J. RADIAT. RES., SUPPLEMENT, 212–230 (1991)
A Review of Forty-Five Years Study of Hiroshima and Nagasaki Atomic Bomb Survivors

II. BIOLOGICAL EFFECTS

Mortality among Atomic Bomb Survivors

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Atomic bomb survivors/Radiation induced cancer mortality/Risk coefficient/Dosimetry change

The Atomic Bomb Casualty Commission and its successor, the Radiation Effects Research Foundation, have conducted a long-term follow-up study of a cohort of 120,000 atomic bomb survivors and non-exposed controls since 1950. The most recent findings regarding cancer mortality during the period 1950-85 in this cohort, based on the DS86 doses are as follows:

1) The dosimetry change does not alter the list of radiation-related cancers. Some city differences in dose-response previously thought to be real are no longer significant with the DS86 doses. Assuming a linear dose-response, and using estimated organ-absorbed doses, the risk coefficients derived from the two dosimetries are very similar. If larger RBE values are assumed, the disparity between the two dosimetries increases because the neutron dose is much greater in the T65 dosimetry.

2) Besides the well-known increase of leukemia, there also have been demonstrated increases in cancers of the lung, breast, esophagus, stomach, colon, ovary, urinary bladder, and of multiple myeloma, but no increase has yet been observed in mortality from cancer of the rectum, gallbladder, pancreas, prostate and uterus, and of malignant lymphoma. In general, radiation-induced solid cancer begins to appear after attaining the age at which the cancer is normally prone to develop (the so-called "cancer age"), and continues to increase proportionately with the increase in mortality in the control group as it ages. Sensitivity to radiation, in terms of cancer induction, is higher generally for persons who were young at the time of the bomb (ATB) than for those who were older ATB.

Non-cancer mortality in the period 1950-78, based on the T65 doses, which is the most recent published report, did not show an increase with dose, but now, with the accumulation of seven more years of follow-up, there seems to be an excess in the very high dose range, particularly for the younger age ATB cohort. Further follow-up is called for to confirm this suggestion.

INTRODUCTION

The Atomic Bomb Casualty Commission (ABCC) and its successor, the Radiation Effects Research Foundation (RERF) have conducted mortality surveillance on a fixed sample (Life Span Study (LSS)) since 1950[1,2]. The LSS was designed to identify and measure the possible late effects of acute radiation exposure from the A-bombs expressed through mortality overall or by specific disease categories. Its strength is that mortality ascertainment is essentially complete, regardless of a person's address in Japan, due to the periodic examination of the Koseki records of the LSS sample members. Its weakness is its reliance on the cause of death as stated on the death certificate. Some of the misclassification that can arise in the cause of death is compensated

for by collateral use of autopsy information and data from the Hiroshima and Nagasaki Tissue and Tumor Registries[3].

Most prior analyses of the mortality experience of the LSS sample have been based on the T65DR (tentative 1965 dose revised) doses. However, as a result of a detailed reassessment of A-bomb dosimetry, a new Dosimetry System was introduced in 1986 (DS86)[4]. Recently, the results of an analysis, based on the DS86 doses, have become available for cancer mortality during the period 1950–85[5,6].

We present here a brief review of both cancer and non-cancer mortality among A-bomb survivors. Firstly, we review cancer mortality, including a comparison of risk coefficients based on the DS86 and T65 doses, the temporal change in risk, factors modifying risk and the nature of the dose-response curve. Then a brief review of non-cancer mortality is presented.

MATERIALS AND METHODS

Exposure Assessment

Radiation related risks among the A-bomb survivors have heretofore generally been analyzed in terms of a system of dosimetry introduced in 1968, known as the T65DR doses[7]. Recently, however, a new system was developed for the estimation of individual doses, termed the Dosimetry System 1986 (DS86)[4]. This system takes into account a survivor's distance from the epicenter, shielding, posture, orientation, and age. In 1988, when the analysis described here was begun, DS86 doses were available on 83% of the 91,000 members in the sample who have T65DR doses; however, within the past two years, doses have been estimated on an additional 12,000 or so persons, so that now doses are available on about 95% of the sample.

The DS86 free-in-air gamma dose increases somewhat in Hiroshima, but decreases in Nagasaki in comparison with the T65DR estimates; whereas the neutron dose decreases to about 10% of its former value in Hiroshima and 30% in Nagasaki[4,5,8]. For kerma in Japanese houses, the average transmission factor for gamma rays, but not neutrons, changes substantially, from 0.90 in the T65DR to 0.46 in the DS86. Accordingly, the DS86 estimates of shielded kerma are lower than the T65DR estimates. For organ doses, the transmission factors are higher than in the T65DR system. Since the changes in the transmission factors for house shielding and organ tissue are in the opposite direction, they tend to nullify one another, and as a result, organ doses do not change much from the T65DR dosimetry to the DS86.

Study Sample

The LSS sample consists of persons who were living in either Hiroshima or Nagasaki at the time of the census of A-bomb survivors conducted by the Japanese government in 1950, five years after the bombing. As originally defined, the sample included 1) most persons who were within 2,500 m of ground zero in either city at time of bombing (ATB), 2) a sample of persons who were between 2,500 and 10,000 m from ground zero, and 3) a sample of persons who were not in the city (NIC) or beyond 10,000 m ATB. The latter two samples were matched by city, sex, and age to a core group of survivors who were less than 2,000 m from ground zero ATB.

In 1985, this 109,000 LSS cohort was expanded to 120,321 by inclusion of 11,000 distally exposed subjects in Nagasaki (LSS-E85)[9].

It has been observed that mortality in the NIC group is lower than that seen among survivors who were in the city ATB but received little or no radiation dose (the distally exposed group). It is generally believed that these differences in mortality are due to factors other than radiation exposure. For this reason the most recent analyses of LSS data have excluded the NIC group.

At present, the LSS-E85 sample consists of 120,321 individuals; however, life status cannot be determined on 193, and they have excluded from consideration here. Among the remaining 120,128 subjects, there are 91,228 exposed individuals excluding 26,517 (NIC) and 2,383 on whom a dose (T65DR) could not be estimated.

In 1988, DS86 dose estimates were available for 75,991 (83%) of the 91,228 members in the sample who had T65DR dose estimates. The present review focuses mainly on an analysis of these 75,991 individuals (DS86 subcohort). Efforts continue to assign DS86 for the remainder of the original sample. Currently, DS86 dose estimates are available for 86,520 subjects (95%).

Ascertainment of death

Deaths are routinely ascertained through the Koseki, the obligatory household registries that exist in Japan, and ascertainment is considered to be essentially complete.

Causes of death are obtained from the Vital Statistics Death Schedules which are based on the death certificates and thus the accuracy of the cause of death is a problem. The accuracy of the stated cause of death on the death certificates, as revealed by autopsy findings for those individuals who came to autopsy, has been examined in terms of confirmation rate and detection rate[10]. Confirmation rates differ according to the cause of death: the rate is high for cancers such as leukemia, lung cancer and stomach cancer, being 70–80%, but the accuracy is poor for cancers such as those of the pancreas and liver where the confirmation rate is less than 50%. In studying a cause of death having low accuracy, it is possible to restrict the study to only those individuals where the tumor was histologically confirmed either through autopsy or surgical pathology cohort.

