15

Ionizing Radiation Carcinogenesis

Otto G. Raabe
University of California Davis, USA

1. Introduction

1.1 Ionizing radiation

Human exposure to ionizing radiation is a natural part of life on earth. These exposures occur every day from radiation associated with naturally occurring radionuclides in soil, air, and food, and also from cosmic rays. In addition, many people are exposed to dental and medical diagnostic procedures and therapy involving: x rays, gamma rays, charged particles, radionuclides, or other ionizing radiation sources. Others may be exposed in their workplace such as in laboratories, hospitals, underground mines, or nuclear power plants. Excessive exposures may lead to the development of cancer by promotion of ongoing carcinogenic biological processes or by independent cancer induction.

Ionization converts a neutral atom to a charged atom. The γ rays and x rays are ionizing electromagnetic radiation with energies above ultraviolet in the electromagnetic spectrum. The difference between x rays and γ rays is a matter of nomenclature. The γ rays are emitted from the nucleus of a radioactive atom while x rays originate in the orbital electrons of a energized atom. The α^{2+} particle has been identified as a positively charged helium nucleus with 2 protons and two neutrons emitted from the nucleus of certain radionuclides. The β^- radiation was identified as negatively charged electrons emitted from the nucleus of certain radionuclides. There are other types of ionizing radiation including most prominently uncharged neutrons emitted from the nucleus of atoms that ionize atoms via nuclear interactions, and positrons and that are positive beta particles, β^+. The measure of absorbed radiation dose in matter or tissue is the gray (Gy) equal to one joule of energy per kilogram of matter or tissue. To account for different types of ionizing radiation, such as gamma, alpha, and beta radiations, the dose from ionizing radiation is corrected for the theoretical relative biological effectiveness of the different radiations in causing cellular damage using a radiation weighting factor, w_R (Sv/Gy), and this is reported as the equivalent dose in sieverts (Sv). Hence, the measure of biological dose is the sievert (Sv), equal to the absorbed dose in Gy times the radiation weighting factor. The γ rays, x rays, and β radiation typically have a radiation weighting factor of 1, while α radiation has a radiation weighting factor of 20 and neutrons may have a radiation weighting factor from 5 to 20 depending on energy. The quantity of radioactivity is measured in becquerel (Bq), equal to one radioactive atomic event or nuclear disintegration per second.

Radiation induced cancer is a complex and not completely understood process involving multiple events including but not limited to cellular DNA damage, up and down regulation of genes, intercellular communication, tissue and organ responses, clonal expansion of

altered cell lines, and possibly eventual malignancy. The current understanding of radiation carcinogenesis is informed by epidemiological studies of human populations exposed to elevated levels of ionizing radiation and controlled studies utilizing laboratory animals. The two major human epidemiological studies have led to sharply contrasting results. Studies of the atomic bomb survivors indicate a linear no-threshold dose-response relationship. Studies of the radium dial painters have led to a sharp threshold relationship. These contrasting findings occur because quite different mechanisms of ionizing radiation carcinogenesis are involved in brief acute exposures at relatively high dose rates and in protracted exposures. Brief acute high dose-rate exposures act by promoting ongoing biological processes that lead to cancer in later life and this promotion effect is proportional to the dose. Protracted exposures induce cancer with a latency that depended on the lifetime average dose-rate of exposure to the target organ. At low dose rates the latent period may exceed the natural lifespan leading to a lifetime virtual threshold for cancer induction. Another observation at lower dose rates is the amelioration of an ongoing pre-malignant process. These findings have important implications with respect to ionizing radiation safety standards.

1.2 Naturally occurring ionizing radiation and radioactivity

There are naturally occurring sources of ionizing radiation that have existed on the planet since its formation (Eisenbud & Gesell, 1997). Naturally occurring radiation sources include cosmic rays, cosmogenic radionuclides, and primordial radionuclides and their decay products. Cosmic rays consist primarily of extremely high energy (mean energy ~ 10 billion electron volts) particulate radiation (primarily protons) and high energy gamma rays. When the particulate radiations collide with the earth's atmosphere a shower of "secondary" radiations are produced, which include high energy electrons and photons. The average person's dose from cosmic radiation is 0.27 mSv per year or ~ 7% of natural background. Exposure to cosmic radiation increases with altitude as there is less atmosphere to absorb the radiation, so populations at high elevations receive higher cosmic doses. For example, people living in Leadville, Colorado, at 3,200 meters above sea level, receive ~ 1.25 mSv y^{-1} or five times the average exposure at sea level. A fraction of the secondary particulate cosmic radiation collides with stable atmospheric nuclei making them radioactive. These cosmogenic radionuclides contribute very little (~ 0.004 mSv y^{-1} or less than 1%) to natural background radiation. The majority of this component of natural background is from the formation of carbon-14 and tritium (hydrogen-3).

Terrestrial radioactive materials that have been present on earth since its formation are called primordial radionuclides. Population exposure from primordial radionuclides comes from external exposure, inhalation, and incorporation of radionuclides into the body. The decay chains of ^{238}U, whose half-life is 4.5 billion years (uranium series), and ^{232}Th, whose half-life is 14 billion years (thorium series), produce several dozen radionuclides that together with natural potassium-40, whose half life is 1.3 billion years, are responsible for the majority of the external terrestrial average equivalent dose rate of 0.28 mSv per year or ~9% of natural background. Traces of these primordial isotopes of uranium and thorium are found in all the soil and rock on the face of the earth. Some regions of the world with high concentrations of primordial radionuclides produce local equivalent dose rates of environmental gamma radiation as high as 25 mSv per year.

Radon, ^{222}Rn, and its decay products, which are constituents of the ^{238}U decay series (Fig. 1), are the most significant source of natural background radiation exposure. Once inhaled, the

majority of the dose is deposited in the tracheobronchial region by its short-lived daughters rather than by ^{222}Rn itself. Radon concentrations in the environment vary widely due to differences in ^{238}U concentration in the soil and differences in ventilation and construction of buildings. All other factors being equal, buildings with less ventilation will tend to have higher radon concentrations and thus, higher level of background radiation exposure. Outdoor concentrations of radon and its decay products are normally low because of the rapid mixing and dilution of radon gas with ambient air.

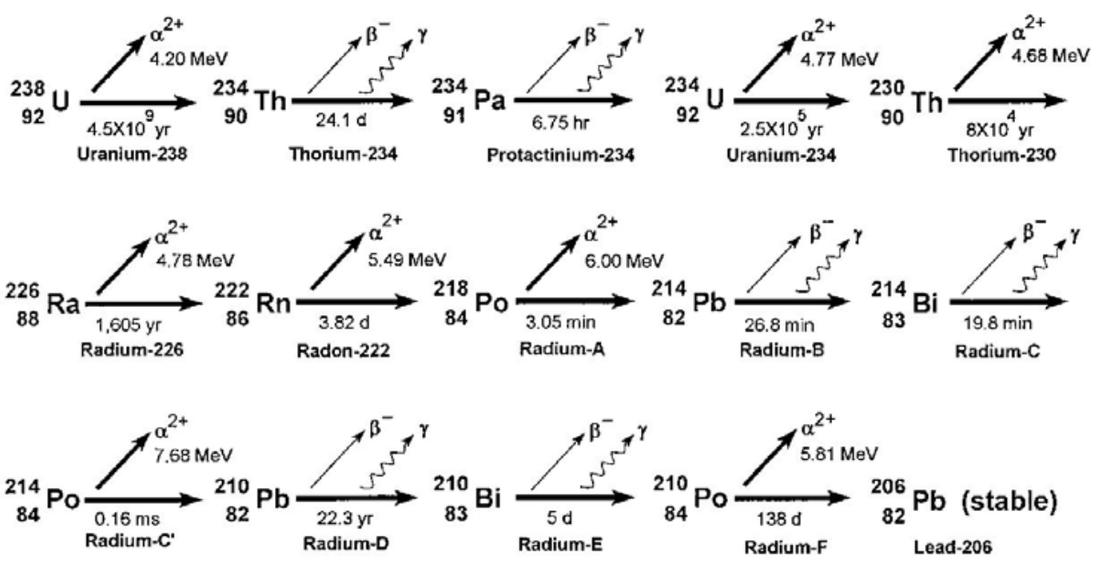


Fig. 1. Schematic illustration of the natural ^{238}U decay series as found in all soil and rock on the surface of planet Earth.

The second largest source of natural background radiation exposure comes from the ingestion of food and water that contain primordial radionuclides (and their decay products) of which ^{40}K is the most important. Altogether this pathway is responsible for an average effective dose rate of 0.4 mSv y^{-1}, or ~ 13% of natural background.

1.3 Typical human exposures to ionizing radiation

Every person who has ever lived has been exposed to ionizing radiation every minute of every day. Among the natural exposures are radiation emitted by nuclides naturally found on the earth (3% terrestrial background), internal exposure to natural radionuclides in food and water (5% internal background), cosmic radiation (5% space background), and radon and thoron gases released from the earth by the decay of naturally occurring radium isotopes (37% radon isotopes alpha irradiation of the lung). A major change has occurred here in the 21st Century from increased exposures that may occur through medical diagnostic use of x rays and radionuclides.

The average per capita "effective" radiation dose in the United States from naturally occurring (or "background") sources is about 3 mSv) per year. The "effective" dose is calculated using the International Commission on Radiological Protection (ICRP) methodology in which a tissue weighting factor is assigned to each organ or tissue and

multiplied by the actual equivalent dose to the organ or tissue (ICRP 26, 1977). In the United States diagnostic medical radiology and nuclear medicine now add about 3 mSv of effective dose to ionizing radiation exposure per year per average person. The percent average contribution of various sources of ionizing radiation exposures of typical residents of the United States population in 2006 is illustrated in a pie-chart (Fig.2) prepared by the National Council for Radiation Protection and Measurement.

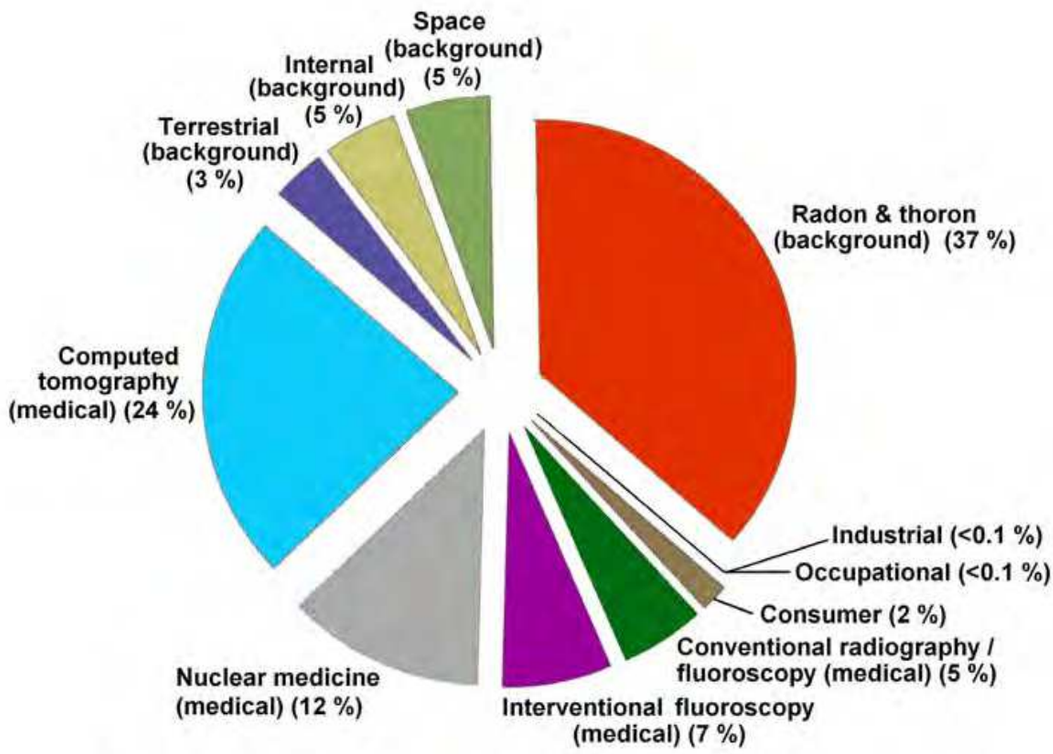


Fig. 2. Percent contribution of various sources of exposure to ionizing radiation to the average annual effective dose (6.2 mSv) per person in the United States population (about 300 million people) in 2006 (NCRP 160, 2009).

There are many places on the earth where natural background doses are much higher because of the natural presence of high concentrations of naturally occurring radionuclides in soil, rock, and water. Studies of these areas of naturally elevated ionizing radiation have not yielded any major deleterious effects associated with these natural exposures. For example, people in some areas of Ramsar, Iran, receive an annual ionizing radiation biological dose from natural background that is up to 260 mSv per year (over 40 times the USA national average). Chromosomal, hematological, and immunological studies and life span and cancer data show no untoward effects or responses (Ghiassi et al., 2002).

1.4 Naturally occurring radium isotopes and decay products

There are many naturally occurring radioactive nuclides that are continually being produced from decay chains in which the parent has a very long physical half life. For example, ^{226}Ra that is present in all the soil and rock on the earth at concentrations of about

25 Bq kg^{-1} is a product of the decay series headed by ^{238}U whose half life is comparable to the age of the earth (4.5 billion years). Consequently, it is also naturally found in ground water and the human body, usually in trace amounts (about 1 Bq per person). The ^{238}U decay series is shown in Figure 1. As shown in the figure, various types of ionizing radiation are emitted by the radionuclides in the chain including alpha radiation (α^{2+}), beta radiation (β^-) and gamma radiation (γ). In addition, similar or smaller amounts of natural ^{228}Ra, a decay product of natural ^{232}Th, are also found in soil and water. A similar ^{232}Th decay chain yields ^{228}Ra, ^{228}Ac, ^{228}Th, ^{224}Ra, ^{220}Rn, ^{216}Po, ^{212}Pb, ^{212}Bi, ^{212}Po, and stable ^{208}Pb (Eisenbud & Gesell, 1997).

As an analogue of calcium, radium that enters the body tends to incorporate into mineral bone where it and its progeny irradiate portions of the skeleton, primarily by alpha radiation emissions. Thorium isotopes tend to deposit on bone surfaces and irradiate surface cells, primarily by alpha radiation emissions. The radionuclide undergoing decay is referred to as the parent nuclide and the transformed nuclide is called the daughter or decay product. The daughter may be no more stable than its parent and may also be radioactive. Successive transformations will occur in a so-called decay chain, possibly yielding several radioactive progeny, until a stable nuclide is reached (Fig. 1).

In this context for ^{226}Ra, the word dose is used specifically to refer to the mean alpha radiation dose absorbed by the irradiated skeleton measured in units of energy deposited per unit mass of skeletal tissue (Gy). Dosage refers to the amount of material that enters the body or is administered (Bq). Burden refers to the amount retained in the body or skeleton with time post intake (Bq). Intake can refer to systemic intake into the blood or other organs of the body, as for the U.S. radium cases (Rowland, 1994), or it can refer only to that material that passes into the mouth or nose during ingestion or inhalation as in radiation protection practice (ICRP-30, 1979). Note that there is a really big difference between ingestion or inhalation intake and systemic intake, sometimes a factor of thousands. Cumulative dose, D, to an organ of the body is derived from the time integral of concentration (or dose rate) in that organ and requires a specified time limit to be meaningful.

2. Internally deposited radionuclides

2.1 Radium in people

Early in the last century people were exposed to high concentrations of ^{226}Ra and ^{228}Ra and their decay products in the luminous dial industry, in laboratory work, and in medical or private therapeutic use of radium. In particular, luminous-dial painters, who were mostly young women, were taught to tip their paint brushes on the tongue to make a sharp brush point; this procedure resulted in the ingestion of considerable radium leading to systemic uptakes of some of the ingested radium. These massive intakes of emulsions of pure radium salts resulted in life-time absorbed doses to the irradiated skeleton of some dial painters as high as a few thousand Sv, with consequent cases of severe injury to the skeleton and/or bone sarcoma as well as carcinomas of the head associated with retained ^{222}Rn and daughters in the nasal sinuses and mastoid spaces.

