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Review

Radiation and leukaemia: Which leukaemias and what doses?

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ABSTRACT

The cause(s) of most cases of leukaemia is unknown. Save for several rare inherited disorders the most convincingly-identified causes of leukaemia are exposures to ionizing radiations, to some chemicals and to some anti-cancer drugs. Data implicating ionizing radiations as a cause of leukaemias come from several sources including persons exposed to the atomic bomb explosions in Japan, persons receiving radiation therapy for cancer and other disorders, persons occupationally exposed to radiation such as radiologists and nuclear facility workers, cigarette smokers, and others. Although ionizing radiations can be a cause of almost all types of leukaemias, some are especially sensitive to induction such as acute and chronic myeloid leukaemias (AML and CML) and acute lymphoblastic leukaemia (ALL). Whether chronic lymphocytic leukaemia can be caused by radiation exposure is controversial. The mechanism(s) by which ionizing radiations cause leukaemia differs for different leukaemia types. I discuss these issues and close with a hypothesis which might explain why haematopoietic stem cells are localized to the bone marrow.

Why are people worried about spent nuclear fuels radionuclides like 137-cesium which stay around for 100 years? Polyurethane foam mattresses never biodegrade. Live near a nuclear power facility or sleep on a foam mattress? Easy question.
Alfred E. Newman.

1. Introduction

There are many types of radiation summarized in Fig. 1. My focus is on the relationship between exposure to ionizing radiations, namely radiations of sufficient energy to cause an ionization in biological material, and leukaemias. Some non-ionizing radiations such as ultraviolet waves are associated with an increased cancer risk but not leukaemias. The controversial issue of whether non-ionizing radiations such as radiofrequency electro-magnetic waves can cause leukaemias is reviewed elsewhere [1,2].

There are also several types of leukaemias. My focus is on the 4 most common leukaemia types, acute and chronic myeloid leukaemias (AML and CML) and acute and chronic lymphoid leukaemias (ALL and CLL). 1st, I discuss radiation exposure and aggregated leukaemia risk. Later I consider these leukaemias individually.

There are extensive reviews of radiation biology which are beyond the scope of this review. The reader is referred to reports from several reliable sources including the National Academies of Sciences, Engineering and Medicine Committee on Biological Effects of Ionizing Radiations (BEIR), especially BEIR VII, reports of the United Nations Special Committee on Atomic Radiations (UNSCEAR) to the General Assembly, the National Council on Radiation Protection and Measurements (NCRP), International Commission on Radiological Protection (ICRP). These reports discuss mechanisms by which ionizing radiations cause leukaemias. Also outside the scope of this review are non-human models of radiation-induced leukaemias.

2. Epidemiology

Convincing evidence leukaemias are cause by exposures to ionizing radiations comes predominately from epidemiological studies. I discuss the most important below.

2.1. Atomic bomb survivors

There are extensive data on leukaemia in A-bomb survivors 1st reported in uncontrolled data from Japanese haematologists within 2 years of the A-bomb detonations. This led to development of an A-bomb

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cancer survivors registry initially by the Atomic Bomb Casualty Commission (ABCC) and later by the Radiation Effects Research Foundation (RERF). Controlled surveillance of survivors and unexposed persons did not begin until 1950 such that cases of leukaemias occurring earlier were not ascertained in these studies. Also, most registry data are based on deaths rather than incidence which may have been satisfactory for leukaemias occurring before 1965 but would no longer suffice because of therapy advances. Another confounder is the several revisions of estimated doses the survivors which have changed leukaemia risk estimates. The latest revision, DS86, allows for estimation of bone marrow dose from gamma and neutron radiations [3] These dose estimates consider only initial radiation exposures but not induced radiation (neutron activation) nor radioactive fallout. However, most data suggest contribution of these sources to total dose is small. []https://www.rerf.or.jp/uploads/2017/09/residualrad_ps_e.pdf] Definitions of leukaemia types and subtypes have been revised several times since 1950 by the World Health Organization [4]. A comprehensive re-review of the Nagasaki leukaemia cases was done in 1988 with >80% concordance [5]. Another cofounder is the presence of adult T-cell leukaemia/lymphoma (ATLL), a leukaemia caused by HTLV-1 in Kyushu Island (Nagasaki) but not Honshu Island (Hiroshima) populations. It's also important to consider that CLL is rare in Japanese and other persons of Asian ancestry which raises the question whether data from Japanese A-bomb survivors apply to populations of predominately European descent [6,7]. The types of bombs also differed, uranium *versus* plutonium as did the topography of the 2 cities. Another consideration is A-bomb survivors were exposed to external acute high-dose and -dose rate mixed radiations. Whether leukaemia risk derived from this population applies to other exposure settings is controversial (discussed below). Lastly, although the average dose to the A-bomb survivors 240 mGy there were no survivors receiving an estimated dose greater than about 4 Gy so the shape of the dose-response curve at higher doses is unknown.[1] These and probably other confounders should be considered when critically analyzing leukaemia risk estimates derived from the A-bomb survivors.

As indicated, excess leukaemias were noted beginning about two years after the A-bomb detonations with excess risk peaking at about 6–8 years after exposure and declining thereafter (except CLL; see below). This pattern contrast with excess risk of most solid cancers which were first noted >10 years after exposure and continued for several decades.