Among a total of 28,737 deaths which occurred during the period 1950–85 in the DS86 subcohort, there were 5,936 malignant neoplasms, 288 deaths from neoplasms of benign or unspecified nature, 20,923 from all disease except neoplasm, 1,515 from external causes and 75 from unknown causes of death.

Statistical methods

The statistical methods used in the most recent cancer mortality report are described elsewhere[9]. Briefly they involve the use of a grouped survival analysis based on an additive relative risk model. Cancer risks are determined by a Poisson regression using person years at risk and the number of deaths stratified by city, sex, age ATB categories and follow-up intervals.

A CANCER MORTALITY

1. The effect of the changes in dosimetry on cancer mortality risk estimates

Dose response

Under the T65 dosimetry system, the dose-response curves differed between Hiroshima and Nagasaki, and the difference was large for leukemia. In Hiroshima, the curve was linear for the entire dose range, whereas in Nagasaki, the curve was non-linear in the low (under 1 Gy) dose range. Under the DS86 dosimetry system, the dose-response curve seems to be more linear as a result of the shifting of subjects with high T65DR doses to lower DS86 doses and the city difference is no longer significant, though non-linearity still remains in the low dose range in Nagasaki (Figure 1).

Figure 2 shows the observed and fitted dose-response curves for leukemia and all cancers except leukemia under the DS86 system in Hiroshima and Nagasaki combined. In both instances, at 2 Gy and over, a downward curvature is observed. Under 2 Gy, the curvature is upwards for leukemia, but not for all cancers except leukemia where the response is linear.

To determine the shape of the dose-response curve, a variety of models were fitted. For leukemia, when the entire dose range is considered, a linear-quadratic (LQ) model with provision for a downwards curvature at the high doses (the LQ-K model) fits better than the linear (L) model, but the LQ model does not fit better than the L model. However, when the dose range is restricted to doses under 2 Gy, the LQ model fits better than the L model. For all cancers except leukemia, non-linear models do not fit any better than the linear model, regardless of

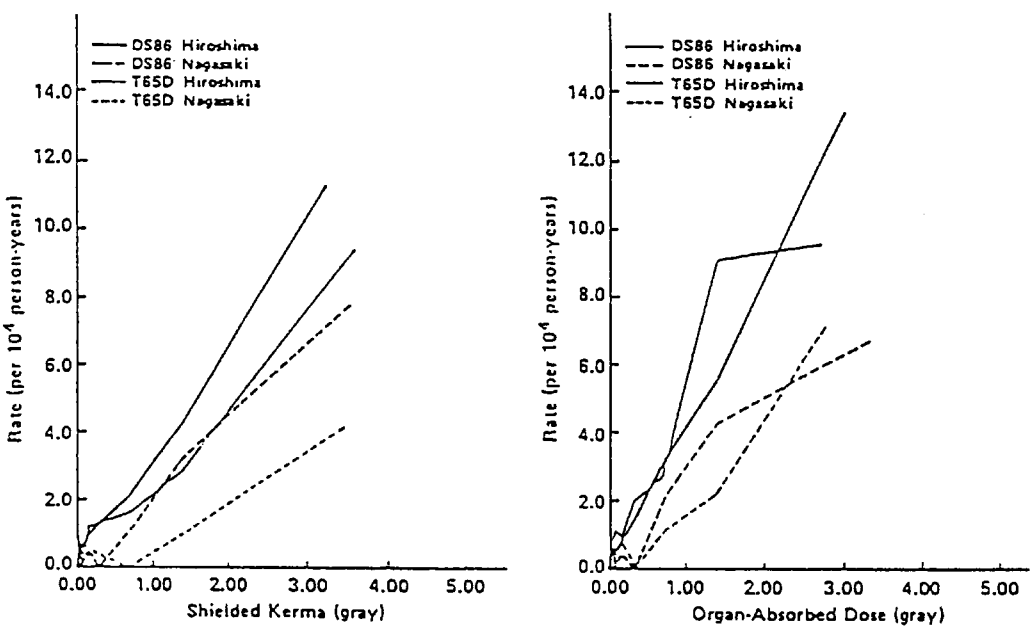
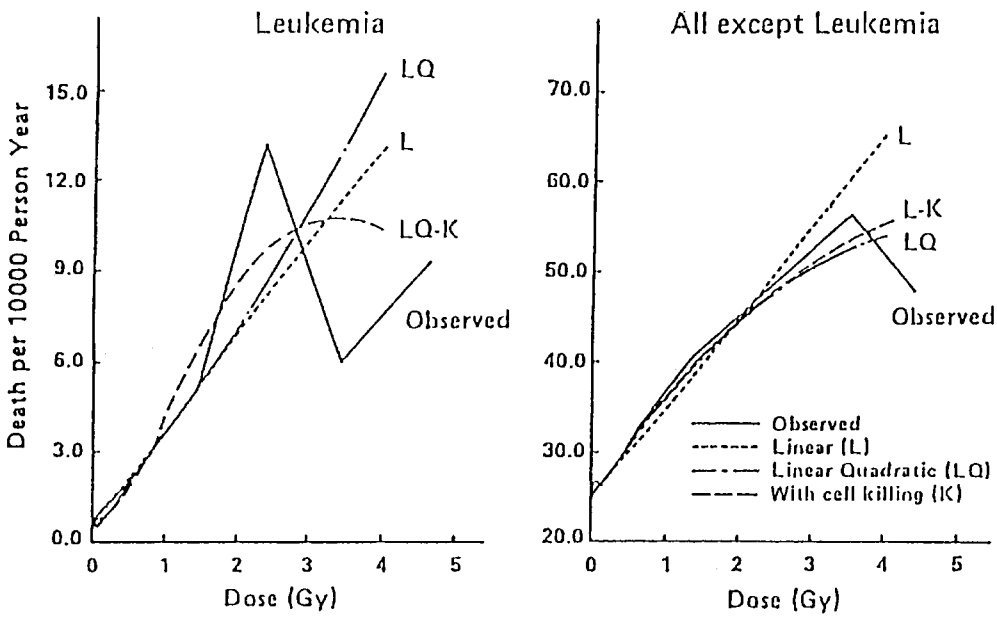


Fig. 1. Shielded kerma and organ-absorbed dose-response curves for mortality from leukemia by city and dosimetry system.
(From ref. 5)



Dose categories used in plots for observed dose-response curves are 0, 0.01-0.05, 0.06-0.09, 0.10-0.19, 0.20-0.49, 0.50-0.99, 1.0-1.9, 2.0-2.9, 3.0-3.9, 4.0+ Gy.

Fig. 2. Observed and fitted organ-absorbed dose-response curves for leukemia and for all cancers except leukemia (From ref. 6)

whether the dose range is restricted or not.