Detailed evaluations of these human cases have been described by Evans (1943), Evans et al. (1972), Evans (1974) and further documented in recent years (Rowland, 1994). Studies of individuals who had accidental intakes of massive amounts of radium have shown that the principal risk of exposure to large quantities of radium is direct damage to bone, bone cancer (but not leukemia), and cancers of the head caused by trapped decay of radon gas produced by decay of ^{226}Ra in the skeleton. It is interesting to note that no person among the

U.S. radium dial painters whose skeletal dose was less than 10 Gy (200 Sv for ionizing radiation weighting factor of 20 for alpha radiation) developed bone cancer because of exposure to ^{226}Ra or ^{228}Ra. An effective or virtual threshold dose, below which there is no radiation-induced cancer from exposure to radium, has been observed (Evans, 1974; Raabe et al., 1980; Raabe, et al., 1990; Raabe, 2010). In addition, serious non-neoplastic (non-cancer) radiation bone injury, such a bone osteodystrophy and fractures, occurred at even higher doses than did cancer.

Since deposition in and protracted irradiation of the skeleton follows systemic uptake, even a single brief intake initiates a period of chronic irradiation from radium and its retained decay products that depends in duration on skeletal retention or radioactive decay of the deposited radium. About 30% of radon-222 is retained from decay of radium-226, and almost all radon-220 is retained following the decay of radium-224 that forms from the decay products of radium-228. In the case of inhalation of radium (or thorium), irradiation of the lung is also an important aspect of the exposure. However, radium (or thorium) deposited in the lung is cleared by the lymphatic flow, coughed up and swallowed or expectorated, or enters the blood. Upon entry into the blood from the lung, inhaled radium is mostly excreted in the urine, while about 20% is deposited and tenaciously retained in the skeleton. The retention of radium in the human body, particularly the skeleton, has been the subject of considerable study and has been described in a mathematical form that allows the ionizing radiation dose to body tissues to be estimated from time of systemic intake until any time after intake (ICRP-20, 1973).

Fig. 3. Early 20th Century photo of young women painting clock dials with luminous paint containing radium. They tipped their brushes on their tongues and swallowed considerable quantities of ^{226}Ra or ^{228}Ra.

Lifetime studies were conducted in the 20th Century of the American radium dial painters (Fig. 3) and others with internally deposited radium isotopes (^{226}Ra and ^{228}Ra). Internally deposited radium chemically behaves somewhat like calcium and deposits somewhat uniformly in bone mineral in the skeleton. Radium is cleared from the body slowly so that a few percent of the intake can still be detected decades after intake. Alpha radiation from radium and its decay products lead to bone sarcoma in some exposed people at the highest doses. For ^{226}Ra (half life 1,600 years), the first decay product is ^{222}Rn gas much of which migrates in the blood to other parts of the body and is exhaled via the lung. Some ^{222}Rn gas sequesters in the sinus and mastoid regions of the head where alpha radiation from radon and its decay products lead to head carcinoma in some of the most highly exposed people. The most extensive studies of people exposed to radium were conducted at Massachusetts Institute of Technology (MIT) and Argonne National Laboratory (ANL). Results have been reported for over 2,000 people including about 1,700 who had significant intakes of radium, mostly to ^{226}Ra (Rowland, 1994). The nuclear physicist, Robley Evans, author of The Atomic Nucleus (1955) lead the early studies. Evans observed that only those people who received skeletal absorbed alpha radiation doses exceeding 1,000 cGy, developed bone sarcoma (Fig. 4), which he called a "practical threshold". He showed that the absence of sarcoma cases below 1,000 cGy was a statistically significant finding (Evans et al, 1972). This finding did not deter others from reorganizing the data into selective groups of cases and advancing a linear no-threshold model for radium induced bone sarcoma (Fig. 5).

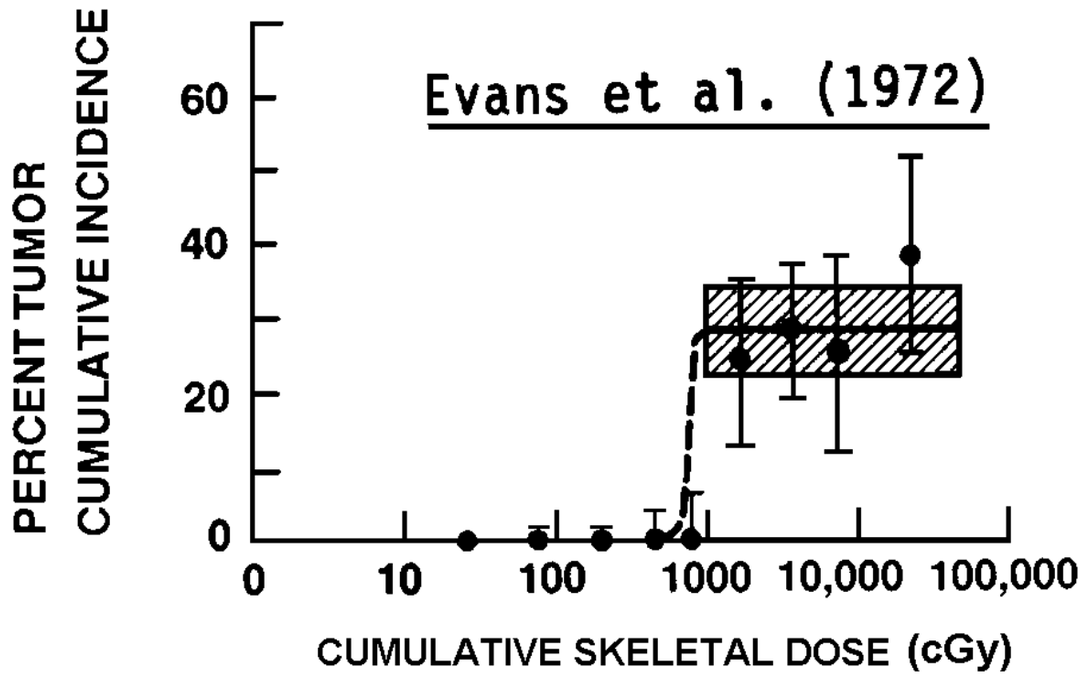


Fig. 4. Bone sarcoma incidence in people exposed to ^{226}Ra as a function of cumulative dose to the skeleton as reported by Evans et al. (1972).

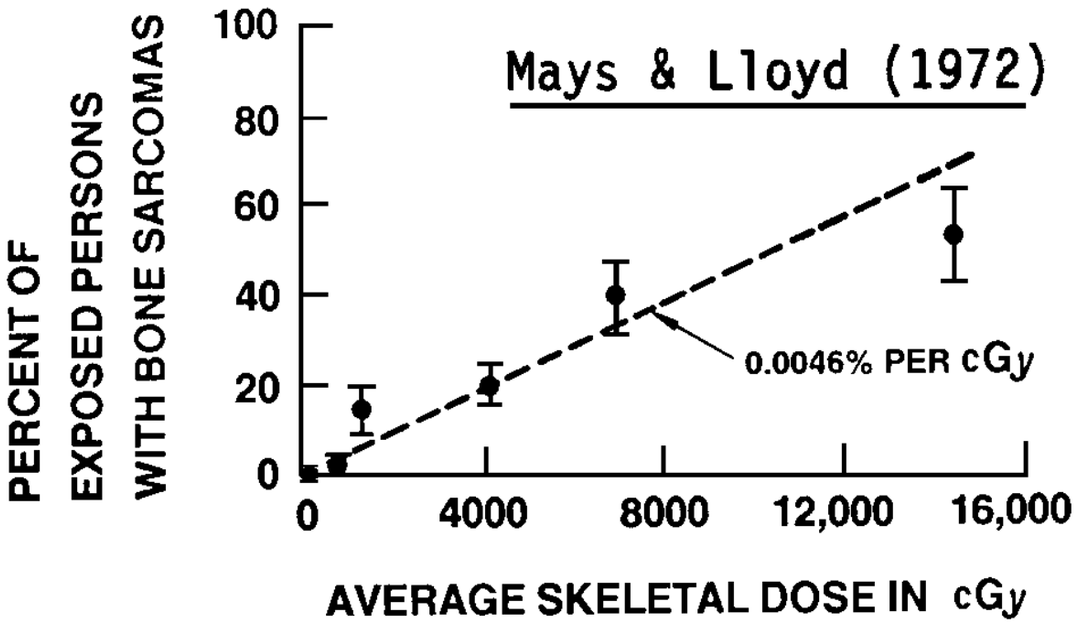


Fig. 5. Misleading linear dose-response model fit to bone sarcoma incidence in people who were exposed to ^{226}Ra as a function of cumulative dose by Mays and Lloyd (1972).

2.2 Radium-226 in beagle dogs

Since human data for exposure to internally deposited radionuclides are usually difficult to evaluate and readily confounded, in the late 1950's, the Division of Biology and Medicine of the United States Atomic Energy Commission conceived a series of carefully controlled scientific studies utilizing purpose-bred dog colonies of pedigreed beagles. These studies were conducted primarily at the University of Utah, the University of California, Davis (UC Davis), Hanford Laboratory, Richland, Washington, and Lovelace Foundation in Albuquerque, New Mexico.

The largest lifetime study of beagles exposed to ^{226}Ra was conducted at UC Davis from 1961 to 1989. Dogs were bred in a manner to maintain and randomize the gene pool and entered into the study over several years in a randomized-block design so that and all dosage levels and controls were represented contemporaneously in each treatment block. Exposure to ^{226}Ra, temporally simulating the dial painter exposures, were by eight intravenous injections two weeks apart in young adults from 435 to 540 days of age (Raabe 1989).

The distribution of deaths and causes are show in Fig. 6 (Raabe, 2010). The bone sarcoma deaths followed a tight lognormal power function of average radiation absorbed dose rate to skeleton with geometric standard deviation of only 1.22. Although the induced cancer response is a tight power function of dose rate, it is not a meaningful function of cumulative dose. For example, at an alpha radiation dose rate of about 0.1 Gy d^{-1} the median time to bone cancer death is about 1,200 days with a total cumulative dose of 120 Gy. In sharp contrast, at a alpha radiation dose rate of 0.003 Gy d^{-1} the median time to bone cancer death is about 4,000 days with a total cumulative dose of only 12 Gy. It would seem that the radiation is ten times more effective at the lower dose rate than at the higher dose rate, but that observation is misleading since it is the dose rate that controls the cancer induction and

latent period. It is the lifetime average dose rate that controls the risk of radiation-induced cancer. Since the extrapolated bone cancer latent period exceeds the natural life span of the beagles at low dose rates, there is a virtual threshold for bone cancer from radium. None of the dogs in the lowest dose group developed bone cancer because they died first from causes associated with natural aging.

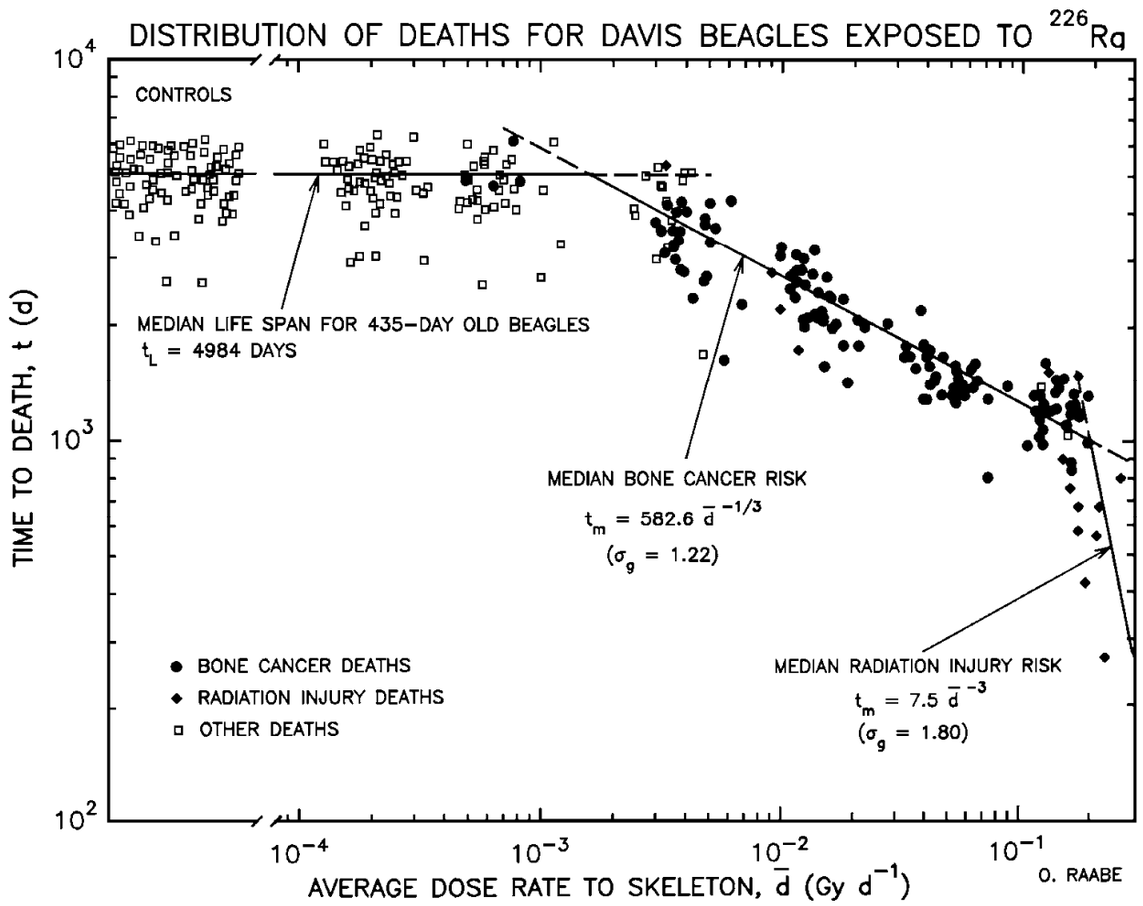


Fig. 6. Two-dimensional logarithmic representation of the data for radiation injury deaths, bone sarcoma deaths, and other deaths in beagles injected with ^{226}Ra at UC Davis, showing time from initial intake at age 435 days to death for each individual dog versus average dose rate to skeleton and fitted lognormal risk functions (Raabe, 2010).

The data shown in Fig. 6 is a two-dimensional representation of a three dimensional phenomenon. The three dimensions are lifetime average dose rate to the skeleton, time to death, and the frequency distribution of bone cancer deaths (Fig. 7). This three-dimensional phenomenon can be expressed in terms of the risk of death from various causes during the beagle lifetime (Fig. 8). The occurrence of beagle bone cancer deaths from ^{226}Ra-induced cancer is displayed as a mound rising out of a Euclidian plane. At low dose rates there are no cases of bone cancer observed because all of the beagles have died of causes associated with natural aging. At high dose rates there are radiation injury deaths.