The most important source of data on leukaemia risk comes from the Life Span Study (LSS) cohort which began in 1950. The LSS is a research programme investigating life-long health effects based on epidemiologic (cohort and case-control) studies. Its major objective is to investigate the long-term effects of A-bomb radiation on causes of death and incidence of cancer. About 120,000 subjects selected from residents of Hiroshima and Nagasaki identified through the 1950 Japan national census have been followed since then including 94,000 atomic-bomb survivors (*hibakusha)* and 27,000 unexposed residents of Hiroshima and Nagasaki not in these cities when the A-bombs were detonated.

Participants were matched for socio-economic co-variates thought to affect health risks including cancer. LSS participants were initially interviewed concerning the circumstances of their exposure and have been subsequently contacted through mail-survey questionnaires which provide data on other factors such as lifestyle potentially relevant to disease occurrence and death. Based on this cohort it is possible to conduct studies of the rates of occurrence of cancer and the causes of death related to radiation exposure and other factors.

Periodic analyses of the LSS cohort data form the basis of a series of

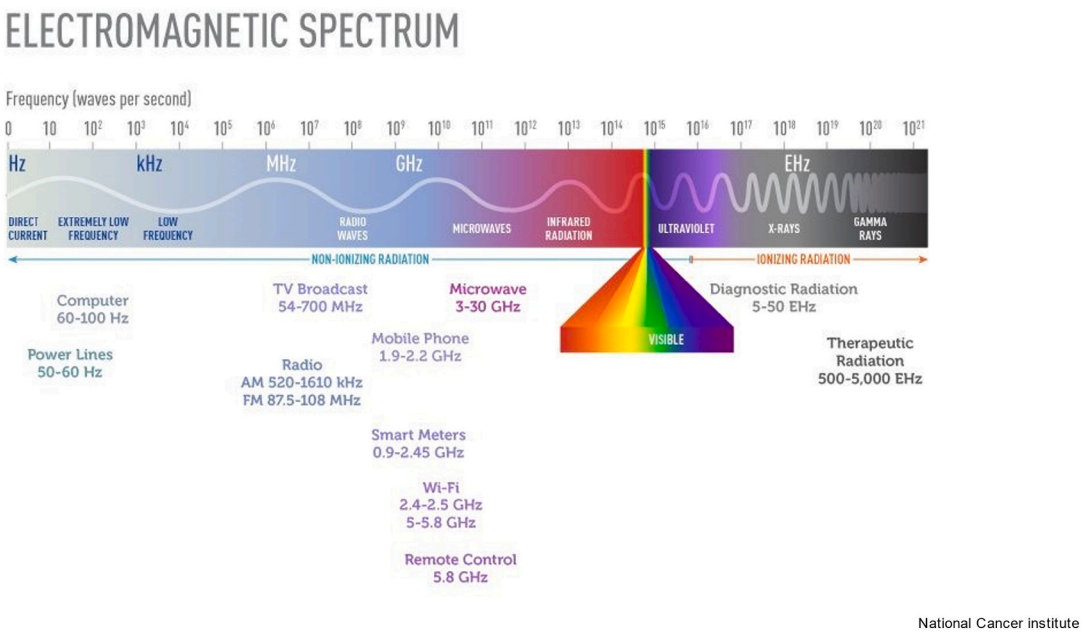


Fig. 1. The electromagnetic spectrum (https://www.cancer.gov/about-cancer/causes-prevention/risk/radiation/electromagnetic-fields-fact-sheet).

[1] I use Gy and Sv interchangeably in this typescript based on how doses are reported in the studies I cite. Gy and Sv are, of course, different. Gy the SI unit for energy absorbed from ionizing radiation (1 Gy = 1 J *per* 1 kg of matter) whereas Sv is the SI unit for energy absorbed from ionizing radiation adjusted for relative biological effectiveness (RBE). 1 Sv is generally defined as the amount of radiation roughly equivalent in biological effectiveness to 1 Gy gamma radiation.

reports on death from cancer and other causes and cancer incidences (https://www.rerf.or.jp/en/library/archives-en/scientific_pub/rrtoc/). The LSS cohort is also the basis for more in-depth studies of individual cancer sites, often conducted through case-control studies. In such studies molecular analyses of cancer samples from survivors are done to elucidate mechanisms of radiation-related cancer and the impact of other co-variates.

As of the 2000 there were 204 leukaemia deaths amongst 49,204 LSS survivors with a bone marrow dose of ≥0.005 Gy 94 of which (46%) are attributable to A-bomb radiations (Table 1; [https://www.rerf.or.jp/en/programs/roadmap_e/health_effects-en/late-en/leukemia]). In persons exposed to a weighted bone marrow dose of ≥0.5 Gy more than one-half of leukaemias are attributable to radiation. At weighted bone marrow doses ≥2 Gy almost all cases are attributable to radiation. As indicated, there were no survivors at doses >4 Gy so the attributable leukaemia risk at high doses is unknown but there is likely to be a decreased risk as a result of cell killing.

