A New Look At Ionizing Radiation Carcinogenesis

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Abstract

The current framework for estimating the risk of cancer induction for exposure to ionizing radiation is, unfortunately, based on misunderstandings. Radiation induction of cancer is not a simple stochastic process as assumed by the International Commission on Radiological Protection but rather it involves numerous inter-relational cellular and radiative events. Also, it is not proportional to cumulative dose, but rather it is a somewhat precise function of life time average dose rate to the affected tissues. Studies that assume that it is proportional to cumulative dose can be quite misleading. At low average dose rates the time required to develop cancer may exceed the natural life span resulting in a life span virtual threshold of several sieverts. In sharp contrast is the study if the Japanese 1945 atomic bomb survivors. These survivors were exposed to up to several hundred times the normal average annual ionizing radiation dose from natural background, but it was delivered in only about one minute. All the cells of the body were irradiated and underwent some type of permanent reprogramming. Many years later and throughout life, some of the exposed survivors developed cancer and remarkably these cancers were of the same types as occurred among the control population, but at higher rates. This lifetime promotion of cancer rates was proportional to that original one-minute radiation dose. This promotion of cancer was independent of age at exposure or the time between exposure and cancer development. Except for early cases of leukemia that were caused by radiation damage to the blood-forming tissues, there were no apparent independent occurrences of unique radiation induced cancers. The current tissue weighting factors and risk models are based primarily on the promoted cancer types in those Japanese survivors and do not apply to radiation induced cancer. These findings suggest possible dose-rate revisions of radiation safety models and protection criteria for internal emitters and other protracted and repeated exposures to ionizing radiation.

Key Words: radiation, ionizing; radiation effects; radiation risks; cancer induction

1. Introduction

Ionizing radiation safety standards developed by the International Commission on Radiological Protection (ICRP) during the past more than 50 plus years were originally based on limiting dose rate to organs of the body below an implied cancer risk threshold. More recent recommendations have calculated cancer risk as a function of cumulative dose using a linear no-threshold cancer risk model based on the acute high dose rate exposures received by the Japanese atomic bomb survivors. The underlying assumption in these current recommendations is that risk of radiation-induced cancer is proportional to cumulative dose without threshold. In conflict with this position are the studies of protracted exposures from internally deposited radionuclides in people and laboratory animals that showed that cancer induction risk is a function of average dose-rate for protracted exposures to ionizing radiation. At lower average dose rates cancer latency can exceed natural life span leading to a life span virtual threshold. The resolution of the conflict of these two cancer risk models is explained by the fact that the increased risk of cancer observed in the atomic bomb survivor studies was primarily the result of acute high dose-rate promotion of ongoing biological processes that lead to cancer rather than cancer induction. In addition, ionizing radiation induced cancer is not the result of a simple stochastic event in a single living cell but rather a complex deterministic systemic effect in living tissues.

2. Radiation Cancer Induction

2.1 Protracted or Fractionated Exposures

Based on the human radium studies of Evans, in 1959 the ICRP established a maximum permissible skeletal content safety recommendation of 3.7 kBq (0.1 microcuries) for ^{226}Ra and extended the dosimetric implications for recommended maximum permissible values for a whole range of radionuclides (ICRP-2, 1959). Evans showed that the induction of cancer from protracted alpha radiation exposure from radium in the skeleton was a

non-linear function with an observed threshold at a cumulative dose of about 10 Gy, calculated to be about 200 Sv with a quality factor of 20 for alpha radiation (Fig. 1) (Evans et al. 1972). In 1974 Evans showed definitively that no linear cumulative dose model of radiation-induced bone cancer is consistent with the U.S. data on radium in people (Evans 1974). Later it was found that the three-dimensional dose-response relationship for radium-induced bone cancer from alpha radiation is properly described as a function of lifetime average dose rate to target tissues rather than of cumulative dose (Raabe et al. 1980). This relationship demonstrated a life-span virtual threshold for bone sarcoma induction when the cancer latency exceeds the normal life-span (Fig. 2) (Raabe 2010).