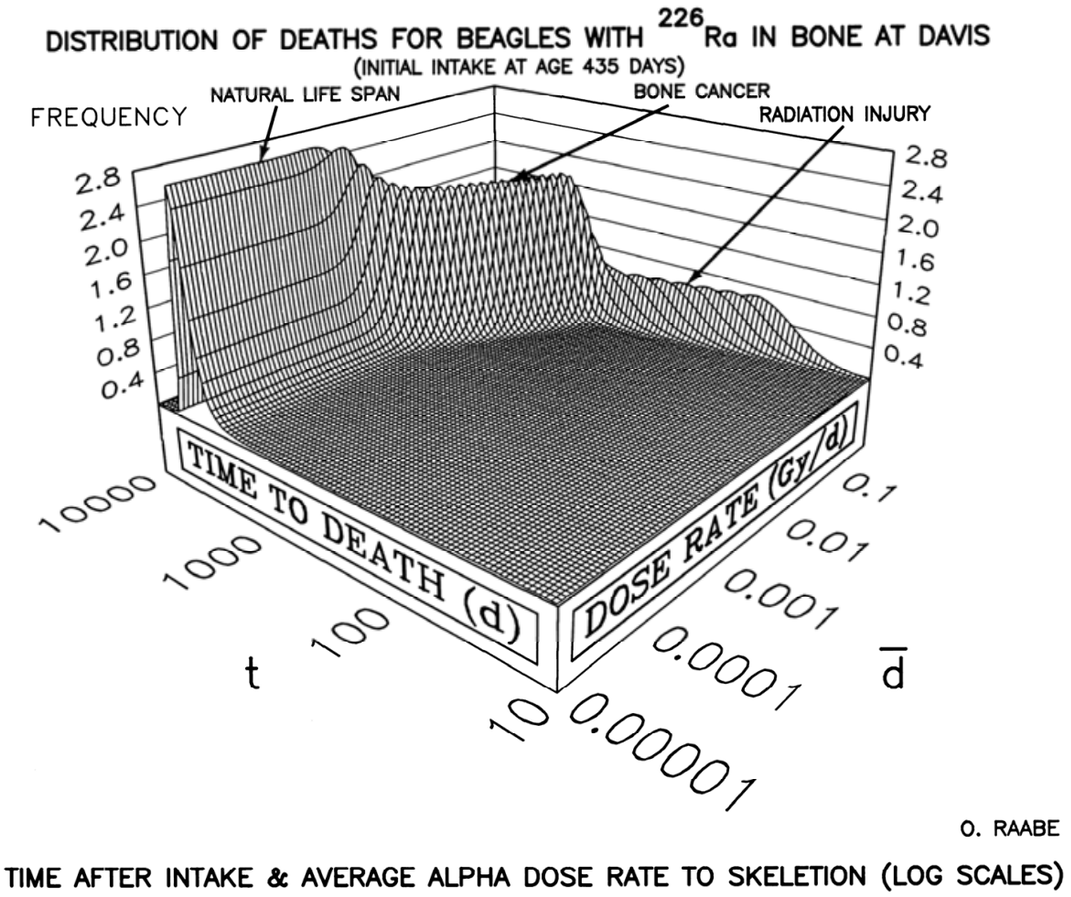


Fig. 7. Three-dimensional logarithmic representation of average-dose-rate/time/response relationships of Fig. 6, for beagles injected with ^{226}Ra at UC Davis, shown as the probability density distribution frequency of the combined risk of dying from causes associated with natural life span, radiation-induced bone sarcoma, and radiation injury, as a function of average dose rate to skeleton and elapsed time after intake at age 435 days (Raabe, 2010).

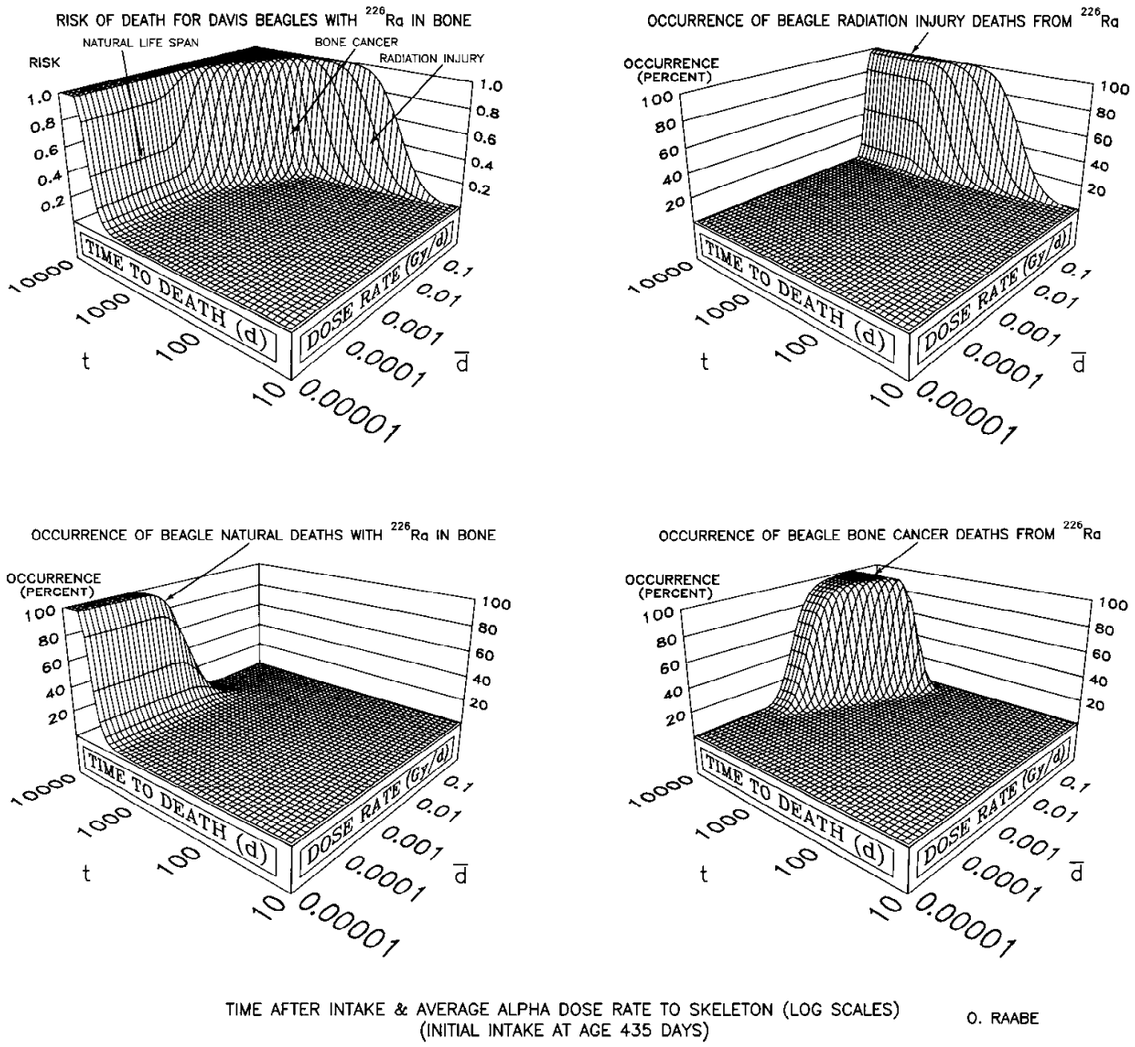


Fig. 8. Three dimensional representation from Fig. 6 of average-dose-rate/time/response relationships for beagles injected with ^{226}Ra at UC Davis shown in the top left panel as the combined risk of dying, and in the successive panels as the occurrence of deaths from radiation injury, natural life span, and radiation-induced bone sarcoma (Raabe, 2010).

The common but inappropriate practice of assuming that the cancer induction risk from exposure to ionizing radiation is proportional to cumulative radiation dose leads to misunderstandings about the true nature of the dose-response relationship. For example, the data from the ^{226}Ra beagle study can be plotted in the traditional fashion (Fig. 9). The common practice of fitting a linear no-threshold line starting at the zero-zero coordinates leads to an imprecise model that completely obscures the virtual threshold at low doses shown by the precise relationship to dose rate (Fig. 6).

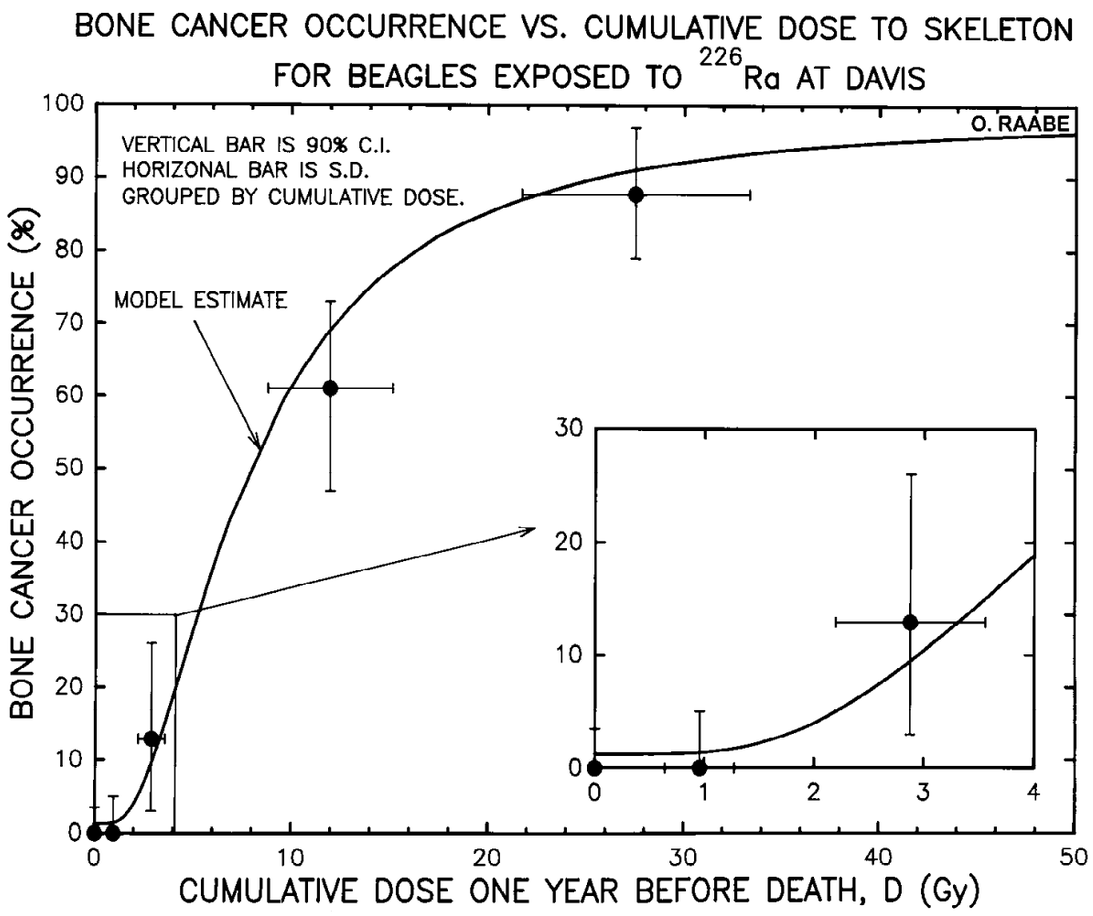


Fig. 9. Two-dimensional representation of the data for radiation-induced bone cancer deaths, in beagles injected with ^{226}Ra at age 435 days of age at UC Davis, showing lifetime bone sarcoma occurrence as percent of population versus calculated cumulative dose to skeleton one year before death. Note the life-span virtual threshold below 1 Gy as shown in the inset that would be obscured by a linear no-threshold (LNT) model of these data that starts at the origin with the only zero or near-zero risk at zero dose (Raabe, 2010).

2.3 Human cancer risk from radium-226

When a three-dimensional analysis is used for an interspecies comparison for radium-induced cancer, the different species display a similar relationship displaced in time based on natural life span (Fig. 10) (Raabe et al., 1980). The greater scatter of data for mice and people is the result of uncertainty and inaccuracy for the dose data compared to the precise beagle study. When the time scale is normalized with respect to natural lifespan for the species, all three sets of data overlay (Fig. 11). These results provided a basis for scaling cancer induction dose-response relationships among difference species. For example, the precise beagle data can be used to predict radium-induced bone cancer deaths in people by life-span normalization. The resulting prediction of median bone cancer risk for people falls almost perfectly at the median of the observed risk although the human data are quite scattered because of the dosimetric limitations (Fig. 12).

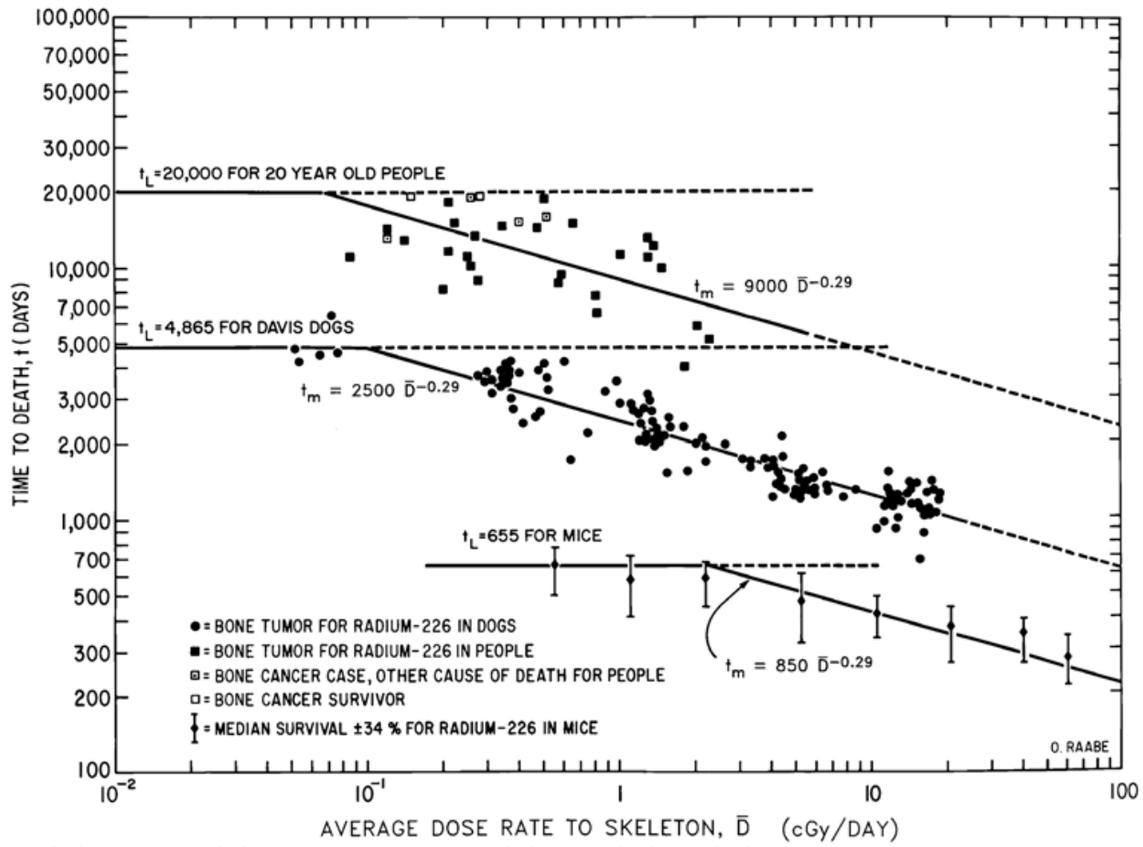


Fig. 10. Primary bone sarcoma deaths from ^{226}Ra in people, beagles, and female mice showing similar dose-response functions indicated by parallel median lines with negative slope of about one-third and t_L are the typical life spans for the three species (Raabe et al., 1980).