The dose-response pattern for leukaemia is best represented by a linear-quadratic model implying low doses may be less effective in causing leukaemia compared with high doses. This dose-response curve differs from the linear dose-response curve for solid. However, even for doses of 0.2–0.5 Gy leukaemia risk is increased (Fig. 2; https://www.rerf.or.jp/en/programs/roadmap_e/health_effects-en/late-en/leukemia).

Although there is controversy regarding a radiation dose threshold for leukaemia induction there were excess cases even at doses <0.1 Gy. Presently most scientists, scientific bodies and regulatory agencies assume there is no threshold for radiation-induced leukaemias implying even the lowest dose, no matter how small, is associated with increased risk. Overall, the relative risk (RR) of an A-bomb survivor getting leukaemia compared with the non-exposed Japanese population at about 1 Sv of radiation exposure is about 5.6-fold. Importantly, there is no detectable increased leukaemia risk in children exposed to A-bomb radiations *in utero* nor in the progeny of parents one or both of whom were A-bomb survivors [8].

Several co-variates affect radiation-induced leukaemia risk. The most important besides dose were age at exposure and sex. For example, the greatest excess leukaemia risk was in children <10 years old at exposure); [https://www.rerf.or.jp/en/programs/roadmap_e/health_effects-en/late-en/leukemia]. I discuss these co-variates in the context of each leukaemia type below.

2.2. Radiation therapy

There are many epidemiological studies of leukaemia risk in persons receiving radiation therapy for cancer and other disorders reviewed in the references cited above and extensively in the BEIR VII report [9]. The 1st reports were of an increased risk of leukaemia in persons receiving radiation therapy for ankylosing spondylitis [10]. Average bone marrow dose was 2.2–3.2 Gy. Increases were observed in ALL, AML and CML with a median latency of about 7 years. Others report similar increases in persons receiving radiation therapy for ankylosing spondylitis [11,12]. Relative risk of leukaemia at 1 Gy was about 7. Other studies of radiation therapy in benign disorders including skin haemangiomas, peptic ulcers, benign breast disorders, uterine bleeding, *tinea capitas* and others report contradictory results. In this context it's important to recall that in epidemiological the *absence of evidence is not evidence of absence*.

Table 1
Temporal patterns of leukaemia risk. [adapted from [76]].

Cohort	ALL	AML	CML
1950–1960	28%	25%	48%
1961–1980	3%	50%	28%
1981–2001	1%	73%	15%

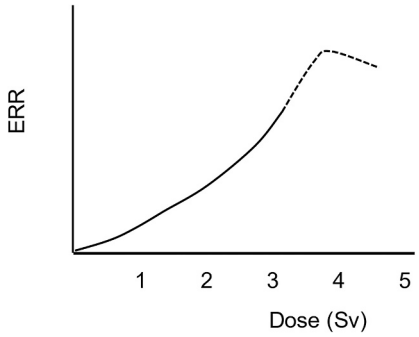


Fig. 2. Dose-response curve for leukaemia in A-bomb survivors adapted from reference [76]. ERR, excess relative risk. Sv, Sievert. Dashed line is predicted ERR.

There are also many epidemiological studies of leukaemia risk in persons receiving radiation therapy for cancer. Several studies of women receiving radiation therapy for cervix cancer report an increased risk of leukaemia [13–15]. However, a review reported no significant increase [16]. There are several contradictory reports of an increased incidence of leukaemia in women receiving radiation therapy for breast cancer (reviewed in 17). One study reported a relative risk of leukaemia of 2.4 in women receiving only radiation therapy which increased to 17.4 when combined with alkylating drugs [18]. Some of these data are confounded by synchronous of metachronous use of drugs independently associated with increased leukaemia risk. Most of these so-called cases of therapy-related leukaemia were AML rather than ALL or CML, a point I discuss below.

There are considerable albeit controversial data on leukaemia risk, especially AML, in persons treated for Hodgkin lymphoma. One study reported a Standardized Incidence Ratio (SIR) of 9.5 (95% Confidence Interval [CI], 6.8, 12.9) after 30 years [19]. However, these data are confounded by diverse radiation fields and doses and concomitant exposure to drugs associated with increased leukaemia risk. In another study risk of leukaemia after radiation therapy only of Hodgkin lymphoma is about 9-fold lower compared with persons receiving chemotherapy [20–22]. In persons receiving only radiation therapy those in whom the bone marrow dose was >20 Gy had an 8-fold increased relative risk of developing leukaemia compared with those in whom the bone marrow dose was <10 Gy. These data suggest that although radiation therapy increases leukaemia risk in a dose-dependent manner most leukaemia risk after combined therapy of Hodgkin lymphoma results from drug exposures [23,24]. Risk of developing leukaemia is also increased in person receiving high-dose total body radiation in the context of receiving haematopoietic cell transplants in the context of lymphomas and plasma cell myeloma [25].

There are several studies assessing leukaemia risk after radiation therapy for solid cancers. For example, no increased risk was detected in men receiving radiation therapy for prostate cancer in one study but contradictory data are also reported [[26,27], https://ascopubs.org/doi/abs/10.1200/jco.2008.26.15_suppl.5073]. There are other reports of increased leukaemia risk in persons receiving radiation therapy for lymphoma and testes cancer [28–30].

