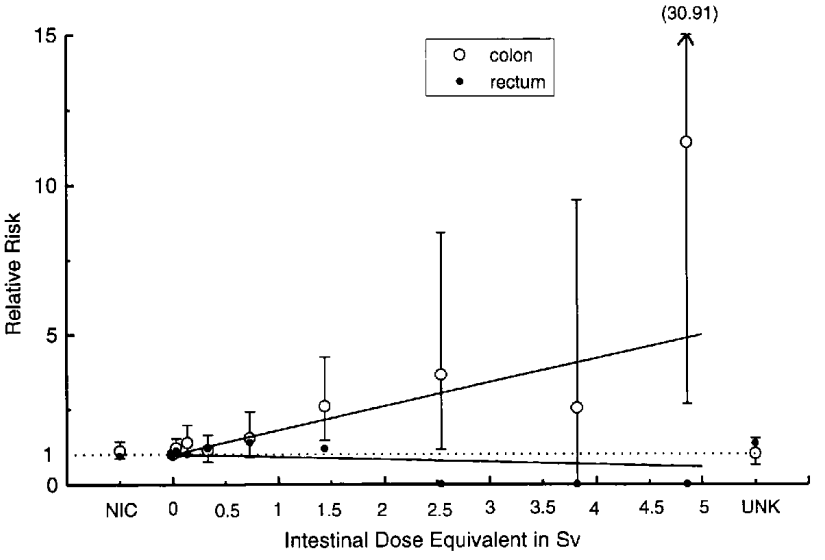

Figure. 1. Dose response of incidence from colorectal cancer by site, 1950–80. (Bars indicate 90% confidence interval of relative risks, NIC: Not In City at the time of bombing, UNK: unknown dose)

either age variable. Neither of the age variables, nor time since exposure, was a significant modifier of the estimated dose response on the additive scale. Parallel analyses (not shown), in which the assumed period of expression was not restricted, gave less crisp results, and tended to confirm the correctness of the restriction used. The fitted models suggest that relative risks, if they change at all over time following exposure, may tend to decrease for cohorts exposed at young ages, and increase for cohorts exposed at older ages.

DISCUSSION

Mortality vs. incidence For cancers of high fatality, like those of the colon and rectum, the main advantages of inferences based on incidence, as opposed to mortality ascertained from death certificates, are more timely ascertainment of cases and greater diagnostic accuracy and specificity. The numbers of cases obtained in the present study, for the period 1950–80, are comparable to the numbers of death certificate cases observed during 1950–85[3]. Certain inferences are very similar, such as the estimates of excess relative risk and the fact that colon cancer risks are elevated at high doses, while rectal cancer retes are not. In both studies there is little evidence that the excess relative risk for colon cancer varied by sex or, for fixed age ATB, over time following exposure; there is some evidence that it declined with increasing age ATB.

The studies differ in that the mortality-based estimates of relative risk for colon cancer were

Table 8. Variation of colon cancer rates and estimated excess RR per Sv, excess risk per 10^4 PYSv by various possible modifying factors. The assumed expression period is 1959–80 and age 35 or older at observation

Modifying Factor		Crude Rate per 10^4 PY	Excess RR† per Sv		Homog.	Excess Risk†† per 10^4 Sv		Homog.
			Est.	90% C.I.	p	Est.	90% C.I.	p
None		1.41	0.932	0.46, 1.55	—	1.629	0.84, 2.63	—
City	H	1.56	0.931	0.42, 1.62	0.999	1.804	0.83, 3.07	0.64
	N	0.91	0.932	−0.06, 2.77		1.268	0.20, 3.05	
Sex	M	1.77	0.860	0.28, 1.73	0.81	1.614	0.28, 3.48	0.97
	F	1.18	1.016	0.33, 2.02		1.635	0.72, 2.88	
Age ATB	<20	0.26	3.746	1.17, 9.83	0.073	1.673	0.63, 3.23	0.77
	20–39	1.73	0.959	0.31, 1.95		1.828	0.63, 3.48	
	40+	3.25	0.309	—, 1.15		0.463	—, 3.49	
Calendar Year	<1959	0.29						
	1959–66	0.95	1.355	0.08, 3.71	0.86	1.561	0.40, 3.38	0.66
	1967–74	2.01	0.768	0.12, 1.79		1.194	0.17, 2.79	
	1975–80	3.39	0.952	0.31, 1.92		2.437	0.86, 4.67	
Approx. Age at Obs.	<35	0.09						
	35–49	0.72	2.473	0.85, 5.64	0.10	1.447	0.61, 2.64	0.92
	50–64	2.29	1.027	0.28, 2.25		1.807	0.30, 3.88	
	65+	5.79	0.271	—, 1.03		2.177	—, 6.11	