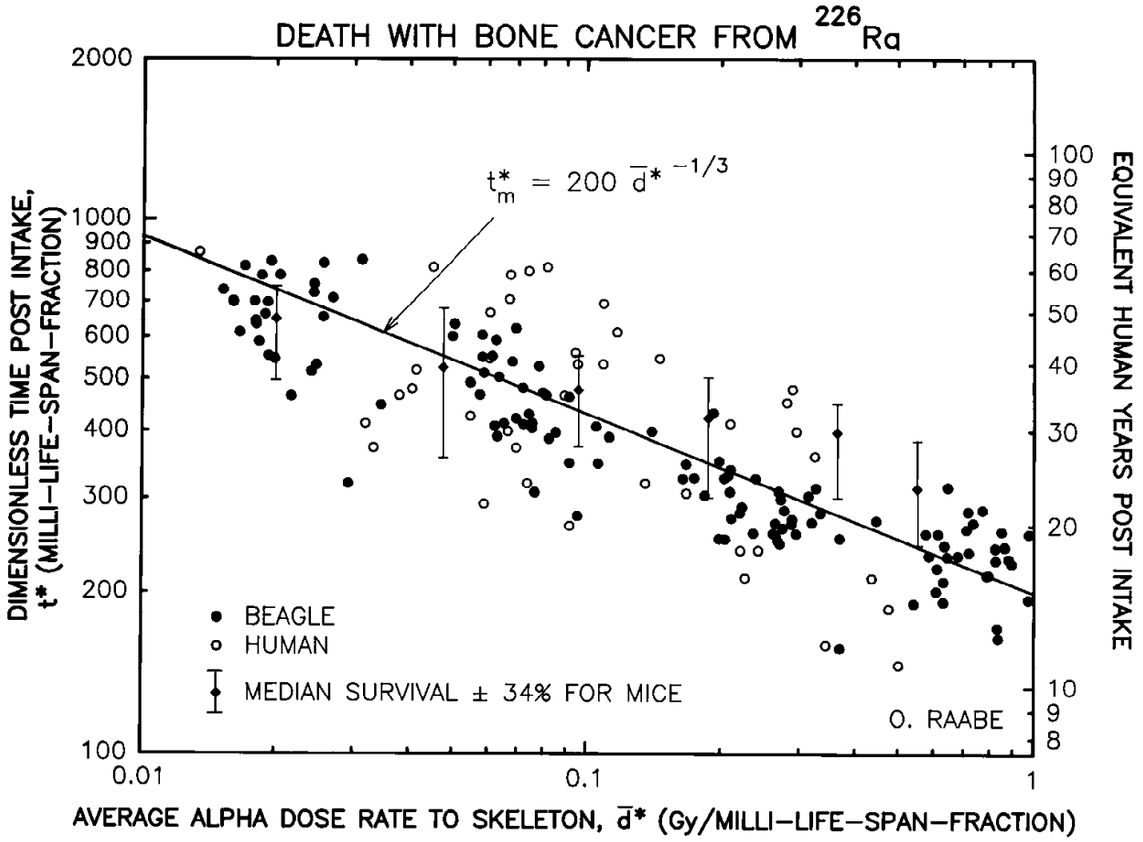


Fig. 11. Life span normalization with respect to dimensionless time and average alpha radiation absorbed dose rate to skeleton for fatal bone sarcoma in beagles, mice and people (Fig. 10) showing a single logarithmic regression line (determined for beagles) represents the median risk for all three species (Raabe, 2010).

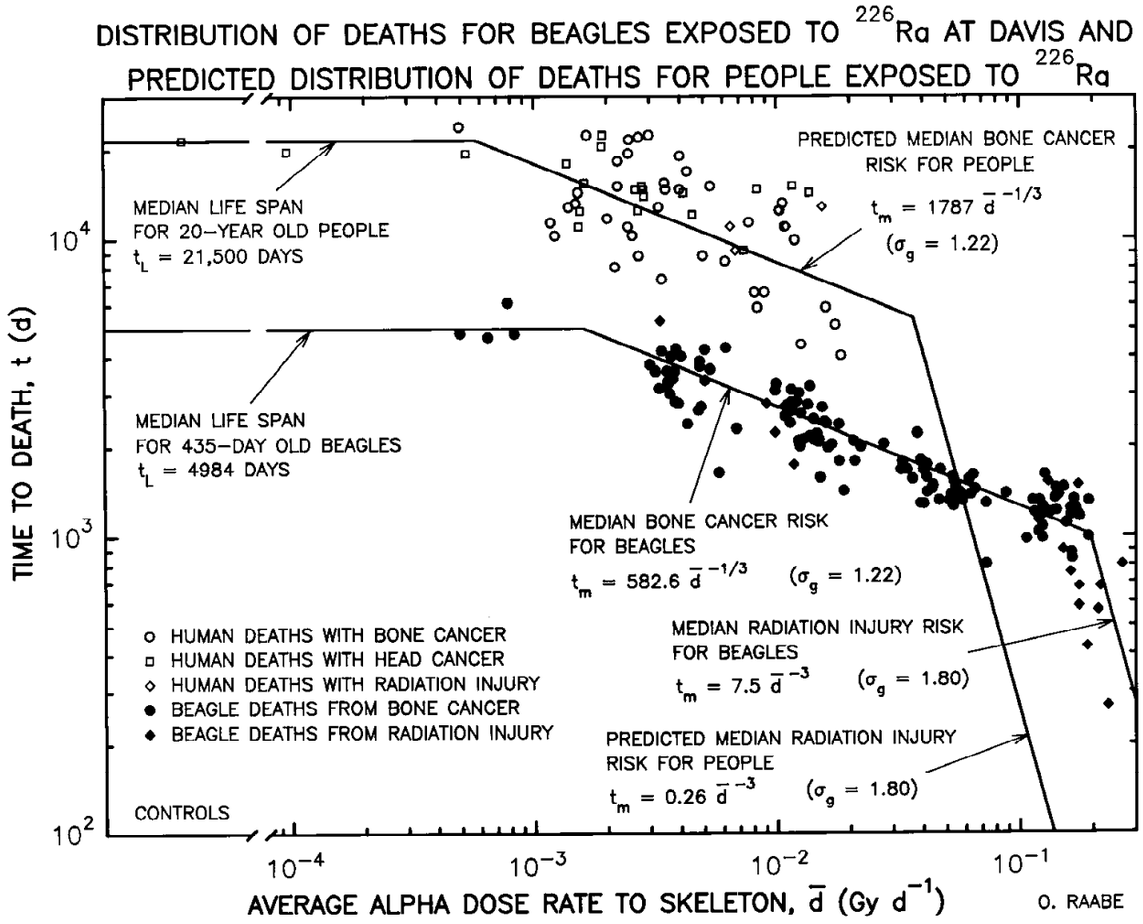


Fig. 12. Distribution of deaths for beagles and predicted distribution of deaths for people exposed to ^{226}Ra along with human data from the U.S. radium studies (Raabe, 2010).

Another form of alpha radiation-induced cancer occurs in people but not in laboratory animals. The radioactive decay of ^{226}Ra yields ^{222}Rn gas, much of which enters the blood stream and some of which sequesters in the nasal sinus and mastoid region of the head which leads to alpha irradiation of the internal tissues in these regions of the head from radon and its decay products. These deaths are somewhat delayed in time. The resulting three-dimensional frequency distribution of causes of death in people with internally deposited ^{226}Ra is shown in Fig. 13. Both head carcinoma and bone sarcoma display virtual threshold cancer risk relationships at low doses and dose rates.

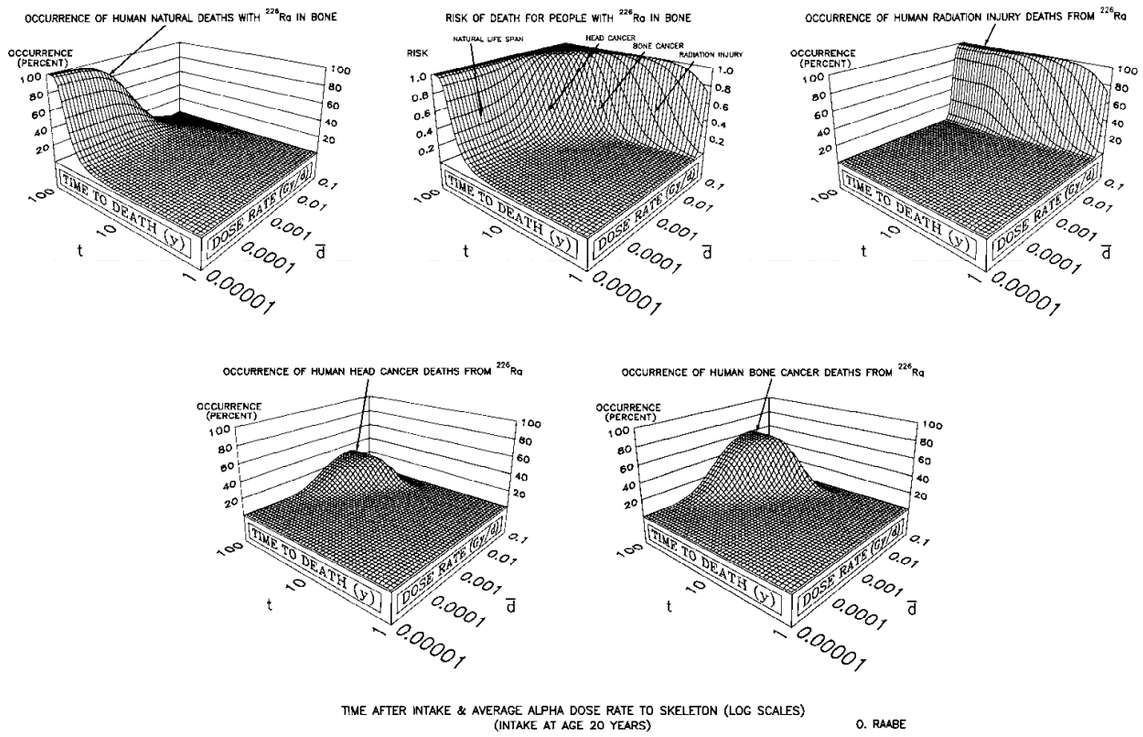


Fig. 13. Three-dimensional representation of the average-dose-rate/time/response relationships for people after intake of ^{226}Ra shown in the top middle panel as the cumulative risk of dying, in the top left panel as the occurrence of deaths associated with natural life span, in the top right panel as the occurrence of deaths from radiation injury to the skeleton, in the lower panels have the occurrence percent of deaths from radiation-induced head carcinoma and bone sarcoma, respectively (Raabe, 2010).

2.4 Strontium-90 in people

Radioactive ^{90}Sr (half life 29 years), a product of nuclear fission of uranium and plutonium, has been released into the atmosphere of the earth by nuclear weapons in Japan in 1945, by numerous atmospheric nuclear weapons tests up until 1966, and by the Chernobyl nuclear reactor accident in Russia in 1986. Strontium is chemically similar to calcium and deposits somewhat uniformly in bone mineral in the skeleton. Released to the environment, strontium is adsorbed and retained by clay in soil, and is found in small amounts in agricultural food products. The ^{90}Sr, a beta particle emitter, decays to ^{90}Y, a short-lived beta particle emitter that decays to stable ^{90}Zr. Everyone born in the Northern hemisphere after about 1950 probably has measurable trace amounts ^{90}Sr in bones and teeth.

2.5 Strontium-90 in beagle dogs

Because of the widespread exposure of people to ^{90}Sr from nuclear weapons testing in the 20th Century, the U. S. Atomic Energy Commission initiated controlled studies of ingested ^{90}Sr in purebred beagles. The largest lifetime study of beagles exposed to ^{90}Sr by ingestion was conducted at UC Davis from 1961 to 1989 in parallel with the study of injected ^{226}Ra.Dogs were bred in a manner to maintain and randomize the gene pool and entered into the study over several years in a randomized-block design so that and all dosage levels

and controls were represented contemporaneously in each treatment block. Exposed beagles received measured amounts of ^{90}Sr in food via the mother during mid-gestation and via their food through adulthood at 540 days of age. The exposed young adult beagles in the study had bones and teeth that were uniformly labeled with ^{90}Sr. The controls were fed food with a high-dose mass equivalent of non-radioactive stable natural strontium, mostly ^{88}Sr (Raabe & Parks, 1993).

Unlike the short-range alpha radiation from ^{226}Ra and decay products in bone that irradiated primarily the bone mineral of the skeleton, the longer-range beta radiation from ^{90}Sr-Y irradiated the bone mineral, the bone marrow, tissue and tissues adjacent to bone and teeth. Induced cancer deaths were associated with four different types of cancer: (a) bone sarcoma, (b) periodontal carcinoma, (c) oral carcinoma, and (d) leukemia. Each of these displayed a virtual threshold relationship (Fig. 14). Although there were 2 cases of bone sarcoma deaths among the 80 controls, there were no cases among the 183 exposed beagles

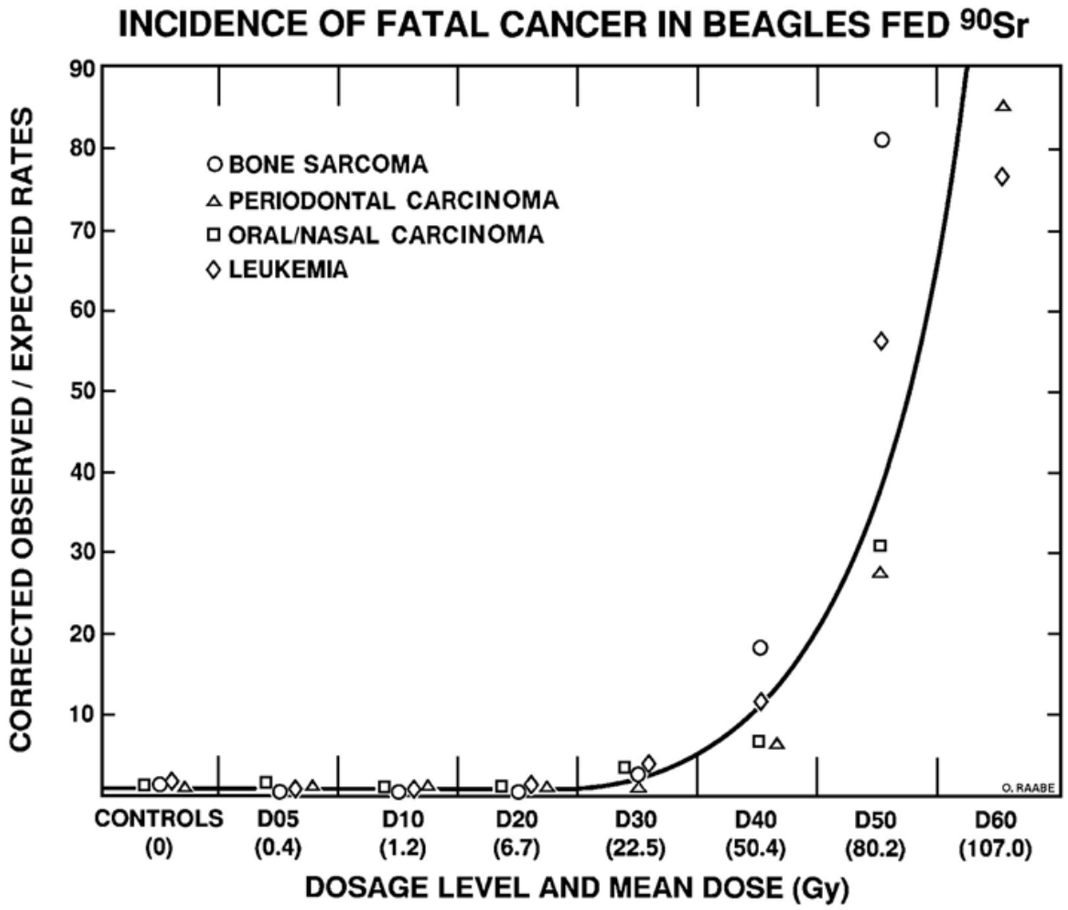


Fig. 14. Statistical evaluation by survival analysis (Peto et al. 1980) of the incidence of fatal leukemia, bone sarcoma, and carcinoma in beagles fed ^{90}Sr from before birth to adulthood at UC Davis demonstrating a life-span virtual threshold with all radiation-induced cancers occurring at calculated cumulative skeletal beta radiation doses above 20 Gy (20 Sv). The absence of bone sarcoma in the lowest three dosage groups is significantly less than those found in the controls ($p<0.047$)(Raabe, 2010).