There are also several studies of leukaemia risk in persons receiving radioactive iodine (^{131}I) to treat hyperthyroidism or thyroid cancer. A recent meta-analysis found no increase in leukaemia in persons receiving ^{131}I for hyperthyroidism [31]. In contrast, several studies and a meta-analysis of ^{131}I use in persons with thyroid cancer report increased leukaemia risks, especially in young persons [32–38]. Interesting, like the A-bomb survivors described above risk of CML was greater than that of AML underscoring the likely contribution of mutagenic anti-cancer drugs to radiation therapy in the development of so-called *therapy-related* AML see below).

The sum of these data are consistent with the conclusion exposure to

ionizing radiations in the context of radiation therapy for benign disorders and cancer increases leukaemia risk. This is so for many but not all settings. Discordances may reflect differences in study-designs, statistical power, underlying diagnosis, radiation dose, field and fractionation, sex and age of the exposed population and other co-variates.

2.3. Diagnostic radiological exposures

Exposure of the US and European populations to diagnostic radiological procedures is increasing exponentially [39]. Of greatest concern are radiation exposures from computed tomography (CT) scans but nuclear medicine studies have also increased substantially [40]. The 2016 rate of CT scans is currently >1 *per* persons in the US although obviously not uniformly distributed. Some populations are at special risk [41]. Almost one-half of the average annual radiation dose to the US population is from diagnostic medical procedures, about two-thirds of which from radiological studies and one-third from nuclear medicine studies [42].

There are several studies of leukaemia risk in persons exposed to ionizing radiations from diagnostic radiological medical procedures [43,44]. Many are in children and focus on CT scans and ALL risk. One study reported a tripling of ALL risk in children receiving one CT scan [45]. There are substantial efforts underway to encourage decreased use of CT scans, and to decrease doses (https://www-pub.iaea.org/MTCD/Publications/PDF/te_1621_web.pdf).

2.4. Exposure from atomic weapons testing fallout

There are several studies of leukaemia risk in persons exposed to radioactive fallout including the Marshall Islanders, residents of French Polynesia, *downwinders* of US atmospheric nuclear weapons tests, troops observing nuclear weapons detonations, Laplanders/Sami (presumed to eat reindeer meat contaminated by fallout from atmospheric A-bomb testing *via* lichen), residents of geospaces contaminated by radionuclides release from the Chernobyl and Fukushima-Daichi nuclear power facility (NPF) accidents and others. Most of these studies report no or only a slight increase in leukaemia risk but are typically complex and confounded and it is difficult to draw strong conclusions regarding fallout exposures and leukaemia risks.

There is considerable controversy whether radioactive fallout from the Chernobyl NPF accident increased leukaemia risk. Most studies are negative and reports from the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) and the Chernobyl Forum report no increased risk [46,47]. However, another study estimated 2400 excess leukaemias in Europe from the accident [48]. This estimate is <0.04% of background leukaemias making it impossible to confirm or refute. Relatedly, an expert panel concluded there was no convincing evidence of an increase in childhood ALL from fallout from the Chernobyl NPF accident [49]. Evidence for an increased leukaemia risk from fallout from the Chernobyl NPF accident are unconvincing but an accurate answer is likely unachievable.

Two studies from the former Soviet Union of people living downwind of the Soviet nuclear weapons test site in Semipalatinsk and people residing near the Mayak plutonium processing plant near the Techa River reported increased leukaemia risks, mostly associated with doses >2 Sv [50,51].

2.5. Background radiations

There are several studies of a possible relationship between exposure to naturally-occurring background radiation and leukaemia risk. Most of these studies are in children, deal with terrestrial radiations and focus on ALL. Most of these studies rely on geospace rather than individual measurement. The most widely-cited study from the UK reported a 12% excess relative risk of ALL per mSv of bone marrow gamma radiation dose [52]. These data are reviewed elsewhere where the authours discuss methodological limitations and suggest no firm conclusion regarding causality [53]. Studies of aircraft crew exposed to high doses of cosmic radiations report no increased leukaemia risk [54,55].

2.6. Nuclear facilities

There have been extensive studies of persons living near NPFs, other nuclear installations and workers in NPFs and nuclear weapons facilities. I discuss these separately as I do workers involved in mitigation of the Chernobyl NPF accident.

There are several reviews of studies of persons living near NPFs (reviewed in 56,57). These studies have been done in several countries including the US, UK, Japan, Canada, Israel and others. Results of most studies have been negative. The most controversial association reported was an increase in ALL in persons living in Seascale and Dounreay in the UK near the Sellafield and Dounreay NPFs. Subsequent studies indicate no link to radiations release from the facility ([58], https://www.gov.uk/government/publications/childhood-cancer-incidence-around-sellafield-and-dounreay). There was also concern paternal radiation exposure might increase the risk of childhood leukaemia but this has been disproved [59,60].