Three-dimensional analyses have been performed of the human radium cases and of twenty-five internal-emitter laboratory studies with beagles for injected ^{226}Ra, ^{228}Ra, ^{224}Ra, ^{228}Th, ^{239}Pu, ^{249}Cf, ^{252}Cf, ^{241}Am, ^{90}Sr, inhaled ^{239}Pu, ^{238}Pu, ^{90}Y, ^{91}Y, ^{90}Sr,^{144}Ce, and ingested ^{90}Sr (Raabe 2010). These radionuclides have principal emissions that include low linear-energy transfer (LET) beta radiation or high LET alpha radiation. For example, lifetime studies of inhaled $^{239}PuO_2$ demonstrated lung carcinoma induction from alpha radiation followed the same pattern of that was observed for bone sarcoma from radium alpha radiation (Fig 3). Low LET beta radiation demonstrated a similar precise dependence on lifetime average dose rate for both bone cancer and lung cancer. However, the characteristic negative logarithmic slope of the temporal pattern of cancer induction is precisely about -1/3 for high LET alpha radiation and the characteristic negative logarithmic slope of the temporal pattern of cancer induction is precisely about -2/3 for low LET beta radiation (Fig. 4). Cancer induction associated with protracted exposures to ionizing radiation is a three-dimensional average dose-rate, time, response process that depends on the parameter, K_m, controlling the median time to cancer induction as a function of average dose rate to the exposed organ. These studies show that cancer induction risk associated with a protracted ionizing radiation exposure is a precise non-linear function of lifetime average dose rate to the affected tissues. Cumulative dose was found to be an imprecise and unreliable indicator of cancer induction risk. Cells in bone and lung appeared equally sensitive to cancer induction either by high LET or by low LET radiation. No tissue-weighting factors are involved.

The other parameters depend on radiation type and characteristic temporal distribution (lognormal for alpha radiation, Weibull for beta radiation). For bone cancer these relationships reduce to a pair of three-dimensional functions, one for alpha radiation and one for beta radiation, after adjustment for potency in irradiation of sensitive cells at bone surfaces. Likewise, for lung cancer these relationships reduce to a pair of three-dimensional functions, one for alpha radiation and one for beta radiation, after adjustment for potency in irradiation of sensitive bronchiolar cells. The resulting cancer occurrence displays a remarkably narrow and consistent range with a long latency and lifetime virtual thresholds below lifetime cumulative organ or sensitive tissue doses of about 10 Sv. For lifetime cumulative skeletal doses below 10 Sv from ingested ^{90}Sr in beagles (Fig. 5) the risk of bone sarcoma was found to be significantly lower than for controls with $p < 0.047$ (Raabe 2010).

The precision and time-delay of the cancer induction phenomenon indicate an underlying gradual biological process involving many altered cells associated with cellular deoxyribonucleic acid (DNA) mutations, clone development depending on cell division cycles, cellular maturation, and average ionizing radiation dose rate over long latency periods. An important finding is that two beta particles were found to equal one alpha particle in the radiation induction process (Raabe 2010). This finding suggests that double strand damage to DNA is involved in the cancer induction process.

Because of the long latency that may exceed the natural life-span, the radiation- induced cancer risk associated with protracted exposures to ionizing radiation involves a life-span virtual threshold when the lifetime average dose rate is low and the cumulative dose to sensitive tissues is below about 10 Sv. Life-span virtual thresholds for radiation-induced cancer risk should exist for other types of protracted and fractionated exposures including radon inhalation and external exposures associated with background levels of ionizing radiation from environmental radionuclides.

2.2 Cancer Induction Risk Assessment

An important conclusion is that the current risk assessment practice of adding so-called committed ionizing radiation effective dose from internally deposited radionuclides to acute dose from high dose-rate external radiation exposures is not appropriate. Risk from the protracted exposure is a function of the lifetime average

dose rate to the sensitive tissues without use of a tissue-weighting factor. The lifetime average dose rate per day to an irradiated body organ or tissue can be estimated from published ICRP dosimetry information as the uncorrected 50-year committed equivalent dose (without tissue-weighting factor, w_T) divided by18,262 days.