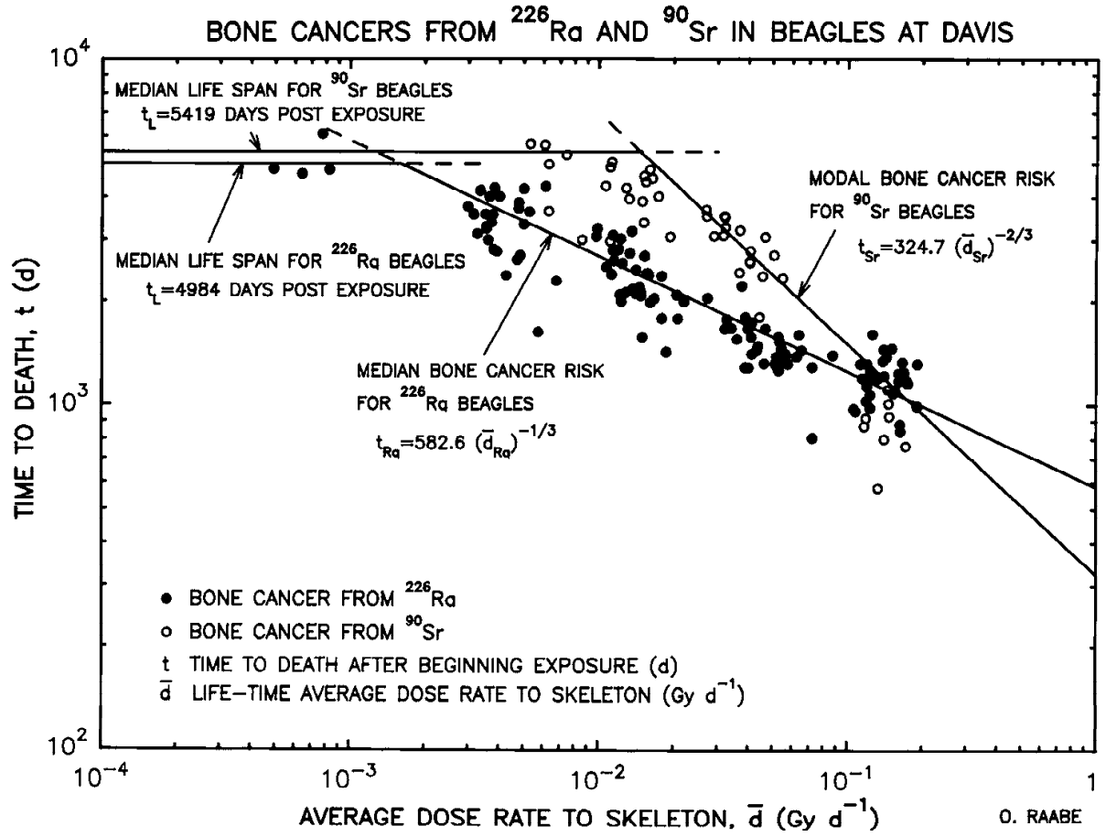


Fig. 15. Comparison of bone sarcoma in beagles at UC Davis from injected ^{226}Ra and ingested ^{90}Sr (Raabe, 2010).

in the three lowest dose groups. The chance of this is p=0.092 (Fisher's Exact Test). Among all 162 controls in the ^{226}Ra and ^{90}Sr studies there were 2 fatal bone sarcoma cases and two with bone sarcoma that died of other causes. With 4 bone sarcoma cases among 162 controls, the absence of bone sarcoma cases in the three lowest ^{90}Sr dose groups is a statistically significant reduction in tumor cancer incidence with p=0.047 (Fisher's Exact Test). The shape of the dose response relationship for ^{90}Sr-induced bone sarcoma is similar to that for ^{226}Ra except it follows a Weibull distribution and the power function slope is twice as steep as for ^{226}Ra indicating that an average of two beta particles are needed to equal the effect of one alpha particle for induction of bone cancer (Fig. 15).

2.6 Inhaled, ingested, and injected radionuclide studies in beagles

An analysis of 25 lifetime studies of inhaled, ingested, and injected internally-deposited radionuclides in beagles show remarkable consistency (Raabe, 2010). Three-dimensional models have been fit to selected data from life-time studies of internally deposited radionuclides in young adult beagles at four laboratories: University of California, Davis (Raabe and Abell, 1990), Lovelace Inhalation Toxicology Research Institute (ITRI) and University of Utah (Mauderly and Daynes, 1994), and Battelle Pacific Northwest Laboratory, PNL (Park et al., 1993). Dose response data were evaluated for beagles with skeletal burdens of ^{90}Sr after exposure by ingestion at Davis, by injection at Utah, and by inhalation at ITRI,

for lung burdens of inhaled ^{144}Ce, ^{91}Y, and ^{90}Sr in fused aluminosilicate particles (FAP) at ITRI, inhaled ^{239}Pu dioxide at PNL, skeletal burdens of injected ^{226}Ra at Davis and Utah and inhaled ^{238}Pu at ITRI, and skeletal burdens of injected ^{228}Ra and ^{241}Am at Utah. Analyses were based on the mean organ absorbed doses to to the target tissues from parent and corresponding doses from decay products in their appropriate proportion, where all x ray and gamma emissions were ignored because of their minor contribution, and where beta emissions are also ignored in the cases where the primary exposures were from alpha radiation. Overall, there were separate injection studies of ^{226}Ra, ^{228}Ra, ^{224}Ra, ^{228}Th, ^{239}Pu, ^{249}Cf, ^{252}Cf, ^{241}Am and ^{90}Sr. There were separate inhalation studies of ^{239}Pu, ^{238}Pu, ^{90}Y, ^{91}Y, ^{90}Sr, and ^{144}Ce (Raabe, 2010).

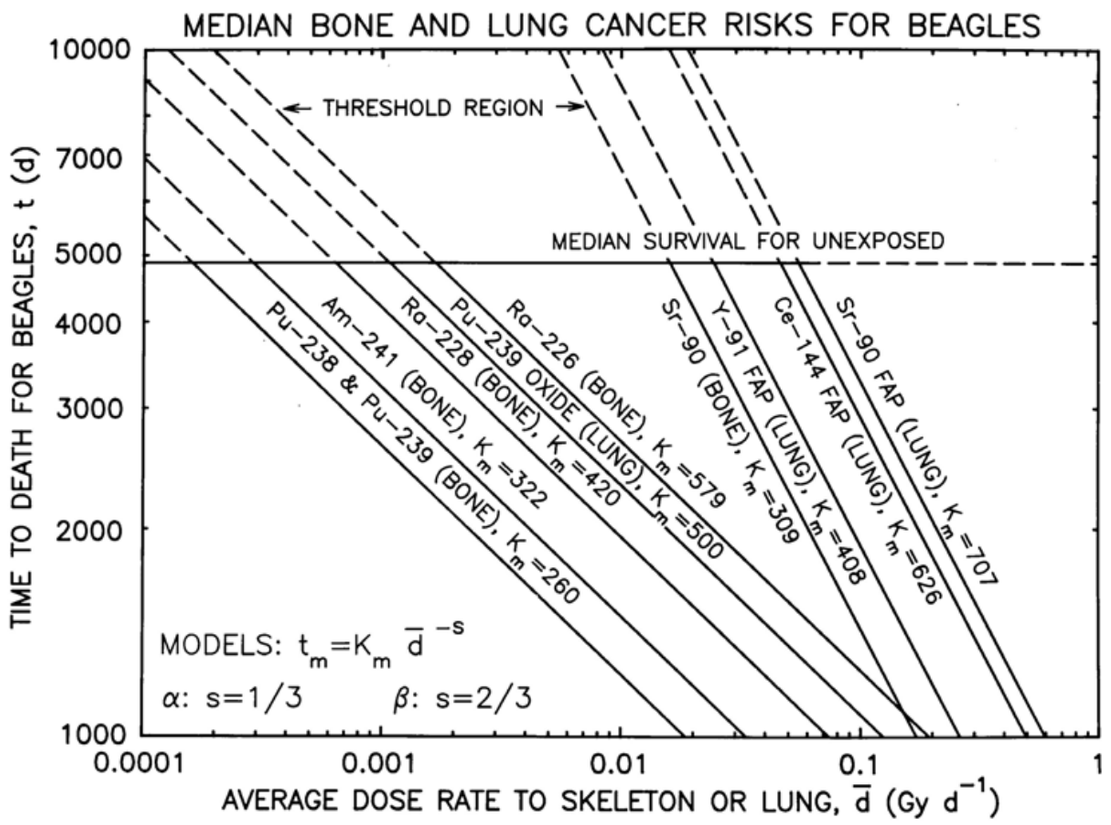


Fig. 16. Summary of bone sarcoma and lung carcinoma risk functions for beagles demonstrating similar target organ dose-rate/time/response patterns illustrating the life-span virtual thresholds at low dose rates. The positions of the lines vary because of inherent differences in irradiation of the target cells by the different radionuclides. Data were selected from life-time laboratory studies of internally deposited radionuclides in young adult beagles including skeletal deposits of ^{90}Sr after exposure by ingestion at Davis, by injection at Utah, lung deposits of inhaled ^{144}Ce, ^{91}Y, and ^{90}Sr in fused aluminosilicate particles (FAP) at ITRI, lung deposits of inhaled $^{239}PuO_2$ at PNL, skeletal deposits of injected ^{226}Ra at Davis, inhaled $^{238}PuO_2$ at ITRI, and skeletal deposits of injected ^{228}Ra and ^{241}Am at Utah (Raabe, 2010).

A selection of these results are shown in Fig. 16. All of the alpha radiation studies followed lognormal distributions with power function slope of negative one-third. All of the beta radiation studies followed Weibull distributions with power function slope of negative two-thirds. The different positions of these functions were shown to be associated with the efficiency of irradiation of the target sensitive tissue in each case. At low dose rates and associated low life-time cumulative doses there was a virtual threshold for ionizing radiation induced cancer. For young adult beagles, bone sarcoma induction from alpha-emitting or beta-emitting radionuclides was unlikely for cumulative doses below about 20 Sv delivered specifically to the sensitive tissues at bone surfaces. For inhaled alpha-emitting radionuclides lung carcinoma was unlikely for cumulative lung doses less than 10 Sv and for inhaled beta-emitting radionuclides lung carcinoma was unlikely for cumulative lung doses less than 5 Sv (Raabe 2010).

3. Radon exposures

3.1 Environmental radon

All of the earth's atmosphere contains low concentrations of radioactive airborne particles and gases associated with various naturally occurring radionuclides. Of particular interest are radioactive isotopes of the inert gas, radon. Three radioactive isotopes of the radon gas ^{219}Rn from the natural ^{235}U decay series, ^{220}Rn from the natural ^{232}Th decay series and ^{222}Rn from the natural ^{238}U decay series are produced in earth's crust and released by diffusion into the outdoor air. The ^{222}Rn with a decay half-life of 3.82 days is therefore the most important. In some cases ^{220}Rn, commonly called thoron, can be important also. The ^{238}U decay series that yields ^{222}Rn and its decay products is shown in Figure 1. The ^{222}Rn is the decay product of the naturally occurring radium isotope ^{226}Ra that occurs naturally in all the soils and rock on the surface of the earth at concentrations of about 25 Bq kg^{-1}. Consequently, ^{226}Ra is also naturally found in ground water and the human body, usually in trace amounts (about 1 Bq per person). When ^{226}Ra undergoes radioactive decay (half-life 1,600 y) it forms gaseous ^{222}Rn, which can percolate through and diffuse out of the soil or rock and into the air. This process has definite temporal limits since the half-life of ^{222}Rn is only about 3.8 d. However, enough radon reaches to the earth's atmosphere to provide an average outdoor concentration of about 10 Bq m^{-3} in outdoor air in the most populated part of the world. Much lower concentrations occur over the oceans and in cold polar locations. The ^{222}Rn decays in air to form radioactive, solid decay products that form radioactive aerosols. In addition to ^{226}Ra, similar or smaller amounts of ^{228}Ra, a decay product of ^{232}Th, are also found on the earth leading to the atmospheric release of the radon gas isotope, thoron, ^{220}Rn. However, the concentration of thoron and its decay products is usually negligible in comparison the ^{222}Rn and its decay products. Very high air concentrations of radon can be found in some mines and elevated levels can be found in most buildings.

When air containing radon gas is inhaled by a person, a small amount of this inert gas dissolves in body fluids. During its radioactive decay emitting an alpha particle and the following decay of its decay products some cells of the body are irradiated, but the level of whole body irradiation is quite small. Much more important is the irradiation of the lungs associated with the deposition in the bronchial airways of the radon decay products which are solid metal atoms rather than gases. While radon gas is inhaled and exhaled, the unattached decay products and those attached to small inhalable airborne particles can deposit in the bronchial airways of the lungs during normal breathing. For example, in the

case of ^{222}Rn , the short-lived alpha-particle emitting isotopes of polonium, ^{218}Po and ^{214}Po, that deposit in the lungs can result in relatively high alpha-particle irradation of bronchial airways. The comparatively small dose associated with the beta-particle emitting decay products is insignificant compared to the alpha irradiation which is about 20 times more biologically effective than beta radiation per unit of energy. The equivalent dose to the bronchial airways from radon and thoron decay products in ambient air in homes for the average person in the USA has been estimated to be about 28 mSv per year (NCRP 160, 2009). In some areas of the USA, the annual dose to the bronchial airways from radon and thoron may be double this average value.

Given sufficient time and other favorable conditions, the decay products of ^{222}Rn will come into radioactivity equilibrium with the radon with each of the short-lived decay products having the same activity concentration in the air as the ^{222}Rn. However, this ideal equilibrium is rarely attained in air containing elevated levels of radon so that measurement of the radon gas concentration does not precisely indicate the concentration of decay products unless that state of disequilibrium is known. Since essentially all of the biologically important radiation dose to the respiratory epithelium is derived from the alpha-emitting radon decay products, their concentration is sometimes described in special units called the working level, WL. The WL unit is defined as any combination of the short-lived radon progeny in one liter of air that will result in the emission of 130,000 MeV of alpha particle energy. Air having a ^{222}Rn concentration of 3.7 kBq m^{-3} with the progeny in secular equilibrium would represent 1 WL. The exposure associated with a typical work month in a uranium mine for 170 h at 1 WL is called an exposure of 1 working level month, WLM. Dosimetric models indicate that the nominal dose to the bronchial epithelium associated with inhalation of radon decay product aerosols by a uranium miner is about 6 mGy/WLM. Assuming an alpha radiation weighting factor of 20, this yields about 120 mSv equivalent dose per WLM to the bronchial region of the lung.

Upon inhalation, the airborne particles containing radon decay products may deposit upon contact onto the surfaces of the respiratory airways. Because of their diffusivity, the very small molecular clusters may efficiently deposit in the head airways or in the trachea and bronchial airways of the lung. Other somewhat larger particles may reach the alveolar region of the lung, as well. Because of their short radioactive half-lives, they usually decay prior to being cleared from the respiratory tract and irradiate the respiratory epithelium. Of primary concern in this regard is the irradiation of the bronchial epithelium by the highly ionizing alpha radiation emitted by radium-A (^{218}Po) and radium-C' (^{214}Po). Since radon itself is an inert gas, it does not readily deposit in the respiratory airways during inhalation and is mostly exhaled. Occasionally an atom of radon gas may decay and emit alpha radiation in air present in the lung irradiating the epithelium, but the fraction of the dose contributed by the radon itself is small compared to that associated with the deposited decay product particles. Because naturally occurring radon decay products are in ambient air outdoors and within a building, the lung is the most highly irradiated organ of the body of a typical person from background radiation sources.

3.2 Radon and radon decay product dosimetry

The dosimetry methodology associated with estimating the alpha radiation dose to the lungs of people from exposure to atmospheres containing radon and thoron is quite complicated and the dosimetry estimates are subject to quite large uncertainties. Consider

the case of radon gas entering an air space as it diffuses from the earth. Initially there are no decay products since they are produced as the radon atoms decay and convert from gas atoms to metallic atoms. This in-growth of ^{218}Po (commonly called Ra-A), ^{214}Pb (commonly called Ra-B), and ^{214}Bi (commonly called Ra-C) is shown graphically in Figure 17 for a concentration of radon equal to 3.7 kBq m^{-3} which at decay-product equilibrium is the level commonly called one working level (WL) associated with underground mining. While ^{218}Po comes to equilibrium with radon in about 20 minutes, it takes more than 2 hours for ^{214}Pb and ^{214}Bi to approach equilibrium. In that time more radon is entering the airspace, ventilation is changing the relative concentrations, and the metallic decay products are being surrounded by water molecules, are undergoing Brownian diffusion and are attaching to larger airborne particles and onto the surfaces of walls, floor, ceiling, furniture, and people. Measurements that are made of radon gas concentrations in a living space or underground mine do not describe the concentration of the airborne solid decay products that deliver more than 90% of the dose the bronchial airways of people in that room or underground mine.