There are also extensive studies of workers at NPFs. Many present contradictory data but most report no convincing increase in leukaemia incidence with 1 exception discussed below. The largest study of >400,000 workers in 15 countries reported no significant increase in leukaemia risk but other data are contradictory [61–63]. Workers at the Mayak NPF and nuclear fuels reprocessing plant in the Techa river region of Russia were exposed to much higher radiation doses compared with similar workers in most other countries. A recent study reported an increased leukaemia risk in this cohort [64]. I conclude under normal international guidelines for occupational radiation exposures workers at NPFs probably do not have an increased leukaemia risk.

There are also several studies of persons living near other nuclear facilities including the Oak Ridge and Hanford nuclear reservations, nuclear fuels reprocessing facilities, uranium mines and nuclear facilities releasing tritium. None report convincing evidence of an increased leukaemia risk. Notably, 2 of 7 persons exposed to neutron radiations from criticality accidents at Los Alamos died from AML. However, there are too few data to characterize the relationship between neutron exposures and leukaemia risk.

2.7. Other occupational exposures and radon

There are several reports indicating increased leukaemia risk in US radiologists and radiology technicians exposed before about 1940 to doses typically >2 Gy but not thereafter [65]. Data on recently exposed Japanese radiologists also indicate no significant increase in leukaemia risk. Similar conclusions apply to US radiology technicians [66,67]. Overall, there seems an increased leukaemia risk in radiologists and technicians exposed before about 1940–1950 and those exposed to the highest doses but not per most persons. There is also no increased risk of leukaemia in radium dial painters or uranium miners or uranium processing workers [9]. A meta-analysis of 400,000 workers occupationally exposed to protracted low-dose ionizing radiations reported an increased leukaemia risk [68]. Other exposures including radon are discussed below. Exposure to radon and radon progeny is ubiquitous in non-occupational settings and discussed in part above under terrestrial radiations. Several studies report no or only a weak association between indoor radon levels and childhood leukaemia [69,70].

2.8. Chernobyl and Fukushima Dai-chi NPF accidents

In addition to persons exposed to fallout from the Chernobyl NPF accident there are several reports of leukaemia incidence in workers involved in mitigating the accident many of whom received relatively high radiation doses. There are several reports most of which are

negative or unconvincing. One case-control study reported an increased leukaemia risk but with several caveats [71]. A recent study reported an increased incidence of CLL amongst Chernobyl mitigators whose average dose was 92 mGy concluding: *Exposure to low doses and to low dose-rates of radiation from post-Chornobyl cleanup work was associated with a significant increase in risk of leukaemia, which was statistically consistent with estimates for the Japanese atomic bomb survivors* [72]. This finding contradicts the widely-accepted notion CLL is not a radiogenic leukaemia. I discuss this controversy below. Considerably less radiation was released from the Fukushima Dai-ichi NPF accident and most of the radioactive plume was deposited in the Pacific ocean. There is no anticipated increase in leukaemia risk based on these considerations. There is considerable current concern over possible radiation releases from NPFs and spent nuclear fuels storge facilities as a result of the war in Ukraine. I review these considerations elsewhere [73,74]. There are also concerns about potential radiation exposures from nuclear terrorism (reviewed in 75).

2.9. Detailed leukaemia risks from the A-bomb data

The most comprehensive, up-to-date analyses of the A-bomb leukaemia data are reported by Hsu and colleagues from the RERF which discusses the 312 leukaemias observed 1950 to 2001 including 43 cases of ALL, 176 cases of AML, 75 cases of CML and 18 cases unclassified [76]. 94 of these cases (30%) are estimated to be radiation-associated including almost one-half in persons exposed to doses ≥5 mGy (the average survivor dose was 240 mGy). In this section I consider several co-variates affecting risk in all leukaemias excluding CLL and ATLL and then focus on individual leukaemias. Important co-variates associated with leukaemia risk include dose sex, age at exposure, interval since exposure and attained age (obviously confounded). I simplified much of these complex data into summary tables and schematic figures. Table 1 shows temporal patters of radiation-associated leukaemia risk after exposure, Table 2, estimated background and excess leukaemias as a function of dose, Fig. 2, the relationship between excess leukaemias and dose, Fig. 3, a schematic of temporal relationship between exposure and development of radiation-associated leukaemias and solid cancers and Fig. 4, a schematic of the time course of development of different leukaemia types after exposure.

There are several important conclusions from these data. For example, the excess relative risk *per* Sv for CML (6.2) is about twice as high as that for AML (3.6). Also, temporal patterns of leukaemia differed with most excess cases of ALL and CML occurring early and most excess cases of AML occurring later (Table 1; Fig. 4). Elsewhere my colleagues and I discuss two mysteries regarding CML after the A-bombs: (1) why no excess cases of CML were detected in Nagasaki A-bomb survivors at doses >200 mSv; and (2) why radiation-induced onset was delayed 3-fold in females compared with males in the A-bomb survivors [77]. Prior RERF reports indicated no significant increase in CLL. However, the most recent report indicates a significantly increased risk at high doses was detected (Fig. 4). Another curiosity is the much greater risk of radiation-induced CML in males compared with females [78]. Considerably more detail regarding leukaemia in A-bomb survivors is presented in the article by Hsu and colleagues cited above. I discuss the question of whether CLL is a radiogenic laeukemia below. It should be noted that the mutation causing CML presumably unrelated to radiation exposure, *BCR::ABL1*, is like that found in the A-bomb survivors with CML suggesting the mechanism of radiation-related CML is,a reciprocal translocation [79].