These results should be expected to apply to all forms of protracted or fractionated ionizing radiation exposure including external exposures since the individual cells of the body do not distinguish between internally or externally originated ionizing radiation. For example, dose-response relationships for high LET proton radiation associated with external exposures to neutrons should be similar to the observed high LET alpha radiation internal dose-rate response relationships. Likewise, dose-response relationships for external low LET gamma radiation exposures should be similar to the observed low LET beta radiation internal dose-rate response relationships.

In studies of 64,172 tuberculosis patients of whom 39% were exposed externally to highly fractionated x ray chest fluoroscopies, lung cancer deaths showed no evidence of cancer risk associated with the x ray exposures with the relative risk at a cumulative doses of 1 Sv being 1.00 [95% confidence interval 0.94-1.07] (Howe 1995). Also, studies of people exposed to unusually high levels of protracted external ionizing radiation associated with natural background (up to 260 mSv y^{-1}) have not detected increased cancer risks (Ghiass-nejad et al. 2002).

3. Radiation Cancer Promotion

3.1 Cancer Risk Models

The principle basis of current radiation safety standards is the study by the Radiation Effects Research Foundation (RERF) and its predecessor organizations of the development of solid malignant tumors in about 79,972 survivors of the1945 Japanese atomic bomb detonations in Hiroshima and Nagasaki (Pierce and Preston 2000, Preston et al. 2003, Preston et al. 2007). These about one-minute exposures involved high-energy gamma radiation and some neutrons. Myeloid leukemia from bone marrow exposures followed a different response course and is usually considered separately from the solid tumor incidence. The traditional approach is to assume that the solid tumors are the result of stochastic initiating events in individual cells that occurred during that about one-minute exposure.

The stochastic model of cancer from ionizing radiation is based on the simple idea that a single cell is randomly altered by a unique ionizing radiation event causing a unique pre-malignant mutation in that cellular deoxyribonucleic acid [DNA] (Moolgavkar et al. 1988; Heidenreich et al. 1997). This single stochastic event is believed to lead to a clone of similar pre-malignant cells. Later, usually much later, a second random DNA alteration is believed to occur in one of the cloned pre-malignant cells that produce a malignant cell that develops into a monoclonal malignant tumor. These processes began with the single cellular event. They may be advanced by promoter agents including ionizing radiation that presumably affect the clonal development, quantity, and maturation of the pre-malignant cloned cells. A cancer promoter is anything that advances the development of a malignancy other than a directly carcinogenic agent or an intrinsic component of the carcinogenesis process.

The internal emitter studies discussed above strongly suggest that multiple double strand DNA damage or a related phenomena are involved in the cancer induction process associated with ionizing radiation. In particular, two low LET beta particles were found to be required to match the radiation induction process associated with each alpha particle (Raabe 2010). Since the exposure of the Japanese atomic bomb survivors was primarily associated with low LET gamma radiation and associated energetic electrons, two hits at the same region of DNA in a target cell would be expected to be required for the induction of cancer. The resulting increase in cancer by induction in this two-hit process would follow a sharply increasing curvilinear power function of increasing cumulative absorbed dose. In fact, the increase in cancer among the atomic bomb survivors tended to follow a linear pattern. Deterministic cancer promotion rather than stochastic cancer induction better explains the increase of solid cancers in the atomic bomb survivor studies.

3.2 Atomic Bomb Survivor Studies

The studies of the atomic bomb survivors demonstrate a linear dose-response promotional effect related to the natural or existing biological processes that may eventually lead to cancer in the exposed population (Fig. 6). These processes involve years of cellular division, clone expansion, and cellular maturation. The exposure to a sudden high dose of ionizing radiation delivered in about one minute at the time of the nuclear detonations may have advanced or stimulated the cellular changes that eventually lead to various typical types of cancer. Hence, some cancers may have appeared at an earlier time than otherwise would have occurred based on the existing underlying cellular and tissue processes (Fig. 7). This promotional effect was observed to advance cancer rates not only relatively soon after exposure but throughout the lives of the exposed individuals. This behavior is proportional to the instantaneous dose just as would be expected for any phenomenon that involves augmentation of existing processes rather than a few random or "stochastic" changes in a few select cells. However, the resulting cancer promotion phenomena should not be expected to describe the effects of similar exposures delivered uniformly or fractionated over a relatively long period of time. Since promotion is a relative process rather than an absolute process, it is not meaningful to try to create absolute risk estimates from relative response information.

