Out of the Ashes and into the Cancer Age:

Radiation-Induced Leukemia and Other Cancers in Atomic Bomb Survivors

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1 — The Atomic Bomb

Every morning at 8:15 AM, a clock in Hiroshima's Peace Memorial Park sounds as a reminder to new generations of citizens; it was at that time on August 6, 1945 that the world was thrust into the atomic age and the lives of thousands of people changed forever when the United States Air Force detonated an atomic bomb 580 meters above the city of Hiroshima, Japan. Testimonials from survivors have described the ensuing chaos vividly, including the strong, blinding light and the mushroom cloud that covered the city. At the time of the bombing, the city of Hiroshima hosted a population of approximately 300 000 individuals of whom 80 000 to 120 000 were killed instantly or within weeks; such was the destruction of the world's first atomic bomb, "Little Boy." Three days later, on August 9, 1945, a second atomic bomb was dropped on Nagasaki claiming the lives of approximately 80 000 people from a population of 250 000. The consequences of these two bombs were far-reaching and would be felt by the survivors for years to come.

The enormous energy generated by the atomic bomb was released as blast, heat and radiation. The blast and heat affected a radius of four to five kilometres from the hypocenter and accounted for approximately eighty-five percent of the energy released by the fission reaction of the atomic bomb[1]. In contrast, radiation expanded over a smaller radius of about two and a half kilometres from the hypocenter and three kilometres from the hypocenter in Hiroshima and Nagasaki, respectively[1]. The Radiation Effects Research Foundation (RERF), stationed in both Hiroshima and Nagasaki, has invested a great deal of effort in establishing estimated doses of radiation. This is because radiation doses received by survivors differed depending on a variety of factors such as shielding by buildings, and distance from the hypocenter. The magnitude of such

a small fraction of radiation from the atomic bomb that was deposited in the ground was greatly felt by the survivors.

2 — Radiation

Radiation can be classified as ionizing or non-ionizing radiation. Briefly, ionizing radiation is the type of electromagnetic wave that can "ionize" an atom or molecule by removing an electron from that atom. Gamma rays, ultraviolet (UV) light and X-rays are examples of ionizing radiation, as shown in Figure 1. Most of the radiation released by the fission reactions consisted of gamma rays and neutrons [1]. Gamma rays have the greatest energy of the electromagnetic waves as they have the shortest wavelength. This form of energy is highly penetrable and causes significant cellular damage that correlates with the extent of the radiation dose.

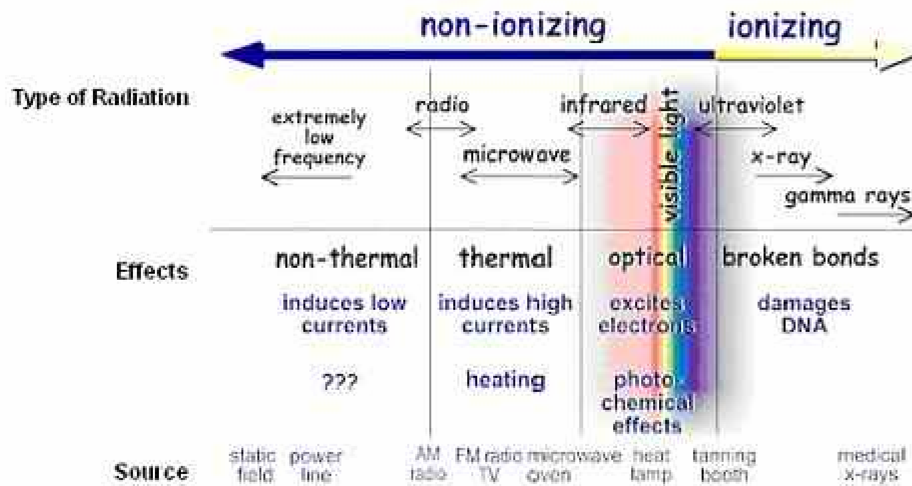

Figure 1 — Types of radiation in the electromagnetic spectrum.[2]