†: based on the statified relative risk model.
$\lambda = \lambda_0 \cdot \{1 + \alpha \text{ Dose} \cdot \text{I(expression period)}\}$, separately for each modifying factor group; λ_0 is statified by city, sex, age ATB and time since exposure;
Dose is in Sv, $\text{I(expression period)} = \begin{cases} 1 & \text{if period is after 1959 and attained age 35 or older.} \\ 0 & \text{others} \end{cases}$

††: based on the additive model with modelled baseline rates
$\lambda = \lambda_0 + \alpha$ Dose·I(expression period), separately for each modifying factor group; $\lambda_0 = \exp(\beta_0 + \beta_1 \text{CTTY} + \beta_2 \text{SEX} + \beta_3 \log(\text{AGE}) + \beta_3 \log(\text{TSX}) + \beta_4 \text{TSX})$, where AGE is attained age and TSX is time since exposure; dose is in Sv.

significnatly different between cities, while those in the present study were practially identical. This anomaly is probably a reflection of statistical instability due to the relatively small numbers of cases at any dose level among Nagasaki survivors. Indeed, given the lack of a major qualitative difference between the doses from the two bombs according to DS86, it is difficult to imagine a biological reason why there should be a radiation-related effect in one city and not in the other.

LSS vs. medically-irradiated populations Given the circumstances of their exposure, it is easy to forget that the overwhelming majority of LSS sample members were exposed to relatively low levels of radiation, and that the highest intestinal doses observed tend to be low in comparison to those in many medically-irradiated populations under study[19–26]. Comparisons with studies of medically-irradiated subjects are complicated by the fact that the colon is not a compact organ

Table 9. Summary of analyses of the modifying effects on colon cancer dose response of age ATB, age at observation for risk, and time following exposure. Expression period 1959–80 and observation age 35 or greater.

A. Stratified relative risk model[†]

Regression Coefficients (Parameter Estimates)										
	Modifying Factors (β)									
Dose (α)[†††]	Age ATB	AGE Obs.	Time	Age ATB Age Obs.		Age ATB Time		Age Obs Time	Deviance	Commentary
0.93									460.044	
1.63	−0.064								454.915	Dose response decreases with increasing age ATB ($p=0.19$) and with increasing age at observation ($p=.014$), but not with increasing time since exposure.
3.43		−0.079							453.799	
0.847			0.011						460.022	
3.57	0.0048	−0.084							453.794	
3.57	−0.079		−0.084						453.794	
3.57		−0.079	−0.0048						453.794	
2.92	0.0099	−0.076		−0.0008					453.713	There is some evidence that excess risk may vary differently over time for different ages ATB or ages at observation.
2.57	−0.320		−0.089			0.021			449.846	
15.2		−0.252	−0.080					0.016	450.220	

[†]: $\lambda=\lambda_0\cdot\{1+\alpha\ \text{Dose}\cdot\text{I(expression period)}\cdot\exp(\beta X)\}$; λ_0 is stratified by city, sex, age ATB and time since exposure; dose is in Sv, X is one or more radiation effect modifiers, such as age ATB, age at observation, time since exposure, or an interaction term and translated to have mean zero.