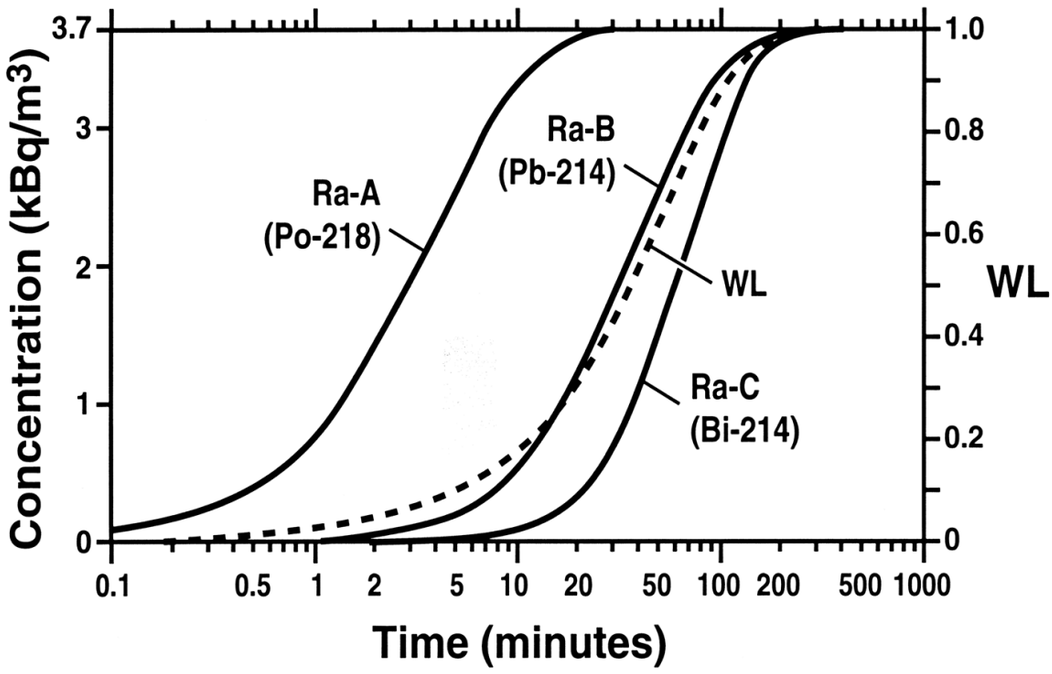


Fig. 17. Ingrowth of radon decay products as a function of time starting with 3.7 kBq m^{-3} of ^{222}Rn yielding one working level, WL.

As each radon gas atom in air decays by emitting alpha radiation it forms an atom of radioactive polonium, ^{218}Po (called radium-A, half-life about 3 minutes). This metallic atom quickly oxidizes and forms the center of a particulate molecular cluster of about 8 Å in diameter. When it decays emitting alpha radiation, a series of short-lived decay products are formed in air. These also form particulate clusters. This radon decay process is shown schematically in Fig 1. The long-lived lead isotope, ^{210}Pb (half-life 22.3 y) provides negligible

radioactivity to the atmospheric aerosols and is, in effect, virtually non-radioactive compared to its short-lived progenitors. These radon decay product clusters represent the smallest airborne particles normally found in ambient air. In addition, these clusters attach upon contact to other, larger airborne particles to an extent that depends upon their concentration. Typically, more than 90% of radon decay product aerosols are associated with particles smaller than 0.5 μm in aerodynamic diameter.

Actually, the dosimetry is even more complicated. The deposition of airborne particles in the bronchial airways during inhalation is a function of the aerodynamic and diffusive properties of the airborne particles to which the radon decay products attach (ICRP 66, 1994). This depends on both the size distribution and concentration of the the airborne particles in the air. When the concentration of airborne particles is quite small, many of the decay products may not be attached to a larger particle (the so called unattached fraction). The unattached fraction efficiently attaches in all parts of the airways because of Brownian diffusion properties of very small particles causing somewhat efficient deposition in the upper airways of the nose and throat as well as the small bronchial airways. The irradiation of the living cells occurs primarily after the airborne particles deposit on the surface of the airways. If the radon decay products are associated with larger airborne parrticles, the deposition in the lung may be less because some of the inhaled particles may be exhaled. If the airborne particles are relatively large, they may deposit in the nose and throat and not readily reach the bronchial airways. Both the concentration and the aerodynamic particle size distribution of the airborne particles will affect the bronchial dose. Smoke in the air space can have a large effect on the bronchial radiation dose from radon decay products. Clearly, a simple measurement of the average concentration of radon in the air is insufficient to provide an accurate estimate of the lifetime average radiation dose rate to the bronchial epithelium of a person. Many reported studies only involve average radon measurements. Many reported studies only reported cumulative exposures to radon decay products in units such as working level months (WLM).

3.3 Lung cancer from exposure to radon and its decay products

Uranium mining in the 20th Century led to the clear realization that protracted and repeated exposures to high concentrations of radon can cause lung cancer. For example, miners working uranium mines in the Colorado Plateau region of the USA were found to have a high incidence of lung cancer depending on the level of exposure. People chronically exposed over extended period of employment to high levels of airborne radon decay products such as are found in uranium mines have developed bronchogenic carcinoma at incidence rates that significantly exceeded the expected rates in either smokers or non-smokers. However, almost all the lung cancer cases in the western U.S. mines occurred in smokers (Saccomanno et al., 1988). The reported excess relative risks of lung cancer as a function of cumulative dose expressed in working level months of exposure are shown in Figure 18. The miners did not have radon dosimeters and it could never be clear how long anyone worked in any of the areas within the mines, hence the working level month (WLM) values are estimates that are intended to represent cumulative radiation dose. As with all cumulative dose plots it is common to fit or draw a linear no-threshold function that begins at the origin obscuring the apparent virtual threshold. This is facilitated by the large dosimetric uncertainties (Lubin et al., 1995).

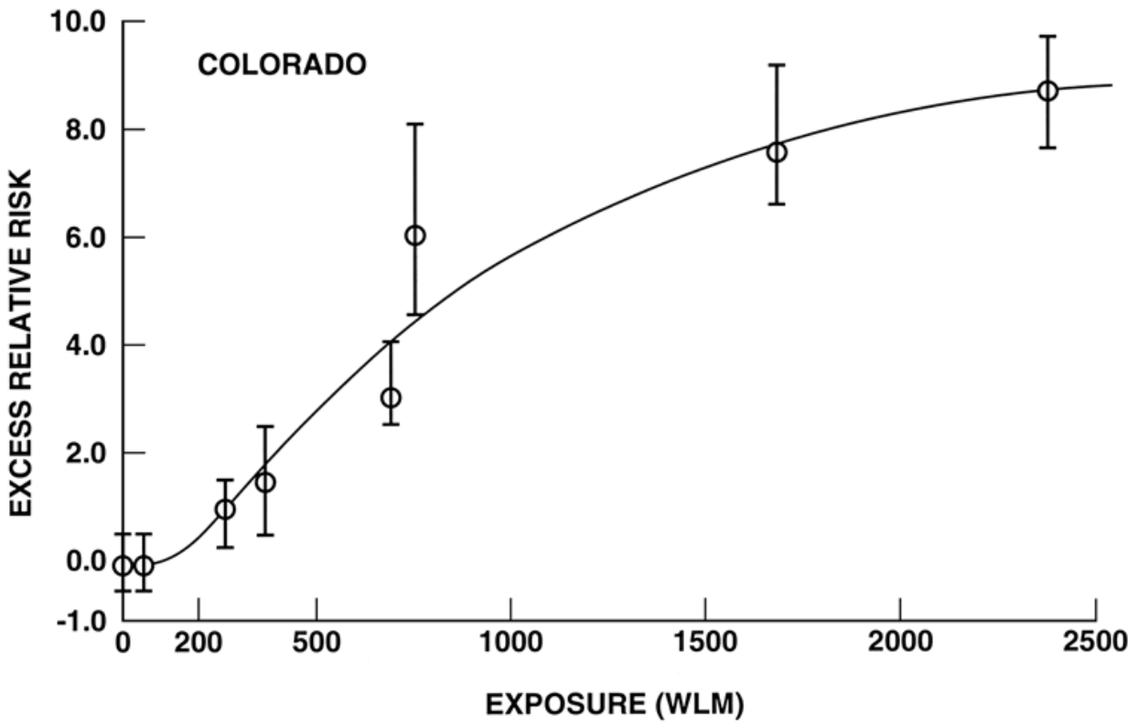


Fig. 18. Historical data of observed lung cancer risk as a function of exposure in working level months (WLM) among uranium miners from the Colorado Plateau in the United States (BEIR IV, 1988). Uranium miner data were routinely expressed in estimated cumulative doses in WLM so that the virtual threshold was badly obscured or ignored and linear no-threshold (LNT) models were assumed to apply in every case (Figure 19).

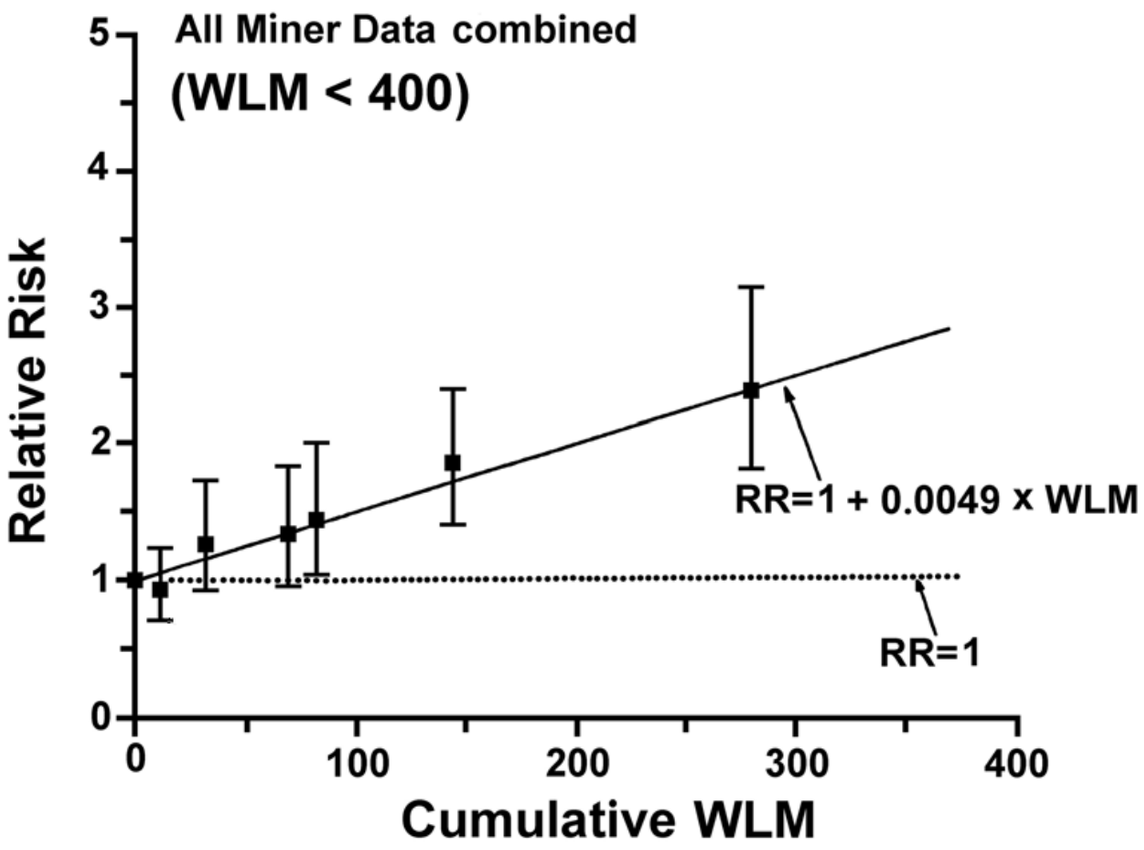


Fig. 19. Observed relative risk (RR) of lung cancer in underground miners versus cumulative airborne radon decay product exposure in working level months (WLM) for WLM less than 400 with a linear no-threshold risk model fit to the data (Lubin et al., 1994).

The reported epidemiological studies of radon in homes are not conclusive and are usually based on average radon concentration measurements rather than on decay product levels and the results were displayed using the standard linear no-threshold assumption. Also, the dosimetric uncertainties are usually not displayed. In Figure 20 the authors created a mathematical relative risk of 1 at a radon concentration exposure of zero but there is no such point in the real world. The major cause of lung cancer in the United States is known to be cigarette smoking (up to 95% incidence) so that cigarette dosimetry is actually more important than radon dosimetry in these types of studies.

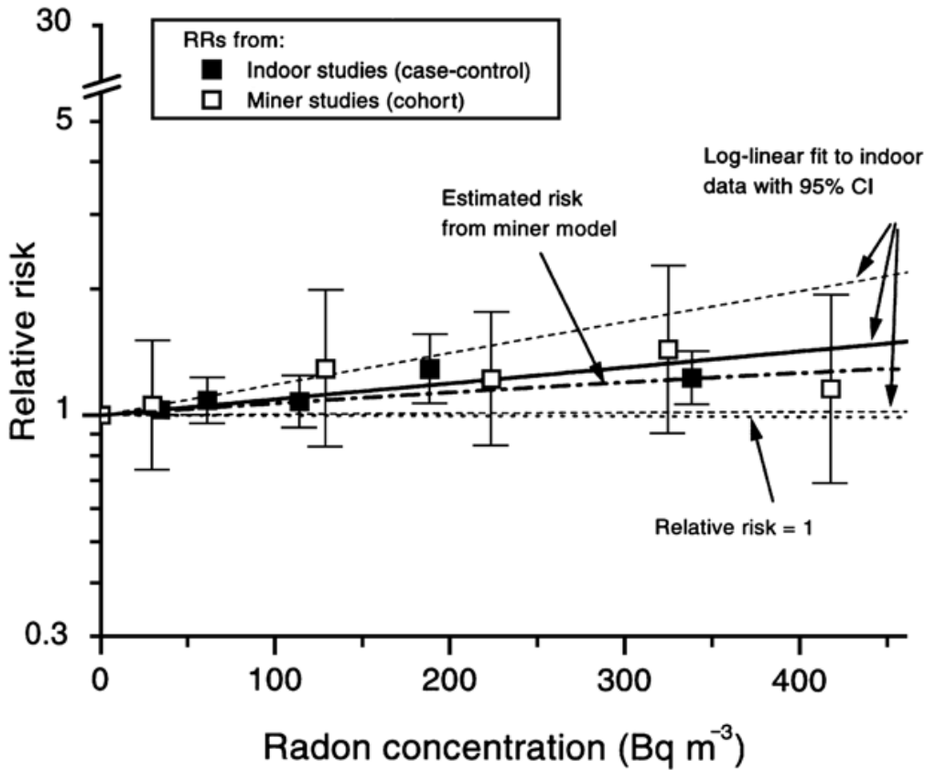


Fig. 20. Summary of calculated relative lung cancer risk mathematical meta-analysis of indoor radon studies along with miner studies (BEIR VI, 1999).