The basic measurement of absorbed dose of ionizing radiation is called the gray (Gy) and defines 1 J of initial energy per kg of tissue [3]. In order to adjust for the various forms of radiation and different tissue types exposed, another measurement was established to

quantify the effective dose, known as the Sievert (Sv). For example, 1 Gy of neutrons corresponds to approximately 10 Sv, whereas 1 Gy of gamma rays is equivalent to 1 Sv. The annual natural dose of ionizing radiation for all living organisms is 2.4 mSv. Cosmic and terrestrial gamma rays or ingestion of radioactive isotopes such as potassium-40 and radon can contribute to the natural radiation dose.[3] In addition to natural sources of radiation, humans are exposed to radiation from medical diagnostics, which accounts for approximately 0.4 mSv per year.[3] The dose received by the people of Hiroshima and Nagasaki ranged from low, moderate, and high, depending on the proximity to the hypocenter as seen in Figure 2.

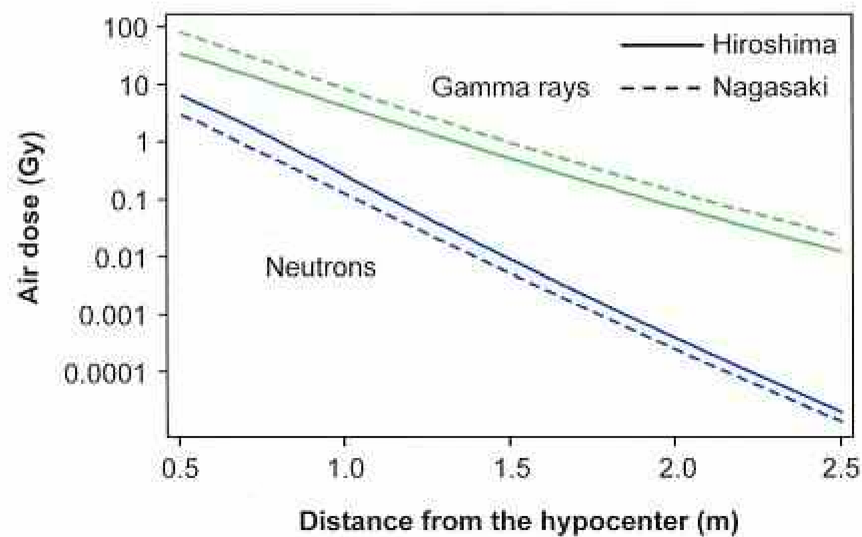

Figure 2 — Air dose of radiation decreases with increasing distance from the hypocenter.[1]

The biological effect on human health depends on the respective radiation dose received. For example, for an ionizing radiation dose of 8 Gy or more, the health consequences are lethal and one would have had to be roughly 800 metres from the hypocenter to receive such a dose.[1] A severe dose is considered to be between 3 and 5 Gy, which results in nausea and vomiting and ultimately loss of life within 60 days.[1] The individuals that

received a dose of 1 Gy or less have an increased risk of developing leukemia and other forms of cancer.

3 — Radiation and Cancer

Ionizing radiation affects cells in a detrimental way by damaging the DNA. For example, UV light causes lesions in the DNA such as pyrimidine dimers and 8-oxoguanine.[4] If these lesions are not repaired by the cell, a mutation can arise which can predispose the individual to developing cancer. Other factors influencing whether a cell becomes cancerous are proto-oncogenes and tumour suppressor proteins. Proto-oncogenes are genes that control cell proliferation and differentiation. Lesions in the DNA can promote abnormal gene expression, which can convert proto-oncogenes into oncogenes. Tumour suppressor proteins deactivate oncogenes, and mutations in a tumour suppressor gene may result in the inability to inactivate oncogenes. For example, mutations in the *p53* tumour suppressor gene have been linked to 50 % of cancers.[4]