Concerning the solid tumor incidence in the atomic bomb survivor studies, Pierce and Mendelsohn (1999) pose the question, "How could it be that the excess cancer rate might depend only on age and not on time since exposure or age at exposure?" Figure 8 shows that the increase in malignant solid tumors in the atomic bomb survivors associated with their radiation exposure follows the same lifetime pattern irrespective of the age at exposure. The simple answer is that the normal progression of cancer incidence in the population was somewhat promoted by the radiation exposure without the actual independent induction of cancer. This promotion is not a stochastic process but rather the result of the almost instantaneous delivery of ionizing charged electrons produced in all the tissues by ionizing radiation from the atomic bombs. The tissues response is complex and unfocused, but can be described as instantaneous aging based on the observed lifetime effects.

The A-Bomb survivor data are unique because they do not in any way predict the observed carcinogenesis associated with protracted exposures as occur in the case of internal emitters. Brenner et al. (2000) summarize observed relative increased risk of cancer for an exposure of Japanese atomic bomb survivors exposed to one Gy for males as a function of age at exposure (Fig. 9). This representation clearly shows cancer promotion. The total risk per year is about the same for everyone! Given an 85 year life span in this figure, the risk per year of life for a five year old boy is about 13% over 80 years = 0.16% per year. For a 25 year old man the risk per year of life is about 9.5% over 60 years = 0.16% per year. For a 45 year old man the risk per year of life is about 6.5% over 40 years = 0.16% per year. The total risk per year is almost independent of age at exposure. This is not explained by any simple stochastic cancer induction model, but is explained by some sort of deterministic cellular reprogramming that promotes the cancer process in a somewhat linear way regardless of age.

3. Discussion

The acute gamma ray exposures clearly represent a completely different mechanism of carcinogenesis from that which occurs with protracted exposure as with long-lived internal emitters. The tissue-weighting factors (w_T) developed by the ICRP to calculate the so-called effective dose are actually a reflection of the convolution of the underlying incidences of different types of cancer in the control population and the relative promotional effect of the whole body exposure to gamma rays and some neutrons in the Japanese atomic bomb life-span studies (ICRP 1977, ICRP 1979, ICRP 1991). Cancers that were somewhat rare in this Japanese population, such as bone cancer, were assigned relatively low tissue weighting factors relative to whole body cancer or assumed genetic risk (such as $w_T = 0.01$ for bone surfaces). Cancers that were somewhat common in this Japanese population, such as lung cancer, were assigned relatively high ratio values relative to whole body cancer or risk (such as $w_T = 0.12$ for whole lung) . These tissue-weighting factors (w_T) can be related to observed cancer promotion, but are unrelated to the cancer induction associated with protracted or fractionated exposure to ionizing radiation. The use of tissue-weighting factors (w_T) recommended by the ICRP is not appropriate for protracted or fractionated exposures to ionizing radiation.

The elaborate Radiation Effects Research Foundation (RERF) studies of the atomic bomb survivors have investigated in rigorous detail the effect of whole body irradiation by high-energy gamma rays (and some neutrons) delivered in about one minute. The A-bomb RERF life-span study clearly describes a meaningful linear dose model of promotion of ongoing biological processes that lead to increased cancer rates for brief high

dose rate exposure to ionizing radiation. The relative risk values might be applicable to other brief high dose-rate ionizing radiation exposures as may occur in occupational exposures or in medical diagnosis and treatment (Hall and Brenner, 2008). However, there is still considerable uncertainty for acute doses less than about 0.05 Sv. Small acute doses may by beneficial as they may promote or stimulate DNA repair or other defensive cellular phenomena that reduce promotional cancer risks associated with ongoing cellular processes that might otherwise lead to cancer (Feinendegen 2005).

Failure to realize the fundamental differences between cancer promotion and cancer induction has been the source of scientific misunderstandings. A wall of separation has stood between the linear no-threshold (LNT) model of cancer promotion in the acute exposures associated with the Japanese survivors and the virtual threshold associated with induction of cancer associated with protracted or fractionated exposures as received from long-lived internally deposited radionuclides in humans or animals. Further, it has led to a systematic overestimation of cancer induction risk from typical exposures to ionizing radiation.