B. Additive model with modelled baseline rates[††]

Regression Coefficients (Parameter Estimates)										
	Modifying Factors (β)									
Dose (α)[†††]	Age ATB	Age Obs.	Time	Age ATB Age Obs.		Age ATB Time		Age Obs. Time	Deviace	Commentary
1.63									728.430	
1.64	0.0060								728.374	There is no evidence of variation in dose-related excess absolute risk by age ATB, age at observation, or time since exposure, whether these variables appear alone or in combination.
1.48		−0.019							727.915	
1.26			0.044						727.780	
1.13	−0.044	0.064							727.189	
1.13	0.020		0.064						727.189	
1.13		0.020	0.044						727.189	
0.71	−0.032	0.086		−0.0019					726.301	
1.10	−0.025		0.060			0.0046			726.334	
1.57		−0.015	0.023					0.0037	726.417	

[††]: $\lambda=\lambda_0+\alpha\text{Dose}\cdot\text{I(expression period)}\cdot\exp(\alpha X)$; $\lambda_0=\exp(\beta_0+\beta_1\text{CITY}+\text{B}_2\text{SEX}+\beta_3\log(\text{AGE})+\beta_3\log(\text{TSX})+\beta_4\text{TSX})$, where AGE is attained age and TSX is time since exposure; dose is in Sv, X is a radiation effect modifier, such as age ATB, age at observation, time since exposure, or an interaction term and translated to have mean zero.

[†††]: Excess relative or absolute risk per Sv, at the person-year weighted mean values of the modifying factors in the model (i.e. at age 24.9 ATB, age 44.2 at obervation, and/or 19.2 years after exposure).

and, depending upon the procedure, may receive markedly non-uniform dose. For example, doses to the rectum from external x-ray sources and intracavity radium used to treat cervical cancer in a large international study[24,25] were uniformly high (30–60 Gy), whereas doses to different parts of the colon ranged from 3.7 to 31.6 Gy, with an average of 24.2. In that study, an excess risk of rectal cancer was found, but colon cancer risk was not increased. In another study, of cancer following intracavity radium treatment (targeted at the ovaries) for uterine bleeding, Inskip et al.[26] found excess cancer risk for the colon but not the rectum. There, however, rectal doses were only about 3 Gy (10th–90th percentiles 1.5–4.8), whereas the median dose was 1.3 Gy (0.6–2.0) for the entire colon but 0.4 Gy (0.2–0.7) for the transverse colon and 2.9 Gy (1.4–4.6) for the sigmoid colon; that is, organ doses and their distribution over the organs of concern here, while not uniform, were more like those received by the A-bomb survivors. A possible exception to the pattern of radiation carcinogenesis at high doses for the rectum and at low doses for the colon is a study of another population irradiated by external x-ray beam for uterine bleeding[22], in which excess risks of both colon and rectum cancer were found. The latter excess (RR=1.5 based on 8 deaths) was not statistically significant, however, and there may well be no anomaly to be explained.

Subsites within the colon The marked difference in radiation sensitivity betwene the colon and rectum demonstrated by this and other studies suggests the possibility of differences within the colon. In fact, however, estimated relative risks were apparently homogeneous among the cecum and ascending, transverse and descending, and sigmoid colon. This finding is new information that could not have been obtained from the mortality studies. The statistical evidence for an excess cancer risk for the sigmoid colon was stronger than for the other parts, but only because the total number of cancers was greater.

Histological type In Japan, about 90% of colorectal cancers examined for histological type are well-differentiated or moderately-differentiated adenocarcinomas, and the proportions of poorly differentiated adeocarcinoma, mucinous carcinoma, and signet-ring cell carcinoma are low[27]. The distribution found in this study was essentially the same, with no evidence of differences by radiation dose for cancers of either the colon or rectum. Castro et al.[23] reported that mucinous carcinoma accounted for a large proportion of colorectal cancers developing after radiation therapy for uterine lesions, but that study population, in which an excess of rectal cancers was observed, received massive local doses of tens of Gy and for that reason may not be comparable with this one. In studies of the A-bomb survivor population involving other cancer sites, no dose-related sub-type differences have been found for thyroid[28] or breast cancer[15,29]. There is some evidence, however, that carcinomas of poor differentiation are more frequent at high radiation doses, such as small cell carcinoma of the lung[30,31] and poorly differentiated adenocarcinoma of the stomach[32]. Given the rather small numbers of high-dose cases with histological diagnoses (Table 2), it is still possible that dose-related differences in histological type may in time emerge.