Table 1 was constructed to determine the lowest dose interval where a statistically significantly higher cancer mortality occurs than that seen in the control (0 Gy) group. The lowest dose interval at which a significant increase in the frequency of leukemia or all other cancers can be demonstrated is 0.20–0.49 Gy. Thus, the experience of the survivors continues to provide little direct insight into the shape of the dose response curve at low doses. However, it should be noted, that when the survivors are divided into two groups, those receiving a dose of less than a half gray and those receiving more, the excess relative risk of leukemia is 2.44 in the former group and 5.53 in the latter (this difference is statistically significant), and this suggests a linear-quadratic response. A similar difference is not seen for all cancers other than leukemia where the comparable excess relative risks are 0.37 and 0.42, respectively. The data are still too sparse to examine the solid tumors on a site-specific basis with much reliability.

Change in absolute risk between the two dose systems with different RBE values

Since the estimation of the effects of exposure to gamma rays depends on the RBE of neutrons, and estimates of the latter vary greatly because of small neutron doses even in Hiroshima, the risk coefficients per sievert were estimated based on assuming arbitrary but constant RBE values of 1, 10 and 20. The results are shown in Table 2 in terms of excess deaths per 10^4 PY Sv for both dose systems.

The absolute risks (excess deaths per 10^4 PY Sv) with the DS86 for an RBE of 10 and (20) are 2.67 (2.40), 9.41 (8.76), 2.36 (2.10), 0.73 (0.69), 1.59 (1.42), and 1.00 (0.82) for leukemia,

Table 1. Estimated relative risk compared to 0 Gray group

Site of Cancer	Organ Absorbed Dose (Gy)						
	.01–.05	.06–.09	.10–.19	.20–.49	.50–.99	1.0–1.9	2.0+
Leukemia	.99	.61	1.08	1.79	4.15	8.01	18.57
All cancers except leukemia	1.06	1.08	1.06	1.12	1.36	1.66	2.05
Stomach	1.06	.93	1.05	1.16	1.28	1.29	1.73
Lung	1.30	1.21	1.02	1.54	1.63	2.45	2.14
Female breast	1.12	1.02	1.10	1.39	2.67	2.39	4.22
Colon	1.04	1.01	.53	.98	1.04	2.23	5.87

Underline: Significant at 5% level
(From ref. 6)

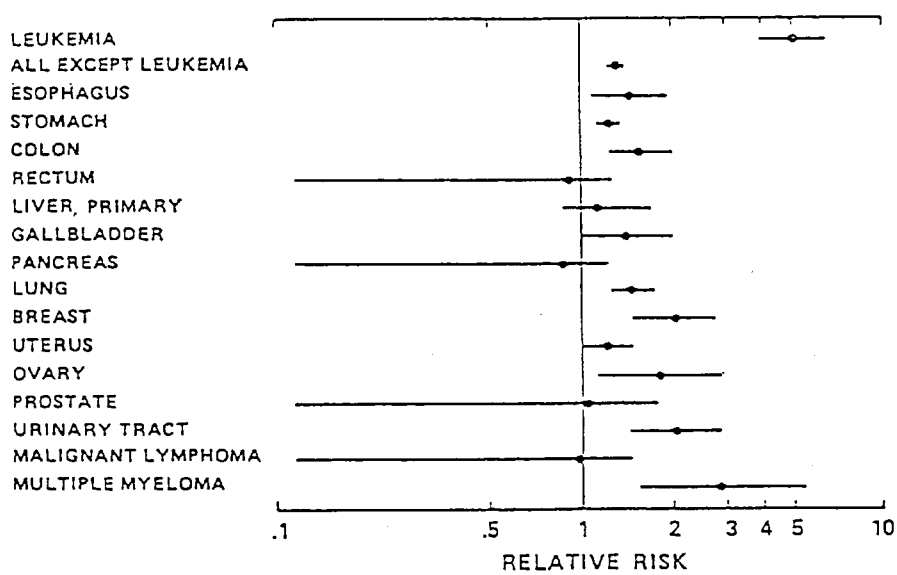


Fig. 3. Relative risk at 1 Gy (Shielded kerma) and 90% confidence interval, 1950-85. (From ref. 6)

Table 2. Comparison of excess deaths per 10^4 person-year-Sv for selected RBE values using the DS86 and T65DR doses (organ dose equivalent)

Site of cancer	RBE	DS86	T65DR	DS86/T65DR
Leukemia	1	2.95 (1.79, 4.15)	3.08	0.96
	10	2.67 (1.62, 3.76)	1.81	1.48
	20	2.40 (1.46, 3.39)	1.23	1.95
All except leukemia	1	10.10 (6.23, 15.3)	13.72	0.73
	10	9.41 (5.79, 14.3)	8.99	1.05
	20	8.76 (5.39, 13.3)	6.34	1.38
Stomach	1	2.63 (1.01, 5.52)	3.38	0.78
	10	2.36 (0.88, 4.96)	2.02	1.17
	20	2.10 (0.77, 4.47)	1.34	1.57
Colon	1	0.76 (0.15, 2.70)	0.93	0.82
	10	0.73 (0.15, 2.50)	0.65	1.12
	20	0.69 (0.14, 2.35)	0.49	1.41
Lung	1	1.80 (0.17, 6.74)	1.90	0.95
	10	1.59 (0.15, 5.85)	1.18	1.35
	20	1.42 (0.13, 5.29)	0.80	1.78
Female breast	1	1.22 (0.31, 3.10)	0.90	1.36
	10	1.00 (0.25, 2.61)	0.43	2.33
	20	0.82 (0.20,2.21)	0.26	3.15

( ): 90% confidence interval.
(From ref. 5)

all cancers except leukemia, and cancers of the stomach, colon, lung and female breast, respectively. These values do not differ significantly with the different RBE (though they decrease slightly at an RBE of 20), because of the small neutron exposure. As is apparent from Table 2, with the T65DR doses, the estimated excess deaths are much more sensitive to the RBE value that is assumed, and the disparity between the two dosimetries grows larger as the assumed RBE increases, reflecting the relative importance of the neutron component in the two systems. At an RBE of 10, for the five specific sites given in Table 2, the increase in the number of excess deaths per 10^4 PY Sv under the DS86 varies from 12% (colon) to 133% (female breast).

2. Cancer mortality by Site

Analyses of mortality based on the Life Span Study sample, 1950–1985, using the recently revised radiation doses have shown a significant excess in mortality from malignant tumors, but the excess in terms of relative risk at 1 Gy, excess death and attributable risk for various malignant

Table 3. Summary measures of radiation dose response for cancer mortality by site; both cities, both sexes (Unless otherwise stated[a]), all ages ATB, 1950-1985 (Shielded kerma)