3. References

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FIGURES

Fig. 1: Cumulative bone sarcoma incidence in people exposed to ^{226}Ra as a function of cumulative dose to the skeleton as reported by Evans et al. (1972).

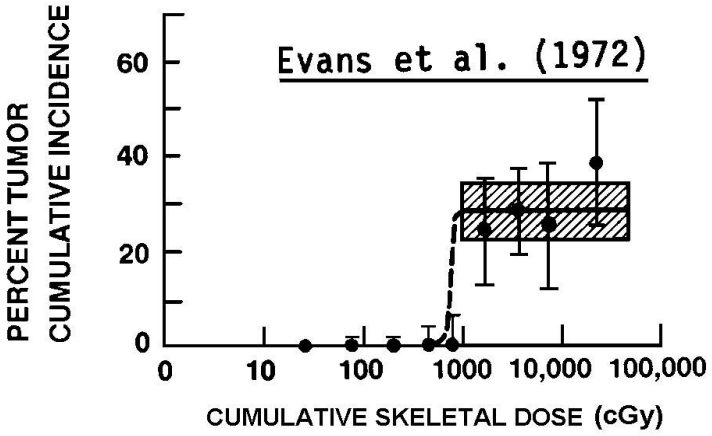

Fig. 2: Two-dimensional logarithmic representation of the data for radiation injury deaths, bone sarcoma deaths, and other deaths in beagles injected with ^{226}Ra at the University of California, Davis (Raabe 2010).

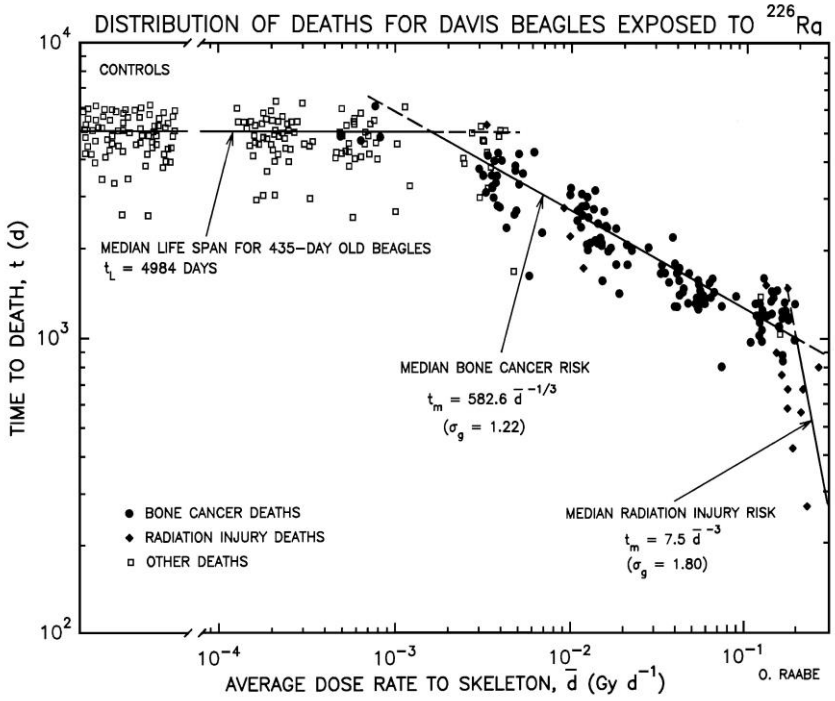

Fig. 3: Distribution of deaths in two life-span studies of beagles inhaling $^{239}PuO_2$ at Pacific Northwest Laboratory (PNL) showing the lung carcinoma and lung injury risk distributions (Raabe 2010).