Cancer affects every gender, age group, and race; it has in particular affected survivors of the atomic bomb. Individuals of both genders and of all ages were exposed to radiation in Hiroshima and Nagasaki, prompting the formation of a large-scale study aimed at investigating the incidence and mortality risks of radiation-induced cancers in atomic bomb survivors. The Life Span Study (LSS), as it became known, is a research program designed to investigate the effects of radiation on human health. Its main purpose is to determine the long-term effects of radiation, such as cancer risks in the survivors. The LSS cohort involves 120 321 individuals, of which 93 741 were in either Hiroshima or Nagasaki at the time of the bombings and the remaining 26 580 individuals are used as a

control population.[5] The participants of the LSS have been studied since 1950, and participate in epidemiological studies. The LSS uses medical records, histological and clinical diagnoses, tumour registries, questionnaires, autopsy records and death certificates to collect data for analysis.

4 — Radiation-Induced Leukemia

In the years following the atomic bombings, physicians were reporting an increased number of leukemia diagnoses. By the late 1940s and early 1950s, there was a clear suggestion of an increased risk of leukemia among survivors from Hiroshima and Nagasaki, prompting the establishment of a special Leukemia Registry to monitor instances of leukemia, lymphoma, multiple myeloma and other hematopoietic disorders.[5] The Leukemia Registry includes residents of Hiroshima, Nagasaki, and the surrounding areas, regardless of their involvement in the LSS. Today, leukemia is regarded as one of the most prevalent consequences of ionizing radiation from the atomic bombs and is sometimes referred to as the "atom bomb disease." This is largely due to the popularization of the story of Sadako Sasaki, a young girl that was exposed to radiation from the detonation of Little Boy at the age of only two years and later diagnosed with leukemia when she was eleven years old.

Sadako believed in an ancient Japanese legend, which says that anyone who folds one thousand origami paper cranes will be granted a wish.[6] In the hopes of overcoming leukemia, Sadako set out to complete the task required by the legend. Several versions of the story exist that relate to whether or not she successfully completed her task, but regardless of the details, sadly, the outcome is indisputable: she eventually succumbed to

leukemia on October 25, 1955, at the age of twelve. It is the story of Sadako that prompted the building of the Children's Peace Monument featuring her likeness as well as her paper cranes and helped to solidify leukemia as a likely consequence of the atomic bomb in the public consciousness.

Leukemia is a cancer of the blood and bone marrow that derives its name from characteristic abnormalities in the development and growth of white blood cells, or "leukocytes".[7] Although mortality from leukemia accounts for only a small percentage of the total number of cancer deaths in survivors from the LSS (approximately 3.2%), a large percentage of estimated excess deaths are attributed to leukemia (approximately 20.7%).[8] Excess deaths are thought to be a result of ionizing radiation from the atomic bombs, and are in excess of the expected number of cancer deaths normally present in a control population. Table 1 shows the incidences of deaths due to leukemia and solid cancers between 1950 and 1990 in participants of the LSS. The table indicates that higher doses of ionizing radiation correlate with an increase in estimated excess mortality in patients with either leukemia or solid cancers. However, the relative increase in cancer mortality is much greater in patients with leukemia than patients with solid cancers. Indeed, the relative risk of developing leukemia after exposure to the atomic bombs is much greater than any other cancer. The RERF has determined the average relative risk of death due to cancer at 1 Sv of exposure to ionizing radiation is 5.6 times the baseline risk, using data collected from 1950 to 1997 [1]. In comparison, the relative risk of developing all other cancers, excluding leukemia, is only 1.5 times the basal level.[1] The relative risk of death due to cancer is shown graphically in Figure 3.