Table 2
Fitted cases of leukaemia [adapted from [76]].

Dose (Gy)	Background	Excess
<0.005	117	0.1
0.1	61	4
0.2	14	4
0.5	14	11
1	8	18
2	4	28
>2	2	29

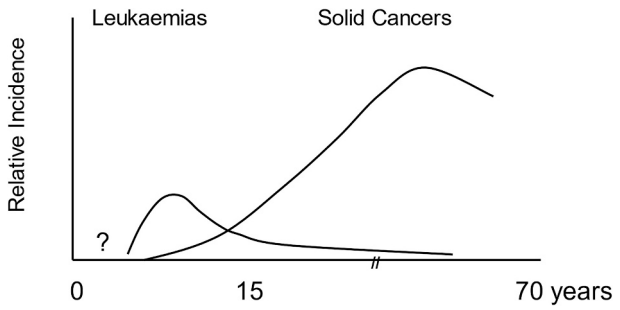


Fig. 3. Schematic of intervals to develop leukaemia *versus* solid cancers in A-bomb survivors.

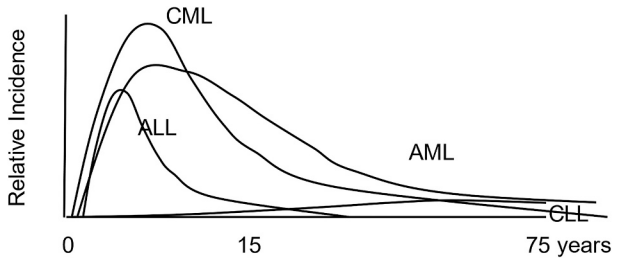


Fig. 4. Schematic of interval to develop different leukaemia types in A-bomb survivors. Adapted from reference [76].

2.10. Outstanding questions

2.10.1. Why do radiation-induced leukaemias occur before radiation-induced solid cancers?

In the A-bomb survivors most radiation-induced leukaemias occurred 10-30 years before radiation-induced solid cancers (Fig. 4). There are several potential explanations. First, average numbers of mutations in leukaemias is 10–50-fold less than in most solid cancers. For example, *BCR::ABL1* is sufficient to cause CML. This is so in some other leukaemias. In contrast, most solid cancers have an average of about 100 mutations some but not all are *driver* mutations. However, it takes considerably more time after radiation exposure for radiation-related solid cancers to acquire the additional mutations need for a neoplastic genotype and phenotype.

Second, haematopoiesis is hierarchical with *stem* and *progenitor* cells which have extraordinary proliferative capacity. This is unlike most other tissues and organs where whether there is a hierarchal structure or stem or *progenitor* cells is controversial. The consequence is a mutation in a haematopoietic *stem* or *progenitor* cells or in a cells which because of the mutations acquires features of a stem or progenitor cell will likely result in rapid clonal expansion and a leukaemia phenotype.

2.10.2. Are the specific phenotypes or genotypes which characterize radiation-induced leukaemias or a preferred therapy?

No specific phenotype or genotype is specific for radiation-induced leukaemias, predominately because we can only say, using epidemiological data, leukaemia incidence is increased but not which excess leukaemias are radiation-induced. It follow that if we cannot accurately identify radiation-induced leukaemias we cannot recommend specific therapies. The poor prognosis of so-called *therapy-related* AML applies to cases caused by DNA-damaging drugs with or without radiation. It does not apply to cases proposed to be caused solely by radiation.

2.10.3. Does radiation cause CLL?

Until recently CLL was considered a non-radiogenic leukaemia based mostly conclusions from the A-bomb survivors discussed above [9,83]. However, as indicated, the most recent analyses RERF report an increased CLL risk at high radiation does after a latency of >50 years implying initiation of leukemogenesis at an early age. Several studies reported increased risks of CLL in uranium miners presumably from radon and possibly gamma exposures [84–87]. However, a meta-analysis of persons occupationally-exposed to low-dose ionizing radiations reported no significant increase in CLL [88]. Our analyses of data from the Surveillance and End Results Program (SEER) found no convincing evidence of an increased risk of CLL in persons receiving radiation therapy for solid cancers [89]. Also discussed above is a report of an increased CLL risk in mitigation workers at the Chernobyl NPF [90,91]. One problem with these analyses is many are based on mortality data where incidence data are more important in evaluating CLL risk. However, 2 studies of incidence data reported no increase in CLL [92]. Taken together these data suggest a possible need to revise our notion CLL is not a radiogenic leukaemia [91,93,94,95].

2.10.4. Why was CML increased in the A-bomb survivors but not after radiation therapy?

Discussed above is the dramatic increase in AML risk in persons receiving radiation therapy for cancers such as Hodgkin lymphoma and benign disorders such as ankylosing spondylitis. An increased risk of CML is less impressive, if any, in these studies. In contrast, the excess relative risk of developing CML in the A-bomb survivors was almost twice that of developing AML(see above). These data raise the question of why so-called *therapy-related* CML is so infrequently reported after persons receiving radiation therapy.