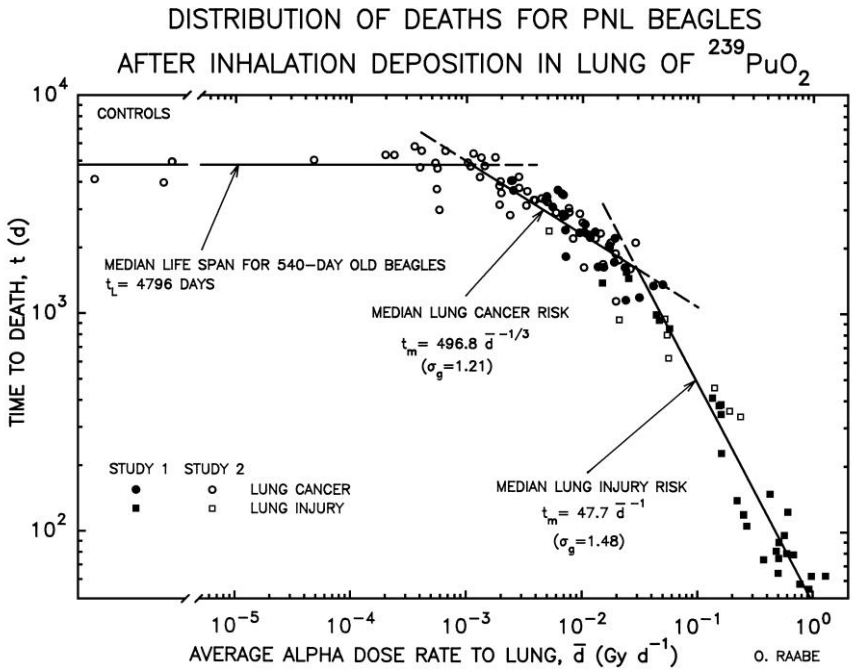

Fig. 4: Illustration of bone sarcoma and lung carcinoma risk functions for beagles demonstrating similar target organ average dose-rate/time/response patterns with life-span virtual thresholds at low dose rates (Raabe 2010). The positions of the lines vary because of inherent differences in irradiation of the target cells by the different

radionuclides and forms. FAP refers to inhaled insoluble fused aluminosilicate particles containing the specified radionuclide.

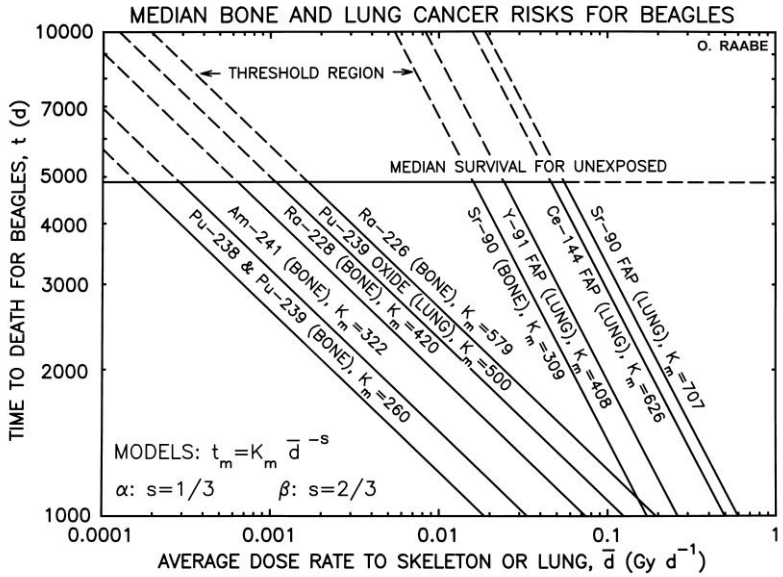

Fig. 5: Statistical evaluation by survival analysis of the incidence of fatal bone sarcoma, periodontal carcinoma, oral/nasal carcinoma and myeloid leukemia in beagles fed ^{90}Sr from before birth to adulthood at the University of California, Davis, as a function of dosage group (with mean cumulative beta radiation dose to the skeleton). The absence of bone sarcoma cases in the lowest three dosage groups is significantly less than those found in the controls [$p < 0.047$] (Raabe 2010).