Table 1 — Cancer mortality in survivors from the Life Span Study from 1950 to 1990.[8]

Age at time of bombing in 1945	No of people in LSS in 1950	Percentage surviving to 1991	Solid cancers		Leukemia	
			Observed deaths	Estimated excess	Observed deaths	Estimated excess
0–9	17,824	94	227	24	35	15
10–19	17,557	86	662	66	43	17
20–29	10,882	77	816	62	32	12
30–39	12,270	51	1688	78	50	20
40–49	13,489	16	2370	72	59	22
50+	14,550	1	1815	32	30	1
Total	86,572	56	7578	334	249	87

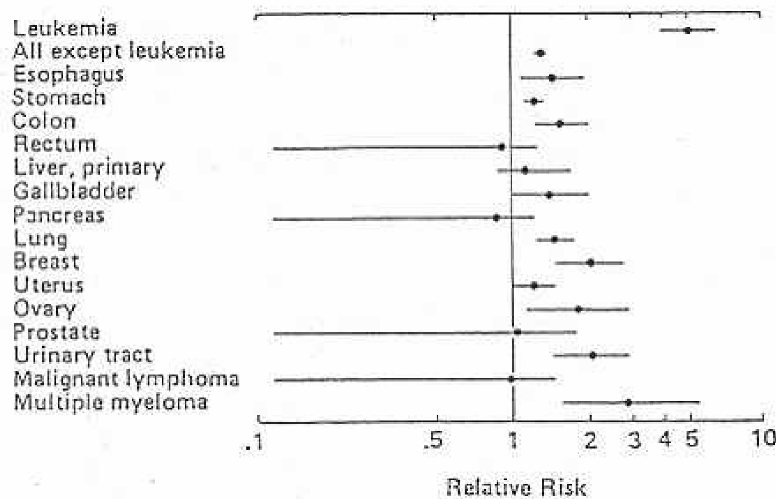

Figure 3 — Relative risk of mortality from various types of cancer at 1 Gy of exposure and 90% confidence intervals. Data collected from 1950 to 1985.[9]

Although initially, cases of leukemia in atomic bomb survivors were identified in a broader sense, a majority of cases have since been reclassified with modern diagnostic nomenclature to update patient information.[5] This reclassification has yielded new information on specific forms of leukemia. Namely, an increase in the relative risk for acute lymphocytic leukemia (ALL) and chronic myelocytic leukemia (CML) is observed in atomic bomb survivors compared to control populations.[5] Additionally, an increased risk of developing acute myelogenous leukemia (AML) has been identified, although the risk is less than that for ALL and CML. No evidence of an increased risk of developing

adult T-cell leukemia (ATL) or chronic lymphocytic leukemia (CLL) has been identified, suggesting that not all forms of leukemia develop similarly following radiation exposure.[5] This is consistent with the differences in relative risk of developing various forms of cancer, suggesting that sensitivity to ionizing radiation differs by site.

Aside from the increased relative risk of mortality, leukemia differs from other types of cancer in several respects. First, radiation-induced leukemia was observed only two to three years following the detonation of the atomic bombs, and incidences peaked within the first eight years.[9] Radiation-induced solid cancers began to appear only after the survivors reached the ages when such cancers typically developed naturally, suggesting a longer latency period than leukemia. The latency period in solid cancers is likely an effect of induction of only the first mutational step in the transformation of a normal cell to a tumour cell, and that a second mutation is required prior to tumour onset.[9]

Additionally, the overall trends in incidence differ between leukemia and solid tumour patients. Survivors that were younger at the time of bombing had a much greater risk of developing leukemia than older survivors, and that risk dissipated at a rapid rate. For example, individuals under thirty at the time of exposure had a much higher relative risk of developing leukemia within the first few years after the bombings, and no excess deaths from leukemia have been observed in that subpopulation after 1970.[9] Acute forms of leukemia, such as ALL and AML are largely responsible for the elevated risk of leukemia in younger survivors.[10] In contrast, older individuals at the time of bombing have a lower risk of developing leukemia, but that risk has not subsided significantly over

time.[9] No excess deaths due to leukemia were observed in individuals older than fifty at the time of the bombings after 1980; however, few of such individuals were remaining at that time, making discernible projections about the decline in risk after time difficult.[9] These differences in age and the rapid decline in relative risk of developing leukemia in younger individuals produce an overall relative risk trend that is in sharp contrast to the trend observed with most solid cancer patients when examined temporally. Figure 4 displays the estimated relative risk at 1 Gy of exposure for each five-year follow-up interval for leukemia as well as other cancers. It can be seen that as elapsed time increases, the overall relative risk of developing leukemia decreases, whereas the overall relative risk of developing other cancers increases. Similar trends for leukemia are also shown in Figure 5, where younger individuals have a higher relative risk than older survivors. Also, gender differences can be seen with respect to the onset of leukemia. Figure 5 shows the estimated excess relative risk for both male and female survivors in the years following the attacks. It can be seen that younger males had an increased relative risk of leukemia immediately after exposure compared to females.