Site of cancer	No. of deaths	Statistical test (P)[b]	Estimated RR at 1 Gy	Excess risk per 10^4 PY Gy	Attributable risk (%)[c]
All malignant neoplasms	5936	0.000	1.39 (1.32, 1.46)	10.0 (8.36, 11.8)	10.2 (8.50, 12.0)
Leukemia	202	0.000	4.92 (3.89, 6.40)	2.29 (1.89, 2.73)	55.4 (45.7, 66.3)
All except leukemia	5734	0.000	1.29 (1.23, 1.36)	7.41 (5.83, 9.08)	7.86 (6.19, 9.64)
Digestive organs and peritoneum	3129	0.000	1.24 (1.16, 1.33)	3.39 (2.27, 4.59)	6.58 (4.41, 8.91)
Esophagus	176	0.02	1.43 (1.09, 1.91)	0.34 (0.08, 0.67)	12.7 (2.92, 25.0)
Stomach	2007	0.000	1.23 (1.13, 1.34)	2.07 (1.19, 3.05)	6.26 (3.61, 9.23)
Colon	232	0.000	1.56 (1.25, 1.98)	0.56 (0.26, 0.91)	15.1 (6.96, 24.7)
Rectum	216	0.67	0.93 (, 1.27)	−0.07 (, 0.25)	−1.93 (, 7.12)
Liver, primary	77	0.57	0.12 (0.87, 1.70)	0.05 (−0.05, 0.25)	3.90 (−4.38, 20.5)
Gallbladder and bile ducts	149	0.13	1.37 (0.98, 1.96)	0.22 (−0.01, 0.53)	8.24 (−0.55, 19.5)
Pancreas	191	0.53	0.89 (, 1.23)	−0.10 (, 0.20)	−3.01 (, 6.21)
Other, unspecified	81	0.29	1.32 (0.87, 2.14)	0.11 (−0.05, 0.35)	7.73 (−3.29, 24.2)
Respiratory system	747	0.000	1.40 (1.21, 1.63)	1.29 (0.71, 1.96)	10.1 (5.50, 15.3)
Lung	638	0.000	1.46 (1.25, 1.72)	1.25 (0.70, 1.89)	11.4 (6.36, 17.1)
Female breast[a]	155	0.000	2.00 (1.48, 2.75)	1.02 (0.53, 1.60)	22.1 (11.4, 34.8)
Cervix uteri and uterus[a]	382	0.08	1.22 (1.01, 1.50)	0.60 (0.04, 1.29)	5.30 (0.34, 11.5)
Cervix uteri[a]	90	0.17	1.43 (0.93, 2.30)	0.26 (−0.04, 0.70)	10.0 (−1.68, 26.9)
Ovary[a]	82	0.03	1.81 (1.16, 2.89)	0.45 (0.10, 0.90)	18.7 (3.97, 37.7)
Prostate[a]	52	0.85	1.05 (, 1.73)	0.03 (, 0.40)	1.89 (, 24.8)
Urinary tract	133	0.000	2.02 (1.45, 2.87)	0.55 (0.26, 0.89)	22.7 (10.8, 37.1)
Malignant lymphoma	110	0.81	0.95 (, 1.40)	−0.02 (, 0.18)	−1.75 (, 13.6)
Multiple myeloma	36	0.002	2.86 (1.55, 5.41)	0.21 (0.07, 0.39)	32.5 (11.3, 59.5)
Other	907	0.03	1.20 (1.05, 1.38)	0.77 (0.19, 1.44)	5.65 (1.37, 10.5)
Liver, including not specified as primary	590	0.02	1.24 (1.06, 1.47)	0.63 (0.17, 1.18)	7.02 (1.87, 13.2)
Kidney	38	0.18	1.58 (0.91, 2.94)	0.09 (−0.02, 0.26)	15.7 (−2.77, 43.3)
Urinary bladder	90	0.003	2.13 (1.40, 3.28)	0.41 (0.16, 0.70)	23.6 (9.31, 40.8)
Brain tumors	47	0.97	1.03 (0.51, 2.09)	0.01 (−0.12, 0.20)	1.0 (−13.0, 22.5)
Tumors of central nervous system (CNS) except brain	14	0.08	3.09 (1.06, 9.74)	0.10 (0.00, 0.24)	35.9 (1.4, 82.2)

( ), 90% confidence interval.

[a] Risk estimation for these sites is based on either males or females only.

[b] P-value based on the test for increasing trend in radiation dose.

[c] Based on 41,791 subjects exposed to 0.01+ Gy (average 0.295 Gy).

(From ref. 6)

tumors, vary considerably by site (Table 3, Figure 3). A significant increase is evident for leukemia, for cancers of the lung, breast, stomach, colon, esophagus, urinary tract, and ovary, and for multiple myeloma. No increase is yet evident for mortality from cancer of the pancreas, rectum, uterus, prostate, or malignant lymphoma. Other studies on the same fixed population have shown no increase in chronic lymphatic leukemia[11], liver cancer[12], intracranial tumors[13] or osteosarcoma[14].

For multiple myeloma a detailed incidence study based on the leukemia registry revealed that the excess risk becomes apparent in the high dose range about 20 years after exposure, which is considerably longer than that of leukemia[15].

Since the risk can be expected to increase in the future as the cohort ages, careful follow-up will be necessary before any conclusion regarding differences in the risk of carcinogenesis by site can be drawn.

3. Temporal Patterns and Latent Period of Radiation Induced Cancer

In man, cancers do not appear immediately after exposure to ionizing radiation, but only after some latent period. Since the A-bomb survivors were exposed to relatively large amounts of radiation almost instantly, they should provide an exceptional cohort in which to investigate the temporal patterns of appearance of radiation induced cancer, when compared with occupational groups (exposed to radiation continuously, but usually to rather small doses) or patients exposed to diagnostic or therapeutic, often fractionated radiation.

The temporal pattern does differ between leukemia and other solid tumors. An increase in leukemia incidence began to appear in both cities about 3 years after exposure to the A-bombs and reached a peak around 1951–1952[16]. Since then, the leukemia rates in the exposed persons have declined steadily. The rate in the Nagasaki exposed survivors has not exceeded that of the control population since the early 1970s, but in Hiroshima there is still evidence of the continuation of a slightly higher leukemia rate in the exposed even in the most recent period of observation from 1981 to 1985[6].

It has been repeatedly noted that the younger the age at the time of bombing (ATB), the greater was the risk of leukemia during the early period, and the more rapid was the decline thereafter. Moreover, the length of the latency period seems to decrease with dose[16].

Malignancies other than leukemia, such as cancers of the lung, stomach, and other organs, exhibit a different latency pattern over time. Radiation-induced cancers begin to appear after the age is attained at which the cancer is normally prone to develop (the so-called "cancer age"). Even for those individuals who had already reached the cancer age ATB, the shortest latency period is 10–15 years with no evident shortening of the latency period in the high-dose group.

For leukemia, the first and second mutational steps necessary for radiation to cause transformation in cells may occur simultaneously or very nearly so. Therefore, the greater the exposure dose, the earlier was the development of leukemia irrespective of age ATB. For solid tumors, such as lung cancer, however, probably only the first mutational step is the result of exposure to radiation and the second and possibly another step occurs only when some other factor acts as a promoter. Cell transformation and proliferation then occur, leading to the development of cancer. In this case, the time when the promoter acts to initiate the second step

may be unrelated to the radiation dose, the initiator of the process. Hence, the latent period is unrelated to radiation dose, and cancer develops only when the age at which it is normally prone to develop is attained. Thus, the two different latency patterns can be explained by a two-(multi-) step mutational theory[17,18].

At least one animal experiment has been designed to test this thesis directly[19,20]. These experimental findings indicate that radiation acts as the initiator and prolactin as the promoter in the induction of breast cancer in the rat. The results of the present analysis of the epidemiological survey generally support this interpretation.