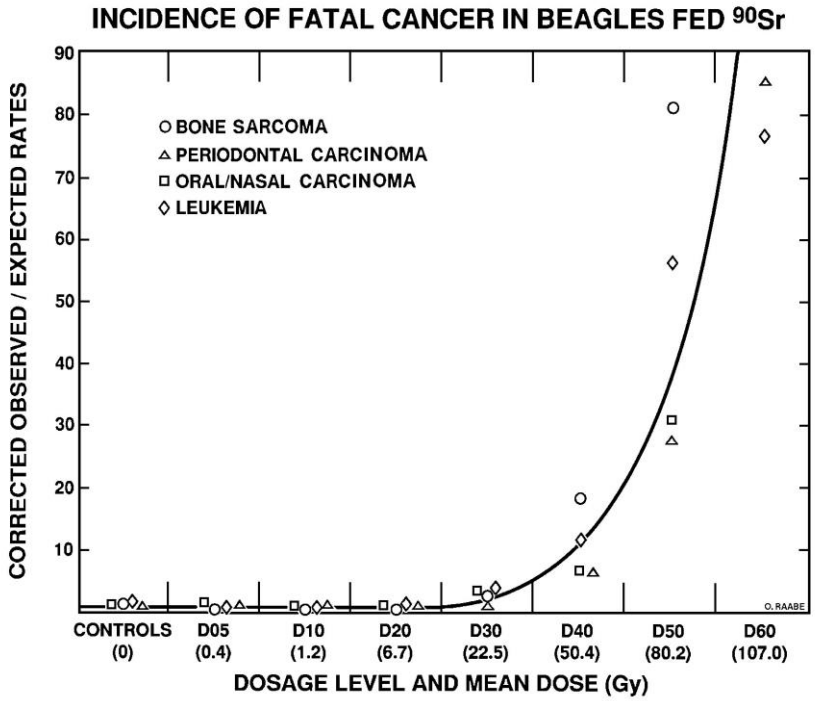

Fig. 6: Linear dose-response relationship of Excess Relative Risk for the promotion of solid cancer in Japanese survivors of the atomic bomb detonations at Hiroshima and Nagasaki in 1945 with respect to survivors who received low radiation exposures as reported by the Radiation Effects Research Foundation [RERF](Preston et al. 2007).

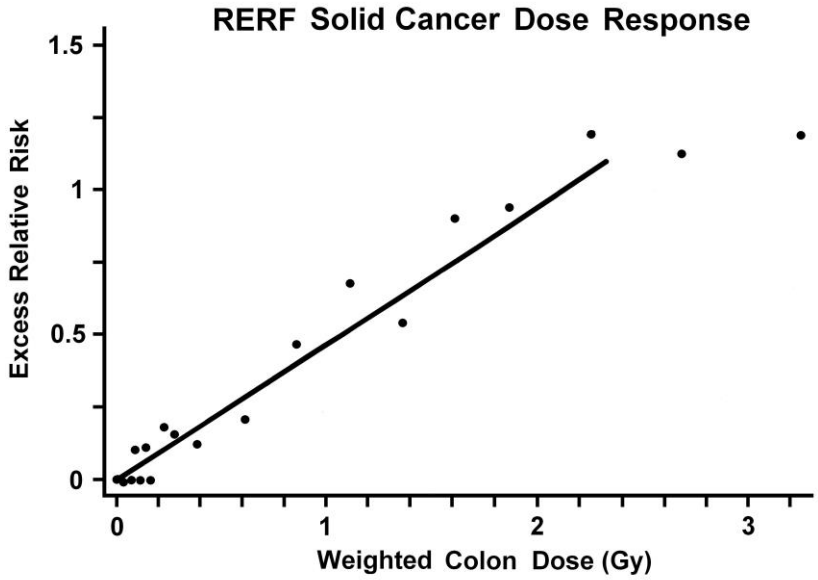

Fig 7: Observed gender-averaged age-specific excess incidence rates at 1 Sv for most major solid cancers over the 1958-1987 follow-up period for ages at exposure 10 y, 30 y, and 50 for the Japanese atomic bomb survivors (Pierce and Mendelsohn 1999). The excess rates appear to depend only on age and not on time since exposure or age at exposure as might be expected for radiation-induced promotion of the cancer types normally found in this population.