A careful ecological study was conducted of the relationship of lung cancer mortality as a function of measured air concentrations in homes in over 1,600 counties in the United States (Cohen, 1995). The remarkable results showed that the counties with homes having the higher radon concentrations tended to have the lowest lung cancer mortality rates (Figure 21). This relation was robust and was demonstrated for widely separated counties in various parts of the United States. His finding were in conflict with the prevailing linear no-threshold theory promulgated by the ICRP and United States Environmental Protection Agency (EPA). A scientific committee formed to review the radon risk data concluded that the results were faulty no matter how robust and reproducible because they were based on an ecological study that could not directly match cases and radon exposures (BEIR VII-2, 2006). Cohen argued to no avail that under the LNT hypothesis the distribution of the doses was irrelevant and his data proved the linear no-threshold model did not apply to exposure to radon in homes. Although it is mathematically possible that Cohen's ecological study is misleading, it seems highly unlikely that such an anomaly would uniformly appear everywhere in the United States. Cohen's result is substantiated by a simple comparison of the County by County radon zones and lung cancer mortality rates (Figure 22).

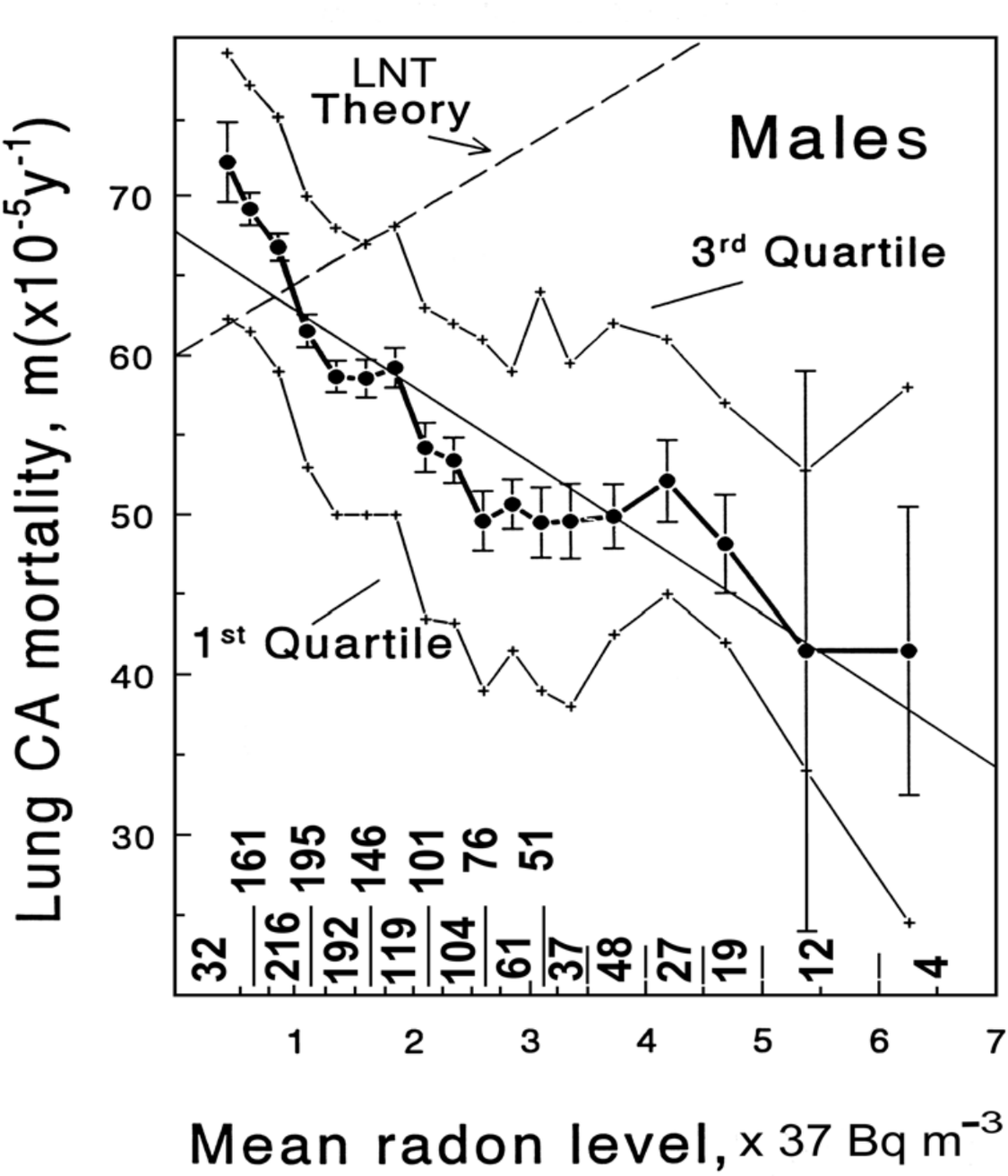
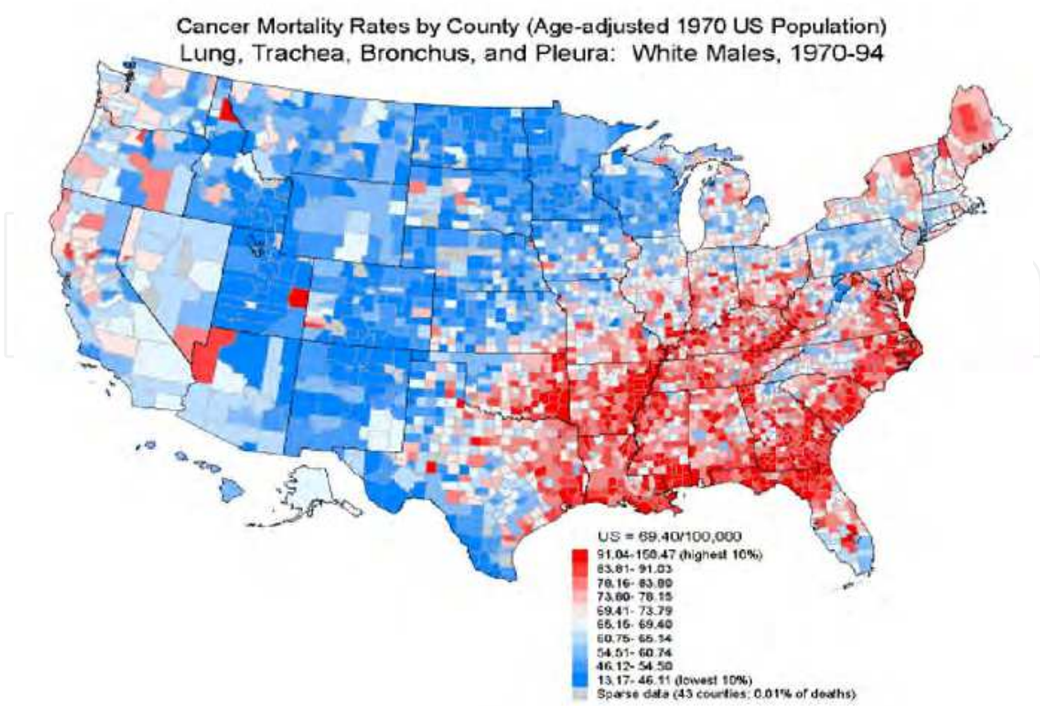


Fig. 21. Lung cancer mortality rates in men versus mean radon level for 1,601 counties spread throughout the continental United States as a function of mean radon level with the abscissa in units of 37 Bq m^{-3} (Cohen, 1995).



LUNG CANCER: Blue Low, Red High ↑

↓ RADON: Red HIGH, Yellow LOW

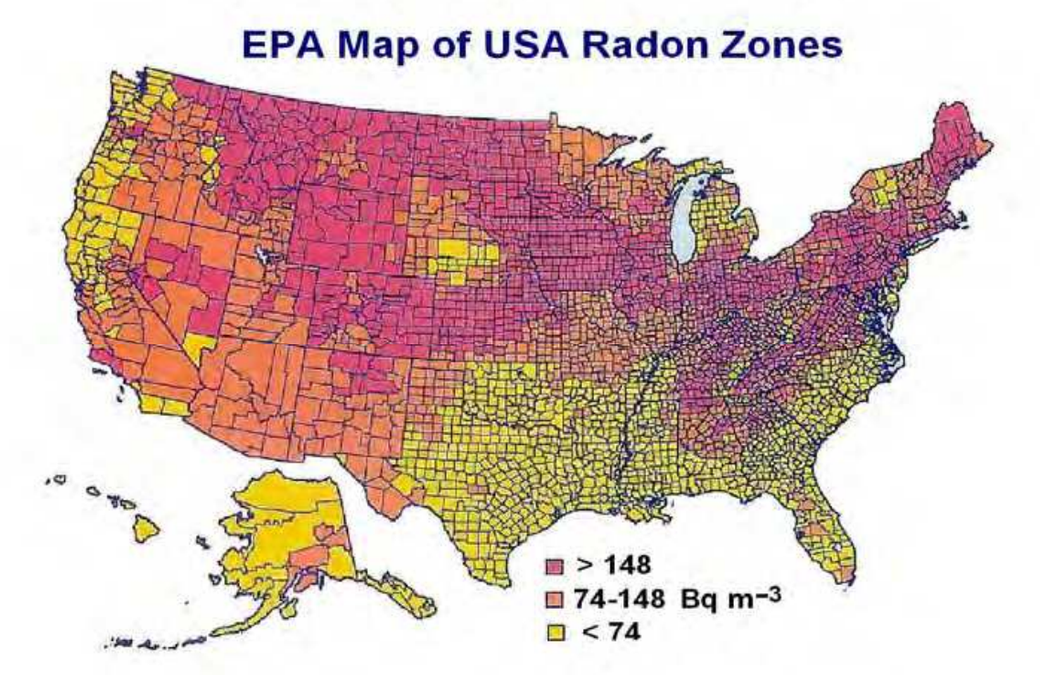


Fig. 22. Comparison of lung cancer mortality rates and radon concentration in homes among the counties of the United States of America.

A conditional logistic regression case-control study of lung cancer risk from residential radon was conducted in the State of Massachusetts in the United States by Thompson et al. (2008). Although their radon dosimetry was limited to average air concentration, they also evaluated cigarette smoking dose in a precise manner by stratifying the data with nine categories of smoking history. This ingenious approach led to results that agreed well with Cohen's ecological study (Cohen 1995). They found that lung cancer rates were the highest in those people with the smallest radon expose levels (<25 Bq m^{-3}). As radon levels were increased the lung cancer rate went down in a consistent manner which was statistically significant in one dose group ($p<0.05$ at 59-75 Bq m^{-3}) and statistically strong in three others ($p<0.1$). Radon induced lung cancer appeared to be present only for average radon air concentrations greater than 250 Bq m^{-3}.

Fornalski and Dobrzynski (2011) reanalyzed the data from 28 published studies of the relationship of lung cancer and radon exposure using Bayesian statistical methods. They concluded that for people exposed to radon concentrations less than 838 Bq m^{-3} in those 28 studies there is no evidence that there is an association between radon exposure and lung cancer incidence.

These studies suggest that radon exposures at low dose levels can interfere with ongoing neoplastic processes in the lung as may be associated with cigarette smoking. Mechanisms such as stimulation of DNA repair may be invoked by low level exposures to ionizing radiation helping to inhibit the damage associated with chemical carcinogens such as cigarette smoke exposures. Similarly, up-regulating and down-regulating of genes at lower ionizing radiation doses can interfere with ongoing carcinogenic biological processes and lead to reduced cancer development.

4. External ionizing radiation epidemiology

4.1 Typical study problems

Several external ionizing radiation epidemiology studies have been conducted. However, some of these studies involve technical problems that affect the reliability of the findings. A distortion of the possible carcinogenic response is associated with the use of cumulative dose as the radiation exposure measure rather than the more appropriate lifetime average dose rate. Several confounders such as exposure to toxic and carcinogenic chemicals are quite difficult to properly evaluate and are often ignored. In years past two carcinogenic agents, benzene and trichloroethylene, were commonly used as cleaning agents in laboratories including nuclear research laboratories. There were few if any records of these exposures or chemical doses. The most important confounder among the predominantly male radiation workers is cigarette smoking. Confounding occurs when the workers who are most likely to receive the highest exposures to ionizing radiation are also the most likely to have been smokers. It is possible that those workers at nuclear facilities (mostly men) who worked most directly in the radiation areas were more predominantly cigarette smokers than workers who had managerial, supervisory, or clerical assignments. This confounding from smoking is most likely important prior to 1960 before the health risks of smoking were well understood. This possibility is most prominent in studies of workers at Oak Ridge National Laboratory in the United States State of Tennessee where nuclear operations began in 1943. Some epidemiological studies of Oak Ridge workers have attributed lung cancer and other smoking-related illnesses to radiation exposure (Wing et al., 1991).

4.2 Atomic worker studies

Two major series and the most important are the ionizing radiation epidemiological studies of multinational radiation works in several countries of the world that have been conducted by Cardis and her numerous co-workers (Cardis et al. 1995, Cardis et al. 2005). The two studies were similar in approach, but the second was much larger and included subjects who were in the first study. In these studies emphasis was on workers who had available ionizing radiation dosimetry records of external photon exposure (x rays and gamma rays) but who did not have major internal exposure or neutron exposure. In the second study internally deposited radionuclide dose was specifically limited to ten percent of the total. Two cause of death risk types were separately evaluated: (a) leukemia excluding chronic lymphocytic leukemia and (b) all cancers excluding leukemia. Simple linear dose-response models of risk that was assumed to be proportional to cumulative external ionizing radiation dose were statistically evaluated. Radiation doses were lagged by 10 years for cancer cases and 2 years for leukemia. Hence, they assumed the cancer risk was proportional to the cumulative dose received prior to the lag period just before death.

If a person developed lung cancer, the radiation dose received in the prior 10 years was assumed to have not been a contributor to the risk. Typical lifetime doses in these studies were well below 1 Sv, so that the risk of radiation-induced cancer would be expected to be very near zero, based on the internal emitter studies discussed above.

In the first study (Cardis et al., 1994; Cardis et al., 1995) 95,673 nuclear industry workers (85.4% men) in the United States, United Kingdom, and Canada were monitored for external exposure to ionizing radiation prior to 1988. A linear cumulative dose response model with Poisson regression was used to estimate excess relative risk per Sv. Eleven dose categories were used. Also, it was assumed that radiation might increase cancer risk but it would not decrease cancer risk, so a one-tailed statistical test was used with significance at the 10% level instead of the usual 5% level. In this study about 99% of the deaths involved lagged doses less than 0.4 Sv. No evidence of association was found between radiation dose and mortality from all causes or from all cancers. However, mortality from leukemia, other than chronic lymphocytic leukemia, had a statistically significant association in a trend test with cumulative external radiation dose (estimated p=0.046, 119 deaths among 15,825 deaths). This estimated trend test p=0.046 is primarily based on 6 cases among 238 deaths above 400 mSv which by itself is not significant. The excess relative risk for leukemia excluding chronic lymphocytic leukemia was reported to be 2.18 per Sv (90% confidence interval 0.1 to 0.99). The excess relative risk for all cancer types excluding leukemia was minus 0.07 per Sv (90% confidence interval minus 0.4 to 0.3). These results may be somewhat affected by the use cumulative dose risk mathematical models rather than the more appropriate lifetime average dose rate models. Exposures to leukemia-causing organic chemicals may have occurred in the workplace.

In the second enlarged study (Cardis et al. 2005) 407,391 nuclear industry workers (90% men) in 15 countries who had available external exposure ionizing radiation dosimetry data were evaluated by a joint analysis group with 50 contributors. These 15 countries included Australia, Belgium, Canada, Finland, France, Hungary, Japan, South Korea, Lithuania, Slovak Republic, Spain, Sweden, Switzerland, United Kingdom, and the United States. Organ doses were estimated by dividing the recorded doses by organ dose bias factors. The colon and bone marrow doses were used for both all cancers excluding leukemia and for leukemia. Eleven dose groups were created. Analyses used a simple linear relative risk

Poisson regression model of the form where relative risk equals 1+βZ where Z is the cumulative equivalent dose in Sv; 95% likelihood based confidence intervals were calculated. Estimates of excess relative risk were stratified for sex, age, and calendar period, facility, duration of employment, and socio-economic status. A total of 24,158 (5.9%) died during the study period including 6,519 from cancer other than leukemia and 196 from leukemia other than chronic lymphocytic leukemia. The leukemia incidence was statistically limited and the risk per Sv was not significantly different from zero.