There are two different models (relative risk and absolute risk models) that have been employed to project the risk of death due to radiation-induced solid cancer during life[21]. The absolute risk model assumes that the excess deaths are constant by age at death throughout one's life, while the relative risk model assumes that the relative risk is constant by age at death throughout life, though excess deaths increase with age at death in proportion to age-specific mortality rates of the control group.

Table 4. Relative risk at 1 Gy and absolute risk (Excess death per 10^4 PYGy) by age ATB and age at death for all cancer except leukemia, 1950-85

A: Relative risk (at 1 Gy)

Age ATB	Age at death						
	<20	20–29	30–39	40–49	50–59	60–69	70+
<10	70.07	5.89	1.96	1.86			
10–19		0.82	1.66	1.59	1.68		
20–29			1.38	2.09	1.74	1.37	
30–39				1.12	1.11	1.23	1.48
40–49					1.12	1.13	1.33
50+						0.95	1.15

B: Absolute risk (excess deaths per 10^1 PYGy)

Age ATB	Age at death						
	<20	20–29	30–39	40–49	50–59	60–69	70+
<10	0.43	1.32	2.85	5.16			
10–19		−0.12	2.00	5.84	13.91		
20–29			1.39	9.40	15.71	14.33	
30–39				1.33	3.16	11.00	41.01
40–49					3.37	7.31	37.30
50+						−2.88	17.21

(From ref. 6)

The absolute risk (excess deaths per 10,000 person-years-gray) and relative risk at 1 gray of "all cancers except leukemia" were observed and classified by seven decades of age at death for six specific age ATB cohorts for the period 1950–1985 (Table 4)[6]. The excess deaths increase with age at death for the same age ATB cohort in proportion to the age-specific death rate from cancer in the control population, whereas the relative risk at 1 gray shows a constant value by age at death for the same age ATB cohort in general. Thus, the present data more strongly support the relative risk model projection.

4. Effects of age ATB and sex

It should be noted that the relative risk of the cohort of the youngest age, i.e. under age 10 ATB, was extremely high at the youngest attained ages, i.e. under 30 years of age as compared with later attained ages (Table 4). This may imply that the latent period of solid cancer induction was shortened in this youngest ATB cohort. To demonstrate this, cumulative mortality rates were calculated using life table methods for the 1.00+ Gy gorup, the 0.50–0.99 Gy group, and the 0–0.09 Gy group (as a comparison) and the results contrasted (Figure 4). In the 1.00+ Gy dose group, the cumulative cancer death rate over the entire study period is four times higher than the rate in the 0–0.09/0.99 Gy group. Moreover, cancers develop earlier than in the 0–0.09/0.99 Gy group. The 0.50–0.99 Gy group exhibits an intermediate pattern. Though the number of

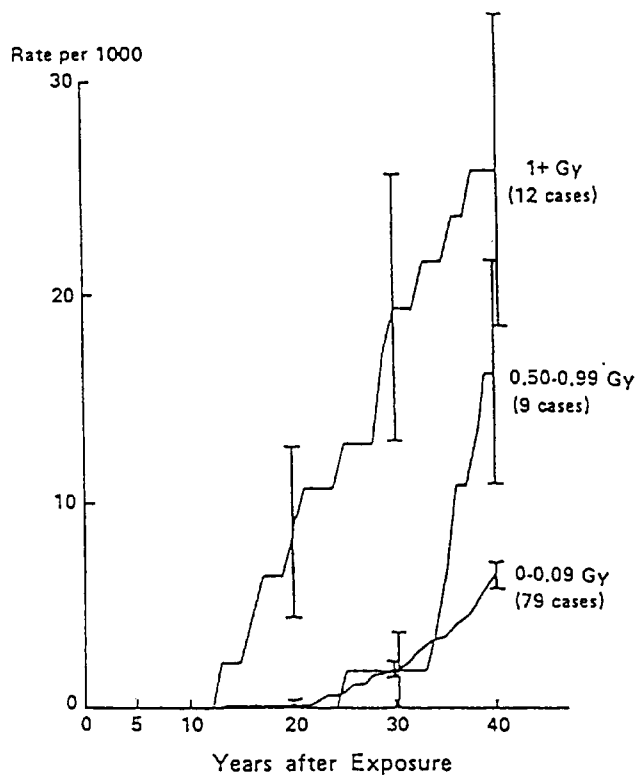


Fig. 4. Cumulative mortality rate from all cancers except leukemia and 90% confidence interval by time since exposure and radiation dose (Shielded kerma) – those exposed under age 10 –
(From ref. 6)

cancer deaths is small, the distribution by site in the high dose group is not conspicuously different from that in the general population. For age-at-death specific groups, the relative risk as well as absolute risk for all cancers except leukemia is high the younger the age ATB (Table 4). The same tendency is also observed for other sites of solid tumors, such as cancers of the lung, breast and stomach.

The risk of cancer induction does not differ by sex in general, but does differ for some sites of cancer. The relative risk of cancer of the thyroid and lung is higher for women than men. For lung cancer, since their absolute risks do not differ, the lower relative risk for males is probably a reflection of their higher background lung cancer mortality rate. The recent mortality analysis discloses the difference in relative risk of lung cancer by sex to be smaller and no longer significant statistically when differences in smoking habits are taken into account[6].

5. Relationship between Radiation and Other Carcinogenic Factors

Both cohort[6,22] and case-control[23] studies suggest that atomic radiation and smoking combine in an additive manner to increase lung cancer risk. This is in contrast to the multiplicative synergism between alpha-radiation from radon and smoking reported among uranium miners[24], though another study indicates no interaction between radon and smoking in lung cancer induction[25].

Table 5. Lifetime Excess Death from Leukemia and All Cancer except Leukemia per Million Persons Following a Single Exposure to 0.1 sv. (based on the risk coefficients under 2Gy organ absorbed dose)

	L		LQ	
	M	F	M	F
Leukemia				
A: Present Study	1193 (1326)	865 (844)	831	609
B; BEIR III	566	384	274	186
A/B	2.1	2.3	3.0	3.3
All cancer except leukemia				
A: Present Study	12865 (8782)	11090 (10756)	11521	10096
B: BEIR III	4226	4852	1917	2133
A/B	3.0	2.3	6.0	4.7

( ): estimates based on 0–6 Gy dose range
(From ref. 6)

In this connection, the attributable risks of radiation in cancer mortality during 1950–1985 among those exposed to 1 rad and over (average exposure dose was 29.5 rad)[6] were 56.6%, 8.04%, 6.41%, 11.6%, and 22.4% for leukemia, all cancers except leukemia, and cancers of the stomach, lung, and breast (Table 3).

6. The lifetime risk of cancer following exposure to ionizing radiation

Although a variety of national and international agencies, such as UNSCEAR[26] and BEIR V[27], have already evaluated the lifetime risk of mortality using the newer risk coefficients derived from the LSS study, Table 5 shows our lifetime risk estimates. We have followed the method employed in BEIR III[21] to compare our projections with theirs, using the stationary population represented in the 1985 Japanese Life Table. We assume an exposure to a single dose of 0.1 Sv of low-LET radiation and an RBE of 10. Incompleteness of diagnosis on death certificates is also taken into account. We have employed the additive (or constant absolute) risk projection model for leukemia, and the multiplicative (or constant relative) risk projection model for all cancers except leukemia. We have calculated lifetime risk estimates using both a linear (L) and a linear-quadratic (LQ) dose-response model, since both fit the available data. This has been done using coefficients based on only those survivors with doses under 2 Gy.