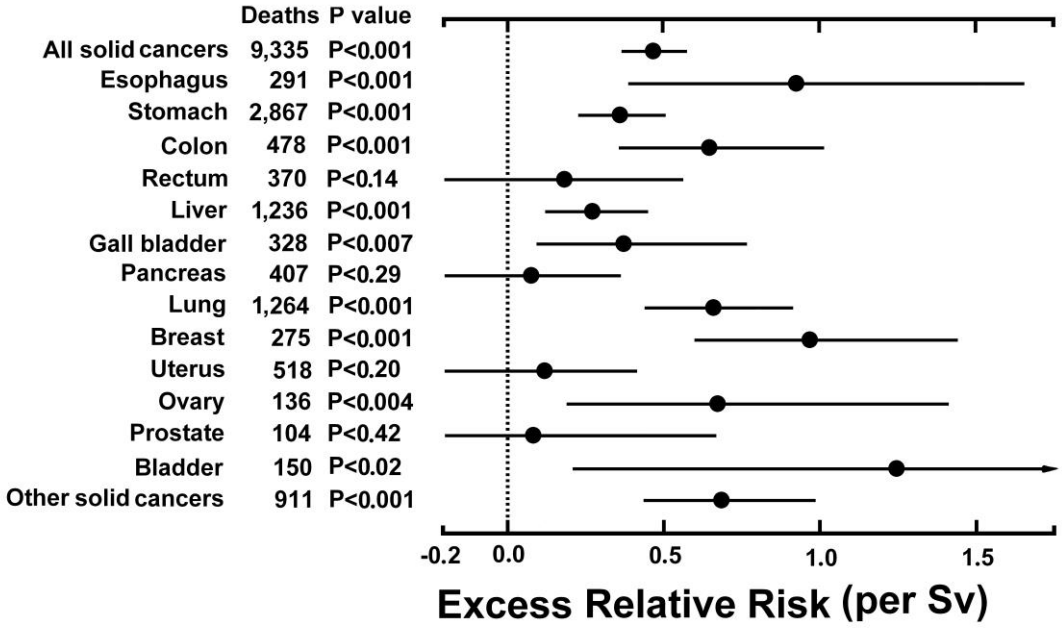

Fig. 8: Observed gender-averaged age-specific excess incidence rates at 1 Sv for most major solid cancers over the 1958-1987 follow-up period for ages at exposure of 10 yr, 30 y, and 50 y for Japanese atomic bomb survivors (Piece and Mendelsohn 1999). The excess rates appear to depend only on age and not on time-since-exposure or on age-at-exposure demonstrating radiation-induced promotion of the cancer types normally found in this population.

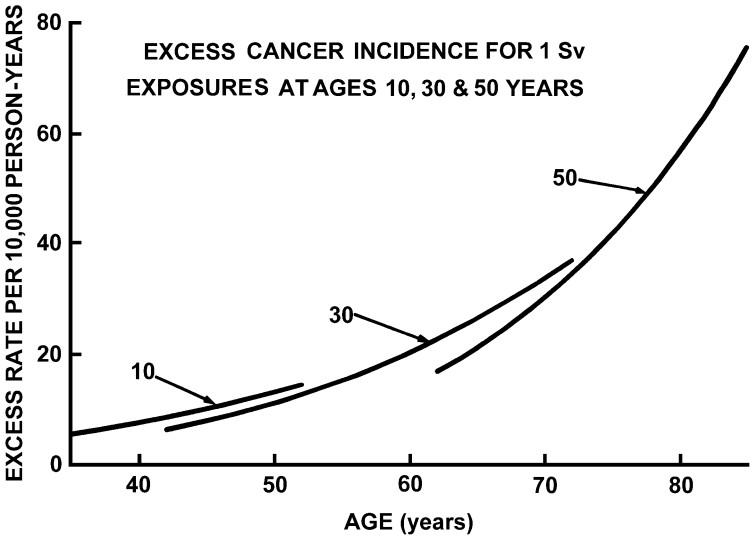

Fig. 9: Lifetime attributable cancer mortality risks for males by cancer type as a function of age after at a single acute exposure of one Gy of gamma radiation based on the Japanese atomic bomb survivor studies as summarized in BEIR V (Brenner et al. 2000). The risk per year is about the same for all exposure times.