Most cases of *therapy-related* leukaemia occur in persons synchronously or metachronously receiving mutagenic anti-cancer drugs and radiation therapy. It seems isolated exposure to sparsely ionizing radiations like in the A-bomb survivors preferentially causes double strand DNA breaks during the G_0/G_1 phase of the cell cycle. The result is translocations in genes which are spatially proximal in the interphase nucleus such as *BCR* and *ABL1* resulting in the *BCR::ABL1* translocation necessary and sufficient to cause CML [96]. These balanced reciprocal translocations are stably transmissible to daughter cells. In contrast, DNA-damaging drugs preferentially produce more complex, less stably transmissible mutations which favour causing AML. My colleagues and I discuss this hypothesis in greater detail elsewhere ((Fig. 5**)**. As I discuss above CML was more increased compared with AML in persons receiving only ^{131}I for thyroid cancer consistent with the hypothesis [32,38].

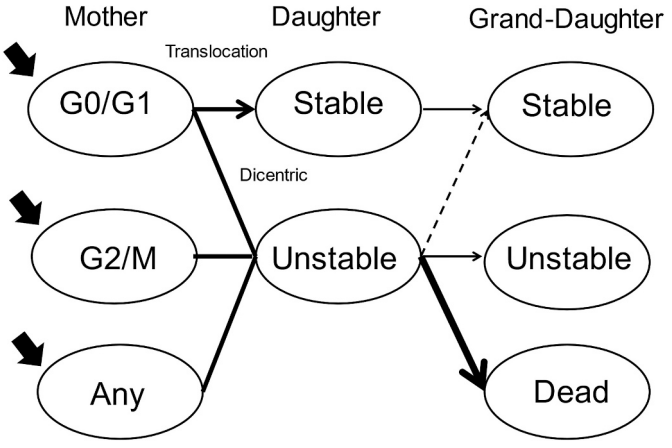


Fig. 5. Hypothesis why A-bomb exposures increased CML risk in A-bomb survivors but not after radiation therapy for cancer given in the context of DNA-damaging drugs. Details in reference [95].

2.10.5. What is my normal radiation exposure? Is it safe to have an X-ray, a CT or to fly

Ionizing radiations are ubiquitous. We are constantly exposed to them from cosmic, terrestrial and manmade sources and we are ourselves radioactive because of internalized isotopes of sodium, potassium and others. The average annual exposure of the US population is 6.2 mSv about one-half of which is from background sources and the other half from mostly medical source. Exposures from the nuclear fuel cycle are small. Radiation sources for the US population are displayed in Fig. 6.

Common concerns of many people are exposures from radiological procedures, especially CT scans, dental X-rays and airport security scanning devices. Most US airports use millimeter scanners which do not expose you to ionizing radiations. Some foreign airports such as in the UK use backscatter X-ray imaging. The dose received from one backscatter X-ray scan, 0.05 μSv is the same as flying for 12 s at 12,000 m or waiting in the security line for screening for 2 min. Full mouth dental X-rays expose someone to the same radiation dose as a transcontinental flight. There are no convincing data supporting an increased leukaemia risk associated with any of these exposures except CT scans is children [97]. However, voluntary radiation exposures should always weight benefit and risk.

2.10.6. Why are haematopoietic stem cells in the bone marrow?

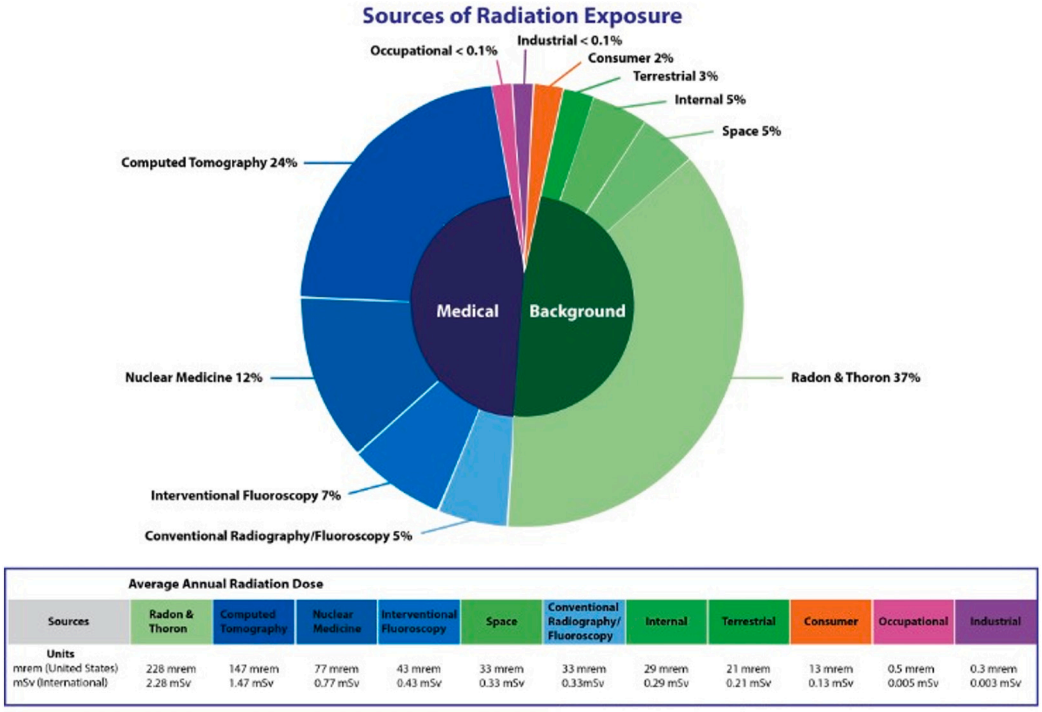
It's interesting to consider why adult haematopoietic stem cells reside in the bone marrow after having started out in the blood islands, then embryonic aorto-gonad mesonephros (AGM) and then fetal liver. When life on Earth began about 3.6 billion years ago cosmic, solar and terrestrial radiation levels were substantial higher than today. Water, where presumably life began, is a relatively effective radiation shield. As animals moved onto land there may have been evolutionary pressure to protect haematopoietic stem cells by placing them in bone which, because of hydroxyapatite, is also an effective radiation shield. Several lines of evidence support this hypothesis. For example, aquatic frogs have solid bones with no bone marrow cavity; their haematopoietic stem cells remain in the AGM region. In contrast, terrestrial frogs have hollow long bones containing bone marrow. (It can also be argued the bone structure of terrestrial fogs is more related to bio-mechanical considerations.) We found similar differences in bats living in trees *versus* limestone caves (Dabrowski and Gale; unpublished). Interestingly, whales and dolphin, aquatic mammals (cetaceans), have their haematopoietic stem cell within bone marrow [80,81]. However, cetaceans are derived from terrestrial mammals (artiodactyls) [82]. Consistent with our hypothesis. Based on these data we suggest protection of long-lived haematopoietic stem cells from the mutagenic effects of ionizing radiations may explain why they migrated to the bone marrow cavity in terrestrial mammals including humans.