Age and time considerations As with most cancer sites, it has proved difficult to determine with any precision the minimum time from exposure until the appearance of an excess colon cancer risk, or the minimum age at which an excess can be seen. In the present analysis the evident influence on additive model risk estimates of the assumed minimum time to expression

may reflect a latent period for radiation-induced cancer, but it is also possible that case ascertainment simply was incomplete for the period 1950–57, that is, before the establishment of the Hiroshima and Nagasaki tumor registires. The additional working assumption, that excess risk was unimportant before about age 34, is consistent with, and partly depended upon, the lack of evidence for a dose response among survivors who were under age 10 ATB; the youngest of this group had barely reached age 35 by the end of 1980.

The possible influences of age at exposure and age at observation for risk are difficult to untangle in these data. For example, sharp contrasts in estimated excess relative risk are obtained for colon cancer by comparing exposure ages under and over 25 (2.96 at one Gy, based on 49 cases, vs. 0.60 based on 314 cases, respectively), and by comparing cases disgnosed before and after age 50 (excess RR per Gy, 3.09, based on 45 cases, vs. 0.65 based on 318 cases at older ages). The higher estimates were based on relatively small numbers of cases; given that all persons who were under age 25 in 1945 were under age 60 during the period 1963–80, and all of the people who were under age 50 during this period were younger than 33 ATB, it is perhaps unsurprising that we have been unable to discriminate between the influences of these two variables, and that no significant improvement in fit was obtained by fitting more complex models in age ATB, age at observation, and time since exposure. The question is an important one, nevertheless, because very different lifetime projections of risk are obtained using models in which excess relative risk per unit dose depends only upon age ATB or, alternatively, upon age at observation. Also, dependence upon exposure age suggests that sensitivity to radiation carcinogenesis may vary with age, whereas dependence upon age at diagnosis might well reflect a competition between radiation and other causes of colon cancer that occur throughout life. It is interesting in this connection that, with the restricted expression period assumed in the analysis, the additive model fit the data about as well as the relative risk model, and that fit was not improved by the addition to the additive model of terms in age ATB, age at observation, and time following exposure (Table 9). Only further follow-up of this population will resolve this complicated issue.

No excess colon cancer risk was observed among survivors 0–9 year of age ATB. This does not necessarily mean that none will occur. In fact, the colon cancer experience as of 1980 bears certain resemblances to the observed breast cancer experince of 6 and more years earlier; the significant, and marked excess first seen in the 1950–80 material[15] was not even suggested by the data for 1950–74[33].

Epidemiological considerations The etiologies of cancer of the colon and rectum appear to differ, especially when the recto-sigmoid junction is distinguished from the rectum proper[34]. Colon cancer has greater variability of rates among different countries, and its risk has a greater tendency to increase among persons who migrate from countries of low incidence, like Japan, to countries of high incidence, like the United States[35]. Colon cancer mortality and morbidity have been increasing rather markedly in recent years in Japan[36,37], a tendency that may possibly be linked to changes in diet, whereas rectal cancer rates have been more stable. Sugano[38] has classified rectal cancer as a "basic" cancer, relatively unsusceptible to changes in environment and life style, as contrasted with cancers of the "changeable" type, including colon cancer. This distinction seems particularly apt with respect to the excess risk associated with radiation

exposure of low to moderate dose.

A question of considerable interest with respect to radiation protection, as well as cancer etiology, is the extent to which other colon cancer risk factors may modify the excess risk associated with radiation exposure. Because Japanese baseline rates for both cancers are low, transport of LSS-based risk estimates to another population with higher baseline rates is highly sensitive to whether relative or absolute risks are assumed to be the same in the two populations[39]. Case-control interview study results now being analyzed[40] may be informative about risk factors such as diet (the factor most often cited as probably responsible for differences in rates between Japan and the U.S.[34,35,37]) in the LSS sample, but it is likely that greater numbers of cases at high dose levels will need to be obtained, through longer follow-up, before useful information can be obtained on possible modification by these factors of radiation dose effects.

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