The lifetime risk of leukemia, or of all cancers except leukemia, based on a linear dose-response model, is close to UNSCEAR values and about two times higher than the BEIR III value. Under the LQ model, the estimate for leukemia is only 70 percent of the value obtained using the L model. For all cancers except leukemia, the LQ estimates are slightly smaller but almost equal to the estimates based on the linear model. The ratio of the present estimates to th BEIR III estimates under the LQ model is much larger than the ratio of the two estimates under the L model.

7. Cancer mortality for early entrants

As described in detail elsewhere, numerous individuals included in the not-in-city group of the LSS sample entered Hiroshima or Nagasaki soon after the bomb for relief or other activities. If early entrants are defined as individuals who entered the city within one month after the bomb, 4,512 (3,698 in Hiroshima and 814 in Nagasaki) are included in the sample. These early entrants can be divided into three groups, a, b, and c, graded with respect to their estimated induced radiation dose, based on date and place of entry (Table 6). The cancer mortality of these groups during the period 1950–78 was compared with the not-in-city group exclusive of the early entrants (22,006 late entrants and the 31,581 subjects in the 0 Gy (T65DR was used) group)[28].

Six deaths due to leukemia (4 in Hiroshima and 2 in Nagasaki) were recorded among early entrants during the entire survey period (Table 6). Leukemia mortality in this group, however, was lower than in the 0 Gy group, but the difference is not statistically significant. Leukemia did not develop among the early entrants during the period 1950–58 when it was frequently occurring in the exposed groups, but developed later.

For all cancer except leukemia, mortality for the early entrants is lower than for the 0 Gy group, and no significant difference is observed between early and late entrants, although the latter are closer to the 0 Gy group. Neither is there evident any difference in mortality between the three groups of early entrants (Table 6). By cancer site, mortality for early entrants for stomach,

Table 6. Observed and expected deaths from leukemia and all cancer except leukemia among early entrants, late entrants, and exposed (0 Gray)

Cancer site	Year	Statistic	Exposed (0 Gy)	Early entrants	Late entrants	Text[a] 1	Text[a] 2
Leukemia	1950–78	0	40	6	11	*	*
		O/E	1.323	1.134	0.512		
All except leukemia	1950–78	0	1,654	276	1,041	*	NS
		O/E	1.025	0.900	0.992		

[a] Two tail test: 1, Exposed (0 Gy) vs. total not-in-city (EE + LE); 2, Early entrants (EE) vs. late entrants (LE).
* Significant at 5% level.
NS, Not significant ($p > 0.10$).
(From ref. 28)

lung, and breast cancer is not significantly different from that for late entrants and the 0 Gy group.

It is difficult to estimate precisely the dose of induced radiation received by early entrants. The mean cumulative dose from the bomb to infinite time is estimated to be no more than 0.02–0.03 Gy in Hiroshima and considered to be less than 1 rad and negligible in Nagasaki[29]. Thus, in view of the magnitude of the exposure dose, and the fact that the irradiation of early entrants was chronic and not acute as in exposure to A-bomb radiation, a remarkable increase in radiation-induced cancer seems highly unlikely as contrasted with directly exposed individuals.

There is one report which suggest an increase in the incidence of leukemia among early entrants[30]. However, there are some uncertainties: 1) the data are based on A-bomb handbook holders who are given free medical care and so will be biased towards inclusion of more leukemia cases; and 2) the population at risk was estimated based on three cross-sectional surveys conducted from 1950–74 and migration was not take into account.

It was recently reported that mortality from leukemia and other cancers was increased among early entrants during 1968–72 based on an analysis of a sample of A-bomb handbook holders in Hiroshima prefecture[31]. As this study is based on A-bomb handbook holders, it should also be affected by similar uncertainties due to the possible bias mentioned above. On the other hand, the RERF LSS data are based on a well-defined sample, but the number of early entrants in the sample is small. Further long-term follow-up is necessary.

B. NON-CANCER MORTALITY

It is important to examine the hypothesis that radiation shortens life through an increase in a variety of causes of death other than cancer. The most recent published report for non cancer mortality among A-bomb survivors is the LSS report for the mortality during the period

Table 7. Cumulative probability of noncancer death (1950–78) by dose, city, sex, and age ATB

	T65 Kerma dose in Gy								Trend statistics for increasing dose-response(Z)*
	0	0.01–0.09	0.10–0.49	0.50–0.99	1.00–1.99	2.00–2.99	3.00–3.99	4.00+	
Total	0.257	0.253	0.252	0.257	0.248	0.258	0.278	0.278A	0.58
Sex: Male	0.314	0.313	0.300	0.306	0.297	0.312	0.360	0.341	−0.33
Female	0.217	0.210	0.217	0.222	0.213	0.219	0.220	0.234A	1.29
Age ATB <10	0.027	0.028	0.026	0.030	0.021	0.043	0.033	0.014	0.29
10–19	0.064	0.058	0.053	0.053	0.067	0.055	0.056	0.089	0.74
20–34	0.101	0.095	0.092	0.114	0.085	0.076	0.092	0.113	−0.28
35–49	0.336	0.333	0.339	0.342	0.322	0.372	0.420A	0.403A	1.72
50+	0.868	0.858	0.853	0.851	0.853	0.840	0.889	0.867	−0.93

Difference in cumulative mortality between 0 Gy group and corresponding dose group is statistically significant (one tailed) at level of A($P<.05$), B($P<.01$), C($P<.001$).

*: Normal deviate
(From ref. 28)

1950–78 based on the T65 dosimetry[28]. Typical results are shown in Tables 7 and 8.

Table 7 shows the cumulative mortality from all causes other than cancer for the 8 exposure groups by sex and age ATB categories. The mortality from all causes of death except cancer, corrected for the competing risks of cancer, indicate little or no relationship between mortality from non-cancer causes and radiation exposure. Only the trend statistic for the 35–49 age ATB group is significant ($P = .043$). These results are consistent with the hypothesis of equal mortalities among the exposure groups. The only evidence of a radiation-related effect on mortality from causes other than cancer comes from the highest exposure group. 4+ Gy. When compared with the 0 Gy group, this exposure category is significantly elevated ($P<.05$) for the entire cohort as well as for female and 35–49 age ATB group.

Table 8 shows the dose-response relationship of mortality for the major causes of death selected for this analysis. There is no cause of death suggestive of a relationship with radiation, except diseases of the blood and the blood-forming organs (ICD 280–289). The accuracy of causes of deaths classified as "diseases of blood and blood-forming organs" is very low, and such deaths often include leukemia and malignant lymphoma. When the misdiagnosed cases were excluded from the high dose groups, in the earlier analysis, the spurious effect disappeared. Accordingly, the dose-response relationships for "all diseases except neoplasms and blood disease" were reviewed further by city and sex, but no significant relationship emerged. This was also true for the other specified (non-cancer) causes of death chosen for analysis. The excess deaths per 10^4 person-year per gray (PYGy) and the 90% confidence intervals are shown in Table 8 for selected major causes of death. There are no significant excess deaths from disease, except those of the blood and blood-forming organs about which we have already remarked.