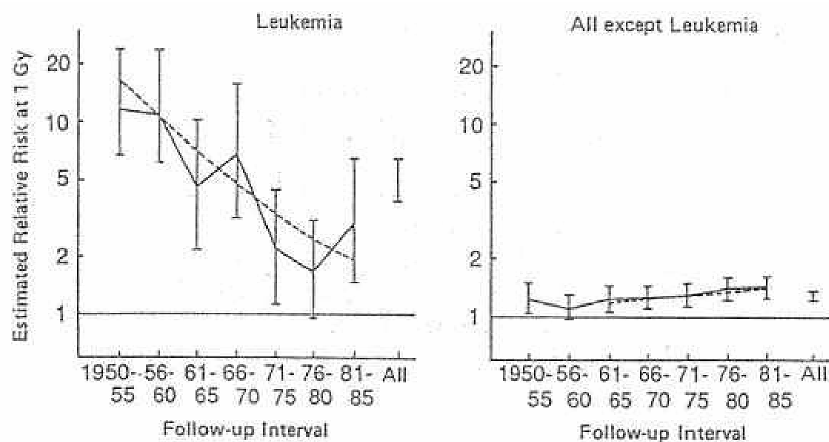

Figure 4 — Estimated relative risk at 1 Gy of death due to leukemia and other cancers in atomic bomb survivors for each five-year follow-up interval from 1950 to 1985. [9]

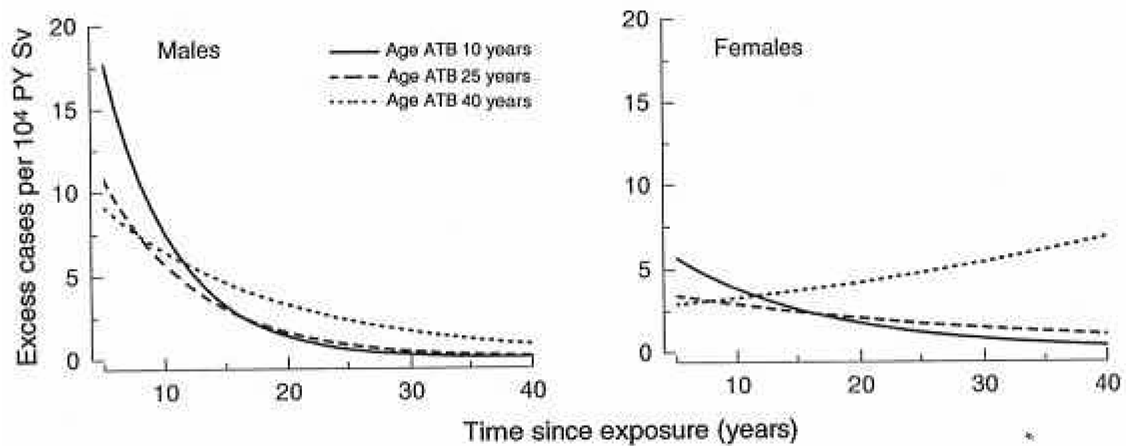

Figure 5 — Estimated risk of leukemia incidence in male and female atomic bomb survivors receiving 1 Sv of radiation. Populations are separated by age at time of bombing (ATB).[5]

The observed dose-response curves for mortality due to leukemia and all other cancers have been examined in an attempt to fit an accepted model with the data. Figure 6 shows the observed number of deaths due to cancer compared to dose for both leukemia and all other cancers, as well as the various models used to predict the observed outcome. It can be seen that with leukemia survivors that received doses less than 2 Gy, the observed data corresponds most closely to the linear-quadratic model, which is a model in which the mortality is linear-quadratic function of the dose. However, at doses higher than 2 Gy, the linear-quadratic model does not fit any better than the linear model unless a provision for a downward curvature at higher doses is considered.[9] In contrast, for all other cancers, non-linear models are not superior to the linear model, regardless of observed dose range.[9] Therefore, the estimated excess mortality due to leukemia shown in Table 1 has been calculated with the linear-quadratic model, whereas deaths due to solid cancers have been calculated using the linear model.