3. Summary

Ionizing radiations can cause leukaemia. Risk correlates with several factors including type of radiation, route, dose, dose-rate, field, fractionation and others. Host factors are also important including sex and age. There are synergistic interactions with other carcinogens such as cigarette smoking. Most risk estimates are from A-bomb survivors but data from other settings are mostly concordant. Most leukaemias are ALL, AML or CML but some recent data suggest CLL may also be increased. Some radiation exposures are preventable and physicians should minimize exposures whenever possible always considering risk-benefit ratios of diagnostic radiological procedures, especially CT scans. It worth remembering more people are cured of cancer by radiation therapy than harmed by exposure to radiation. We discuss how to communicate radiation risks to the public elsewhere [98].

Future considerations

The relationship between exposure to ionizing radiations and



Average Annual Radiation Dose

Sources	Radon & Thoron	Computed Tomography	Nuclear Medicine	Interventional Fluoroscopy	Space	Conventional Radiography/ Fluoroscopy	Internal	Terrestrial	Consumer	Occupational	Industrial
Units											
mrem (United States)	228 mrem	147 mrem	77 mrem	43 mrem	33 mrem	33 mrem	29 mrem	21 mrem	13 mrem	0.5 mrem	0.3 mrem
mSv (International)	2.28 mSv	1.47 mSv	0.77 mSv	0.43 mSv	0.33 mSv	0.33mSv	0.29 mSv	0.21 mSv	0.13 mSv	0.005 mSv	0.003 mSv

Fig. 6. Sources of radiation exposure to the US population. (National Council on Radiation Protection and Measurement Report 160).

leukaemia risk is clear and not controversial. What is less certain is the shape of the dose-response relationship at very low-dose and dose-rate. Although most scientists and regulatory agencies operate under the linear no-threshold (LNT) hypothesis ultimately this is imposition prove or disprove. Regardless, it is the most conservative hypothesis to protect public health. What's needed is greater physician education of leukemogenic radiation risk such that an accurate assessment of risk:benefit from doing diagnostic radiologic procedures can be made. Physicians also need education in how to express radiation risk to the public. Lastly, there is a need to reduced controllable radiation exposures to the lowest achievable and reasonable dose.

Practice points

1. Exposure to ionizing radiations is a cause of leukaemia;
2. Consequently, radiation exposures, especially from radiological diagnostic procedures such as computed tomography (CT) scan, should always weigh benefit and risk;
3. Few cases of leukaemia are caused by exposure to ionizing radiations but this should be considered in appropriate circumstances.

Research agenda

1. The relationship between low-dose (< 200 mSv) exposure and leukaemia risk is based on mathematical models. Experimental confirmation would be nice but probably impossible;
2. Efforts to confirm the potential impact of terrestrial radiations and leukaemia risk are needed;
3. The hypothesis what exposure to ionizing radiations increases CML risk in the A-bomb survivors but not after radiation therapy needs testing.

Declaration of Competing Interest

RPG is a consultant to: NexImmune Inc., Annexa Pharma, Ascentage Pharm Group, Antengene Biotech LLC. Medical Director: FFF Enterprises Inc. Partner: AZAC Inc. Board of Directors: Russian Foundation for CanctageAner Research Support;. Scientific Advisory Board: StemRad Ltd.

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