Table 8. Observed Number of Deaths and Ratio of Observed to Expected Deaths by Dose, and Excess Deaths per 10^4PYGy for Major Causes of Death, 1950-78

Cause of death		T65 Kerma dose in Gray									Test (P-value)*		Excess death 10^4PYGy (90% confidence interval)
		Total	0	0.01–0.09	0.10–0.49	0.50–0.99	1.00–1.99	2.00–2.99	3.00–3.99	4.00+	Homo	Trend	
All diseases except neoplasms	Obs.	17149	6963	4842	3279	918	601	243	126	177	.28	.42	.17 (−1.19, 1.54)
	O/E		1.01	1.00	.99	.96	.96	.94	1.08	1.11			
Tuberculosis	Obs.	1140	403	344	242	58	52	11	14	16	.03	.53	−.02 (−.42, .38)
	O/E		.94	1.03	1.14	.88	1.00	.48	1.38	1.15			
Vascular lesions of CNS	Obs.	5108	2066	1443	985	270	187	74	40	43	.91	.62	−.14 (−.89, .61)
	O/E		1.01	1.01	.99	.94	1.01	.98	1.17	.92			
Diseases of circulatory system except CNS	Obs.	3724	1518	1013	721	234	126	51	29	32	.43	.44	.06 (−.58, .69)
	O/E		1.01	.96	.99	1.14	.95	.94	1.19	.96			
Diseases of blood and blood-forming organs	Obs.	132	38	32	29	10	7	7	3	6	.00	.00	.46 (.34, .59)
	O/E		.72	.87	1.14	1.33	1.38	3.25	2.08	4.74			
Diseases of digestive system	Obs.	1822	751	498	350	88	70	32	9	24	.43	.18	.26 (−.20, .71)
	O/E		1.03	.96	1.00	.88	1.04	1.16	.72	1.37			
Diseases not specified above	Obs.	5223	2187	1512	952	258	159	68	31	56	.01	.82	−.42 (−1.17, .32)
	O/E		1.04	1.02	.94	.89	.86	.89	.90	1.21			
Infectious disease	Obs.	227	103	68	39	12	0	4	0	1	.05	.99	
	O/E		1.16	1.03	.89	.95	0	1.12	0	.44			
Respiratory disease	Obs.	1489	573	471	267	72	58	20	11	17	.12	.38	
	O/E		.96	1.12	.93	.86	1.06	.89	1.08	1.21			
Urinary tract	Obs.	458	211	110	83	25	13	7	2	7	.24	.34	
	O/E		1.13	.86	.94	1.00	.81	1.04	.65	1.70			
All disease except neoplasm and blood disease	Obs.	17017	6925	4810	3250	908	594	236	123	171	.23	.64	−.29 (−1.65, 1.07)
	O/E		1.02	1.00	.99	.96	.96	.92	1.06	1.08			

* Homo: Homogeneity of 8 dose groups regardless of pattern.
Trend: Linear increase with dose (one tailed)
(From ref. 28)

Thus, no increase in cause-specific mortality from causes other than cancer was seen among A-bomb survivors in the period 5–33 years after the bomb. Until more evidence is in, however, especially, for those exposed at younger ages, the results mentioned above cannot be regarded as disproving the hypothesis of lifeshortening through an increase in non-cancer death. Moreover, since the initial mechanisms in the induction of arteriosclerosis[32] (more generally many chronic disease[33]) and cancer may be similar, it is possible that an effect of ionizing radiation on non-cancer death will still emerge. Incidentally, preliminary results from the study of non-cancer mortality during the period 1950–85 with the new dosimetry are as follows[34]. Although the evidence is still limited, there seems to be an indication of an excess risk from non-cancer death at high doses (2 or 3 Gy and over), particularly for younger age ATB in the recent period. However, we must await further follow-up to reach a definite conclusion, since many members of the younger age ATB group have not yet entered those ages at which mortality normally increases appreciably. Therefore, it is important to continue periodic re-testing of the hypothesis of an increase of non-cancer mortality.

Other studies with which these findings can be compared are few. However, the follow-up study of ankylosing spondylitis patients who received radiation therapy[35], suggests that there was a 51% increase in deaths from diseases other than neoplasm. The high mortality is not confined to those diseases that have been recognized clinically to be associated with spondylitis, but was observed also for all other groups of disease, though to a lesser extent. The report[35], however, concluded the excess was likely to be associated with the disease itself rather than X-ray treatment. Because a similar excess has also been observed in unirradiated patients[36]. Among U.S. radiologists[37], a higher mortality has been reported not only from cancer, but also from cardiovascular diseases and from other nonneoplastic diseases when compared with other medical specialists. However, among British radiologists[38], an increase in mortality from non-cancer causes was not observed.

REFERENCES

1. Beebe, G.W., Kato, H. and Land, C.E. (1978) Studies of the mortality of A-bomb survivors, 6. Mortality and radiation dose, 1950-74. Radiat. Res. **75:** 138-201.
2. Beebe, G.W. and Usagawa, M. (1968) The Major ABCC Samples. ABCC TR 12-68.
3. Wakabayashi, T., Kato, H., Ikeda, T. and Schull, W.J. (1983) Studies of the mortality of A-bomb survivors, 7: Part 3. Incidence of cancer in 1959-1978, based on the tumor registry, Nagasaki. Radiat. Res. **93:** 112-146.
4. Roesch, W.C. (Ed.) (1987) Final Report of U.S.-Japan Reassessment of Atomic Bomb Radiation Dosimetry in Hiroshima and Nagasaki. Radiation Effects Research Foundation, Hiroshima.
5. Shimizu, Y., Kato, H., Schull, W.J., Preston, D.L., Fujita, S. and Pierce, D.A. (1989) Studies of the mortality of A-Bomb survivors, 9. Mortality, 1950-85: Part 1. Comparison of risk coefficients for site specific cancer mortality based on the DS86 and T65DR shielded kerma and organ doses. Radiat. Res. **118:** 502-524.
6. Shimizu, Y., Kato, H. and Schull, W.J. (1990) Studies of the mortality of A-bomb survivors, 9. Mortality, 1950-1985: Part 2. Cancer mortality based on the recently revised doses (DS86). Radiat. Res. **121:** 12-141.
7. Milton, R.C. and Shohoji, T. (1968) Tentative 1965 Radiation Dose Estimation for Atomic Bomb Survivors, Hiroshima and Nagasaki. ABCC TR 1-68.
8. Preston, D.L. and Pierce, D.A. (1988) The effect of changes in dosimetry on cancer mortality risk estimates