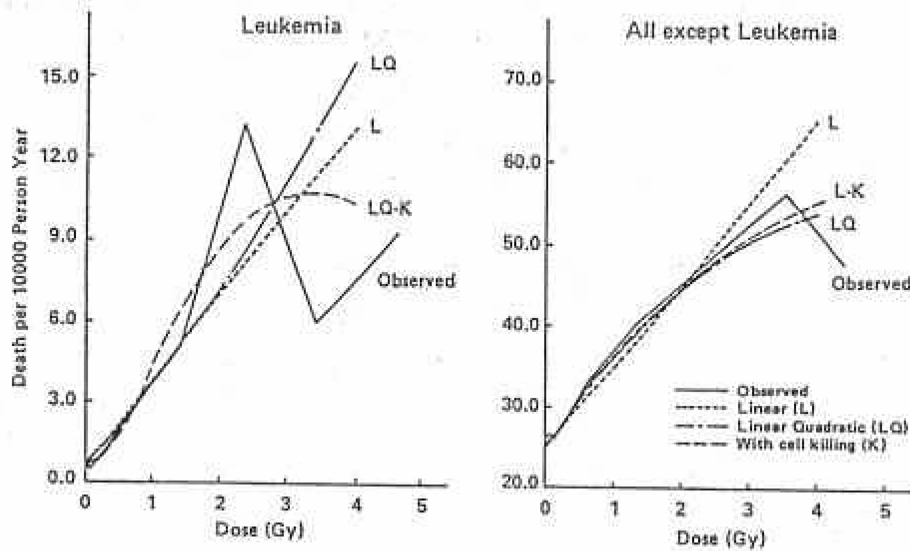

Figure 6 — Observed and estimated dose-response curves for deaths due to leukemia and other forms of cancer. Predicted models include linear (L), linear-quadratic (LQ) and linear-quadratic with cell killing (LQ-K).[9]

5 — Radiation-Induced Solid Cancer

The effects of radiation can be detrimental for a cell if cellular damage results. A change or a mutation in DNA can have serious implications for a cell. There are two outcomes associated with radiation: deterministic and stochastic effects.[11] If the probability of causing damage by radiation increases directly with dose, the effects are called deterministic. Above a certain threshold dose, there is greater damage as the dose increases, whereas below the threshold, no effect is observed. These effects are primarily observed within days or weeks following high acute radiation exposure (mostly > 0.1 Gy) and have deleterious effects on humans, such as acute radiation syndrome, haematopoietic syndrome and in most cases, death.[12] In contrast, stochastic effects do not have a threshold dose and the severity of the effect has not been shown to be dependent on dose.[12] Stochastic effects describe the late health effects to which humans

are at risk of developing when exposed to ionizing radiation, such as genetic defects and cancer.

The connection of low-dose radiation exposure to the risk of developing cancer is well established. The LSS allows scientists to make predictions on the risk of cancer incidence and mortality in atomic bomb survivors to be used as a reference for other populations. Data collected from the LSS are advantageous as the study population includes both genders and various age groups and allows scientists to draw broader conclusions about the health effects of ionizing radiation than other isolated incidents of radiation exposure. The atomic bomb survivors have experienced acute radiation exposure, whereas medically-treated and occupationally-exposed populations receive radiation over a longer period of time. Therefore, the results of studies on the atomic bomb survivors provide a clearer picture of the relative risk of radiation-induced cancers.