in the atomic bomb survivors. Radiat. Res. **114:** 437-466.
9. Preston, D.L., Kato, H., Kopecky, K.J. and Fujita, S. (1987) Studies of the mortality of A-bomb survivors, 8. Cancer mortality, 1950-1982. Radiat. Res. **111:** 151-178.
10. Yamamoto, T., Moriyama, I.M., Asano, M. and Guralnick, L. (1978) Radiation Effects Research Foundation Pathology studies, Hiroshima and Nagasaki 4. The Autopsy program and the Life span study, January 1961-December 1975. RERF TR 18-78.
11. Ichimaru, M. and Ishimaru, T. (1975) Review of thirty years study of Hiroshima and Nagasaki atomic bomb survivors, 2. Biological effects. D. Leukemia and related disorders. J. Radiat. Res. (Suppl.) **16:** 89-96.
12. Asano, M., Kato, H., Yoshimoto, Y., Seyama, S., Itakura, H., Hamada, T. and Iijima, S. (1982) Primary liver carcinoma and liver cirrhosis in atomic bomb survivors, Hiroshima and Nagasaki, 1961-75, with special reference to hepatitis B surface antigen. J. Natl. Cancer Inst. **69:** 1221-1227.
13. Pinkston, J.A., Wakabayashi, T., Yamamoto, T., Asano, M., Harada, Y., Kumagami, H. and Takeuchi, M. (1981) Cancer of the head and neck in atomic bomb survivors. Hiroshima and Nagasaki, 1957-76. Cancer **48:** 2172-2178.
14. Yamamoto, T. and Wakabayashi, T. (1969) Bone tumors among the atomic bomb survivors of Hiroshima and Nagasaki. Acta Pathologica Japonica **19:** 201-202.
15. Ichimaru, M., Ishimaru, T., Mikami, M. and Matsunaga, M. (1982) Multiple myeloma among atomic bomb survivors in Hiroshima and Nagasaki, 1950-76: Relationship to radiation dose absorbed by marrow. JNCI **69:** 323-328.
16. Ichimaru, M., Ishimaru, T. and Belsky, J.L. (1978) Incidence of leukemia in atomic bomb survivors, Hiroshima and Nagasaki 1959-71 by radiation dose, years after exposure, age and type of leukemia. J. Radiat. Res. **19:** 262-282.
17. Kato, H. and Schull. W.J. (1982) Studies of the mortality of A-bomb survivors, 7. Mortality 1950-78: Part 1. Cancer mortality. Radiat. Res. **90:** 395-432.
18. Land, C.E. and Norman, J.E. (1978) Latent periods of radiogenic cancers occurring among Japanese A-bomb survivors. In: Late Biological Effects of Ionizing Radiation. International Atomic Energy Agency, Vienna, (ST1/PUB/489) vol. 1: 29-47.
19. Yokoro, K., Nakano, M., Ito, A., Nagano, K., Kodama, Y. and Hamada, K. (1977) Role of prolactin in rat mammary carcinogenesis: Detection of carcinogenicity of low-dose carcinogens and persisting dormant cancer cell. J. Natl. Cancer Inst. **58:** 1777-1783.
20. Kamiya, K., Inoh, A., Fujii, Y., Kanda, K., Kobayashi, T. and Yokoro, Y. (1985) High mammary carcinogenicity of neutron irradiation in rats and its promotion by prolactin. Jpn. J. Cancer Res. (Gann) **65:** 449-456.
21. National Research Council, Committee on the Biological Effects of Ionizing Radiation. Effects on Populations of Exposure to Low Levels of Ionizing Radiation (BEIR-III). (1980) National Academy of Sciences – National Research Council, National Academy Press, Washington, DC.
22. Kopecky, K.J., Nakashima, E., Yamamoto, T. and Kato, H. (1986) Lung cancer, radiation and smoking among A-bomb survivors. RER TR 13-86.
23. Blot, W.J., Akiba, S. and Kato, H. (1984) Ionizing radiation and lung cancer: A review including preliminary results from a case-control study among A-bomb survivors. In: R.L. Prentice and D.J. Thompson (eds.), Atomic Bomb Survivor Data: Utilization and Analysis. SIAM. Philadelphia.
24. Whittemore, A.S. and McMillan, A. (1983) Lung cancer mortality among US uranium miners: A reappraisal. J. Natl. Cancer Inst. **71:** 489-499.
25. Radford, E.P. (1984) Radiogenic cancer in underground miner. In: J. Boice and J. Fraumeni (eds.), Radiation Carcinogenesis: Epidemiology and Biological significance. Raven Press, New York: 225-230.
26. United Nations Scientific Committee on the Effects of Atomic Radiation (Annex G): Radiation carcinogenesis in man, 7. Risk projections. (1988) United Nations, New York.
27. National Research Council, Committee on the Biological Effects of Ionizing Radiation. Health Effects of Exposure to Low Levels of Ionizing Radiation (BEIR-V). (1990) National Academy of Sciences – National

Research Council, National Academy Press, Washington, DC.
28. Kato, H., Brown, C.C., Hoel, D.G. and Schull, W.J. (1982) Studies of the mortality of A-bomb survivors, 7. Mortality, 1950-1978: Part 2. Mortality from causes other than cancer and mortality in early entrants. Radiat. Res. **91:** 243-264.
29. Hashizume, T., Maruyama, T., Kumamoto, Y., Kato, Y. and Kawamura, S. (1969) Estimation of gamma-ray dose from neutron induced radioactivity in Hiroshima and Nagasaki. Health Phys. **17:** 761-771.
30. Hirose, F. (1968) Leukemia in atomic bomb survivors Hiroshima, 1946-1967. Acta Haematol. Jpn. **31:** 765-771.
31. Kurihara, M., Munaka, M., Hayakawa, N., Yamamoto, H., Uèoka, H. and Ohtaki, M. (1981) Mortality statistics among atomic bomb survivors in Hiroshima Prefecture, 1968-1972. J. Radiat. Res. **22:** 456-471.
32. Benditt, E.P. (1977) The origin of atherosclerosis. Sci. Am. **236:** 75-85.
33. Trosko, J.E. and Chang, C.C. (1980) An integrative hypothesis linking cancer, diabetes and atherosclerosis: The role of mutations and epigenetic changes. Med. Hypotheses **6:** 455-468.
34. Shimizu, Y., Kato, H., Schull, W.J. and Hoel, D.G. Life Span Study Report 11, Part 3. Non-cancer mortality in the years 1950-85 based on the recently revised doses (DS86). In preparation.
35. Darby, S.C., Doll, R., Gill, S.K. and Smith, P.G. (1987) Long term mortality after a single treatment course with x-rays in patients treated for ankylosing spondylitis. Br. J. Cancer **55:** 179-190.
36. Radford, E.P., Doll, R. and Smith, P.G. (1977) Mortality among patients with ankylosing spondylitis not given X-ray therapy. New Engl. J. Med. **297:** 572-576.
37. Court Brown, W.M. and Doll, R. (1958) Expectation of life and mortality from cancer among British radiologists. Brit. Med. J. **2:** 181-187.
38. Matanoski, G.M., Seltser, R., Sartwell, P.E., Diamond, E.L. and Elliott, E.A. (1975) The current mortality rates of radiologists and other physician specialists: Specific causes of death. Am. J. Epidemiol. **101:** 199-210.