Most early studies involving the LSS cohort have focused on cancer mortality due to radiation exposure. Although the information gained from these studies is important, newer studies have shifted to determining overall cancer incidence as a result of radiation exposure. Incidence studies, together with cancer mortality studies, provide a great deal of information that can be used for cancer risk inferences. The advantages of determining mortality rates are that they are widely collected as death certificates are mandatory in Japan, and a standard nomenclature has been adopted worldwide for recordkeeping. Cancer mortality risks were estimated based on individuals from a subpopulation of the LSS that were exposed to radiation within 10 kilometres of the

hypocenter and consists of 86 572 people.[13] An increased number of deaths due to cancer has been observed in the LSS cohort, including lung, breast, thyroid gland, large intestine, stomach and solid cancer in general. The relative risk of death due to either lung or breast cancer at 1 Sv of radiation exposure is 1.8, whereas the mortality risk for urinary bladder and colon cancer is 2.2 and 1.5, respectively.[14] The relative risk of death due to all cancers except leukemia is 1.5.[14] This data was collected between 1950 and 1990 from survivors of both genders and who were exposed to radiation prior to the age of 30.

Preston *et al.* (1997) released a follow-up study reporting an additional 440 radiation-induced cancer-related deaths from 1990 until 1997.[13] It was estimated that eighty percent of deaths were attributable to radiation. It was also found that at low doses (0 to 150 mSv), the excess cancer risks showed a linear relationship with radiation dose and increased during the study period.[13] A significant increase in risk of death due to cancer was determined for lung, colon, esophageal, breast, stomach, liver, gallbladder, ovarian, and bladder cancers at a confidence interval of ninety percent. Site-specific cancers such as rectal, pancreatic, uterine, and prostate cancers did not exhibit a significant increase in excess cancer risk. However, as at least half of the LSS cohort was still alive at the time of the study (1997) the mortality risks could rise. In addition, it has been suggested that the excess cancer mortality rates are highest in the survivors exposed at childhood[13] and as a consequence the determination of radiation-induced excess cancer is ongoing.

In recent years, greater emphasis has been placed on collecting cancer incidence data. Obtaining incidence results from the LSS cohort can lead to more accurate estimates of cancer risk as treatment options have improved and death is not necessarily the final outcome. Seventy-five percent of the cancer incidence data collected from the LSS cohort was determined by histological assessment[15,16], while the rest remaining data was established by direct observation, clinical diagnoses and death certificates. It was found that there was a significant excess relative risk at 1 Sv (ERR $_{1Sv}$) for all cancers excluding leukemia in the atomic bomb survivors.[15] For individual cancers, significant excess relative risk of developing cancer was detected for stomach, colon, lung, breast, ovarian, urinary bladder and thyroid cancer with an ERR $_{1Sv}$ of 0.37, 0.72, 0.95, 1.59, 0.99, 1.02, and 1.15, respectively.[15] In addition, Thomson *et al.* (1994) reported an increased relative risk of developing radiation-induced liver and non-melanoma skin cancer. Recent reports have also associated radiation with nervous system cancers.[15,17,18]

Interestingly, no significant increased excess relative risk was found for cancers of the rectum, gallbladder, pancreas, larynx, uterine cervix, prostate or kidney.[15] It is possible that these cancers have a lower incidence rate compared to other cancers and may not have occurred at the time of the study. These results also suggest differential tissue sensitivity to radiation dose and could indicate that the surface area of a particular tissue or organ plays a significant role in terms of radiation exposure.

Differences in cancer incidence risk between females and males were also observed. When combined solid tumours were analyzed, there was a two-fold increase in the

relative risk in females when compared to males, which is in contrast to the trend observed for leukemia. Females also had a greater relative risk of developing respiratory and urinary system cancers compared to males.[15,16] The excess relative risk was greater with increased attained age for all combined solid cancers. Conversely, excess relative risk for developing solid cancers decreased with increased age at exposure. Therefore, older individuals at the time of bombing have a lower risk of cancer incidence than their younger counterparts.[15,16]

Both mortality and incidence studies provide useful information to estimate radiation-induced cancer risks. However, there are some differences between these methods that need to be addressed. Mortality rates rely heavily on death certificates, which are not always supported by autopsies and therefore the underlying cause of death might be non-cancer related. Furthermore, it has been reported that 23% of the 9014 individuals included in the LSS with primary incident cancers are still alive and were not included in the mortality risks data.[16] Differences in results also arise due to nonfatal cancers and other non-cancer diseases that can lead to mortality in cancer patients. As all of these factors influence the outcome of the analysis, it is not surprising that the estimated excess relative risk of cancer incidence for solid tumours is 40% higher than the risk derived from mortality data.[16]

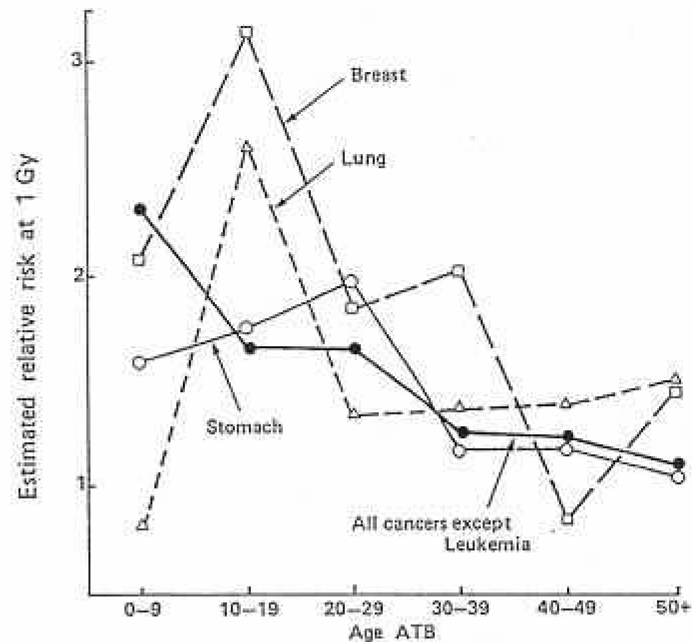

Figure 7 — Relative risk of death due to various types of cancer at 1 Gy according to age of survivors at the time of bombing (ATB).[9]

One of the solid cancers that is prevalent among the radiation-exposed atomic bomb survivors is breast cancer. Previous studies have reported that the relative excess breast cancer risk is significantly increased in the female atomic bomb survivors.[15,16,19,20] For example, Land *et al.* (2003) reported a significant correlation between breast cancer and radiation dose. A subpopulation of the LSS cohort involving 1059 breast cancer cases diagnosed between 1950 and 1990 was utilised. This study was one of the five follow-up studies of breast cancer incidence, and reported increases in the number of breast cancer cases. One of the striking conclusions of the study was that 50% of the cancer cases diagnosed during the specified time interval occurred in women who were under the age of 20 at the time of bombing.[20] It is apparent that the relative risk of developing cancer decreases with increased age at the time of exposure[19,20] as viewed in Figure 7. It can be seen that women exposed to radiation during their childhood or adolescence show a greater risk of developing breast cancer in their lifetime when compared to women who

were exposed later in their life. The ERR_{1Sv} was a thirteen-fold increase for onset of breast cancer prior to the age of 35 in women exposed to radiation before the age of 20.[20] Terminally-differentiated cells have been shown to be less susceptible to radiation effects compared to undifferentiated cells.[21] Older women have a greater amount of terminally-differentiated cells compared to adolescent women and thus are likely less sensitive to radiation. Another trend that can be explained by this phenomenon was a correlation between time of menarche (the first menstrual period) and risk of cancer.[19,20] Although not statistically significant[19,20], it was observed that women who started menstruating at the age of approximately sixteen had a lower cancer risk compared to women menstruating before the age of 14.[19]

From these studies it can be concluded that radiation poses a serious risk to the atomic bomb survivors. Studies are consistent in reporting increased radiation-induced risks for developing leukemia and other cancers. Reports also suggest that age at the time of exposure is significant in determining the relative risk of developing cancer. Overall, the LSS and other studies play a pivotal role in determining these risks.

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