The key results of this second study for cancer other than leukemia (Cardis et al. 2005) are summarized in Fig. 23. None of the cohorts were found to have excess relative risk of cancer other than those in Canada. The overall combined excess relative risk per sievert for all cancer excluding leukemia was 0.97 (0.14 to 1.97 ninety-five percent confidence range). The excess relative risk per sievert for all cohorts for non-leukemia cancers excluding lung and pleural cancers, which may be related to smoking, was no longer significantly different from zero [0.59 (-0.29 to 1.70 ninety-five percent confidence range)]. Of the fifteen countries, the calculated excess relative risk of cancer that was observed in Canada appear to be anomalously high for some unknown reason. When the study analyzed only the other 14 countries the excess relative risk of cancer (other than leukemia) per sievert was no longer significantly different from zero [0.58 (-0.22 to 1.55 ninety-five percent confidence range)]. With this abridgement, there would be no significant cancer risks observed in this study.

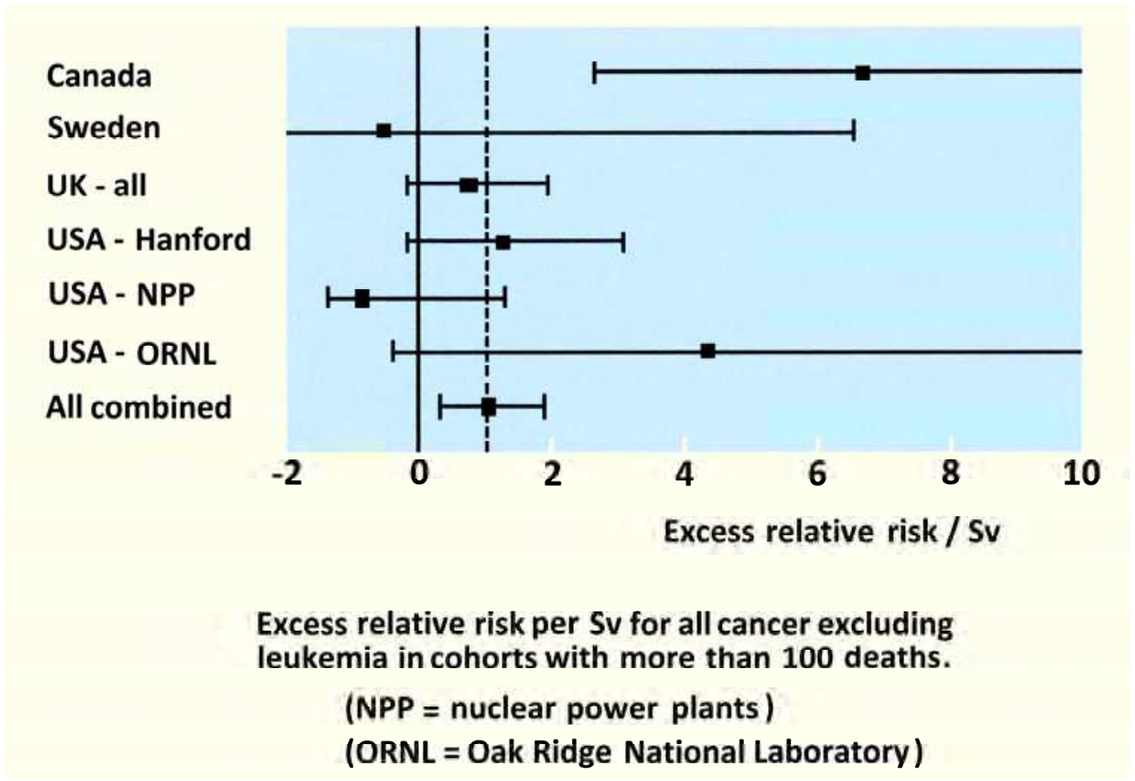


Fig. 23. Excess relative risk per Sv for all cancer types except leukemia in cohorts with more then 100 deaths in radiation worker study of 15 countries; NPP = nuclear power plants, ORNL = Oak Ridge National Laboratory in Tennessee, and Hanford = the Hanford Laboratory in Richland, Washington (Cardis et al., 2005).

5. Nuclear power plant accidents

5.1 Three Mile Island

The accident at the Three Mile Island in Dauphin County, Pennsylvania, USA, on March 28, 1979, drew attention to the possible exposures of people to radionuclides that might be released from a nuclear power during an accident involving the overheating of the nuclear fuel. Because of the design issue and instrument confusion, the plant operator of the Unit 2 reactor was led to think that the cooling water level was high when in fact it was low. Eventually, feed water pumps failed and the reactor overheated. Steam and water were vented through a relief valve and the reactor control rods scrammed in and the reactor shut down. Even though the fission chain-reaction process had been terminated, the heat generated by the highly radioactive fission decay products overheated and melted part of fuel elements and their containment tubes. Volatile radionuclides such as ^{131}I and ^{137}Cs were released from the reactor containment but because of high efficiency particle filters and activated charcoal filters, very little was released to the outdoors. The extent of the risk to people living near the reactor was not clear as the accident progressed. Fortunately, no member of the public received a serious exposure. The maximum total radiation exposure to the members of the public was estimated to be only a few μSv from small releases of radioiodine, ^{131}I. The Unit 2 nuclear reactor unit was damaged beyond repair. The twin Three Mile Island Unit 1 nuclear reactor is still operational.

5.2 Chernobyl

An extremely serious and catastrophic Chernobyl nuclear reactor accident in the Ukraine occurred on 26 April 1986 when a nuclear reactor number four went super-critical during a systems test of the control rods. This reactor did not have a strong containment building and used graphite carbon for a neutron moderator. The resulting super-critical reaction destroyed the fuel elements, ruptured the reactor vessel, and exposed the graphite moderator which, with exposure to air, began to burn. The seriously damaged containment allowed the resulting smoke and effluent of radionuclides to mix with the outdoor atmosphere and spread fallout over much of the Ukraine, Soviet Union, and other parts of Europe. Not only did the most volatile radionuclides such and ^{131}I and ^{137}Cs escape but also many other fission product radionuclides such as ^{90}Sr and ^{144}Ce were part of this widespread airborne contamination. Twenty-six power plant workers died of acute whole body radiation overdoses.

The large population exposure to long-term protracted ionizing radiation associated with the 1986 Chernobyl reactor accident in the Ukraine was predicted with the linear no-threshold model to result in a virtual epidemic of long term radiation-induced cancer (Anspaugh et al. 1988). Instead, there was no apparent major health effects of this widespread protracted exposure to ionizing radiation except for thyroid disease associated with very high acute radiation doses from short-lived (half life 8 days) radioiodine (^{131}I) contamination in cow's milk and dairy products (WHO 2006, Jaworowski 2010).

5.3 Fukushima Daiichi

Three of the six boiling water nuclear power plants at Okuma, Fukushima, Japan, underwent destructive meltdown of the nuclear fuel along with widespread releases of radioactive fission products to the environment as a result of massive flooding associated with the Tohoku earthquake and tsunami on March 11, 2011. Although plants safely shut

during the earthquake, the tsunami that followed completely flooded the plants and shut down all sources of local and nearby electricity. Without electricity it was not possible to operate water pumps needed to cool the reactor fuel to prevent overheating associated with the natural radioactive decay of fission product radionuclides produced during normal operations.

When the quake occurred units 1, 2, and 3 were operational, but unit 4 had previously been defueled and units 5 and 6 had been shut down for maintenance. Ultimately the fuel elements in units 1,2, and 3, overheated and ruptured, The special zircaloy cladding reacted with steam to produce large quantities hydrogen gas which vented into the containment buildings and subsequently exploded injuring workers and damaging the building walls and roofs.

Ultimately, there were widespread releases to the outdoor air of smoke and volatile fission products from the damaged nuclear fuel. These releases lofted into the atmosphere and were diluted and carried for long distances. The most important human exposures were probably those associated with contamination of water and food. Two most prominent fission products released in this accident were short-lived (half life 8 days) radioiodine (^{131}I) and long-lived (half life 30 years) radiocesium (^{137}Cs). Both of these radionuclides are beta radiation emitters that can efficiently irradiate body organs if inhaled or ingested. Associated gamma rays contribute a more diffuse and less important portion of organ doses when these radionuclides are internally deposited in the body of a person.

Ingested ^{131}I primarily follows the grass to cow to milk route of human exposure. Ingested iodine tends to concentrate in the small thyroid gland where it can efficiently irradiate the thyroid tissue. The very efficient release of iodine from damaged nuclear fuel and the short radioactive half life of ^{131}I means that the risk of exposure is relatively short-lived after an accidental release but the acute doses to the thyroid gland can be quite large. From studies of children who ingested ^{131}I from the Chernobyl nuclear reactor accident, it has be observed that the risk of thyroid cancer is primarily associated with thyroid cumulative radiation doses larger than about 10 Sv.

Ingestion or inhalation of ^{137}Cs leads to very uniformly widespread irradiation of body because cesium is quite soluble in most of its chemical forms and behaves somewhat like potassium in the human body. Although ^{137}Cs has a long physical half-life, it has a relatively short biological half life on the order of about one month. For an acute single intake, very little remains in the human body after one year. In the environment, cesium tends to strongly bind by ion-exchange with clay in soils, somewhat limiting its uptake into plants.

In order to evaluate the biological risk, including carcinogenesis, associated with the intake of ^{137}Cs, fifty-four beagles were injected with graded dosages of ^{137}Cs as cesium chloride from 32.5 to 148 MBq per kg body weight and held for lifetime study at the Inhalation Toxicology Research Institute (Mauderly and Daynes, 1989)(Fig. 24). Because of the relatively short biological retention half-time of about 30 days (Boecker, 1969), about half of the whole body absorbed dose from ^{137}Cs beta rays and ^{137m}Ba daughter gamma rays was delivered in the first 30 days after the injection and nearly all of the dose was delivered within one year. Those deaths that occurred prior to one-half year after injection were associated with direct injury to the blood forming organs by beagles receiving the highest dosages of ^{137}Cs. There were only 12 unexposed controls assigned to this study, but the fate of 52 other controls assigned to contemporaneous studies was used for comparison to the exposed dogs. Those beagles that survived the acute injury phase in the very highest dose groups lived about as long as unexposed controls and had insufficient cases of radiation induced cancer to develop a meaningful three-dimensional model.

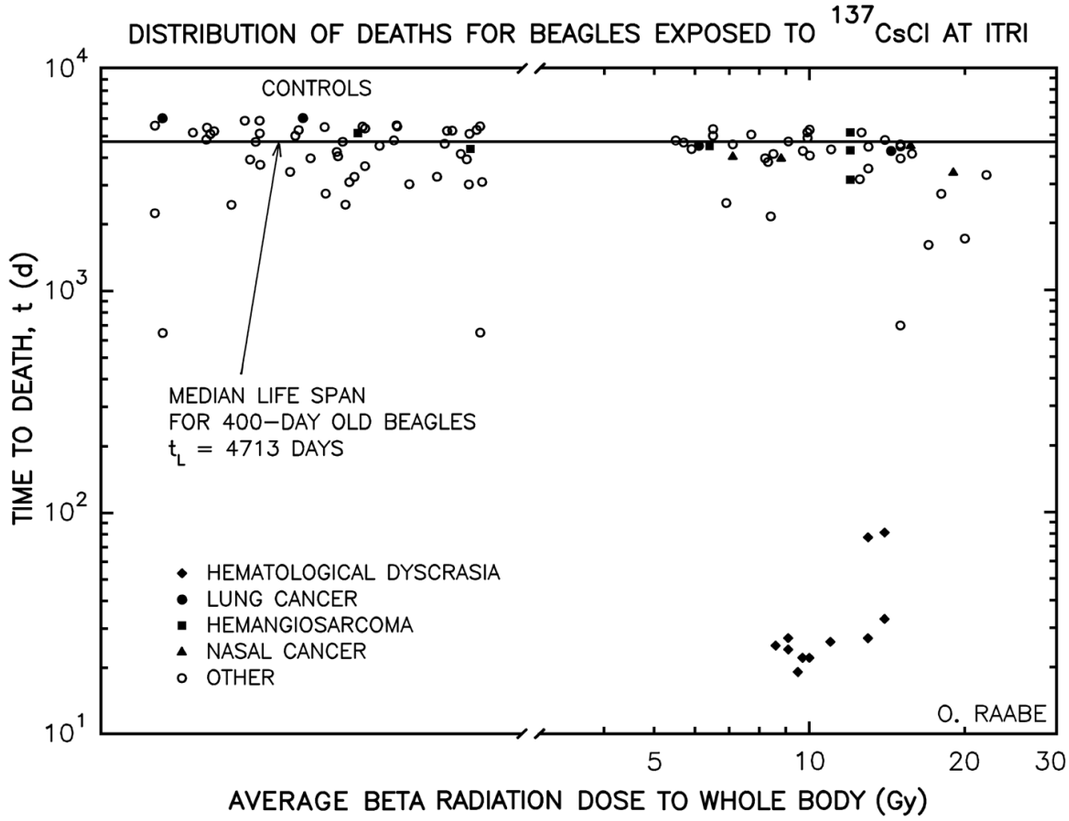


Fig. 24. Distribution of deaths in lifetime studies of beagles injected with ^{137}CsCl at ITRI (Raabe,1994).

A Peto trend test (Peto et al, 1980) of the cancer cases showed that two cancer types had a statistically significant occurrence: (a) nasal carcinomas reported in 4 exposed dogs and not observed in controls, and (b) hemangiosarcoma in different organs (4 cases) with one case in controls. The lowest lifetime cumulative whole body radiation dose associated with a death with nasal carcinoma was 7.7 Gy; this compares with the lowest skeletal beta radiation dose of 18.4 Gy associated with the occurrence of nasal carcinoma in beagles exposed to ^{90}Sr at Davis. There was no statistically significant incidence of lung, liver, or bone cancer, and no reported cases of leukemia. This result is consistent with the expected risk of radiation-induced cancer from protracted exposure as discussed above.

6. Summary of protracted and repeated exposure cancer induction risk

As presented in the previous sections, the studies of repeated and protracted exposures to ionizing radiation have shown that radiation induced cancer follows a sharply non-linear upward temporal pattern with a virtual threshold at lower life-time average dose rates (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, clonal development depending on cell division cycles, cellular maturation, and average ionizing radiation dose rate over long latency

periods. Studies described above of protracted exposures to ionizing radiation from internally deposited radionuclides in people and laboratory animals have demonstrated that cancer induction risk is actually a somewhat precise function of average dose-rate and that at lower average dose rates cancer latency can exceed natural life-span.

Because of the long latency at low dose rate 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. The organs, tissues, and cells of the body cannot distinguish between ionizing radiation emitted by internally deposited radionuclides or entering the body from external sources. Low linear energy transfer (LET) gamma rays from external sources yield ionizing energetic electrons in the body and beta particles from internally deposited radionuclides are also ionizing energetic electrons. High LET neutrons from external sources yield ionizing energetic protons whose radiation quality weighting factors are similar to high LET ionizing alpha particles from internally deposited radionuclides (Raabe, 2011).

Another important finding is that two beta particles are about equal on the average to one alpha particle in the radiation induction process (Raabe 2010). This finding suggests that double strand damage to cellular DNA is involved in the cancer induction process. While one alpha particle hitting DNA may produce the necessary double-strand break, two beta particles almost simultaneously hitting the DNA are apparently needed to produce similar double-stand breaks. Also, the shape of the cancer-induction dose-response curve is not linear but rather sharply increasing as a function of cumulative dose delivered from virtually zero risk at low doses to high risk at high doses as a function of dose rate.

7. Single acute exposures to ionizing radiation

7.1 Atomic bomb survivor studies

A quite different phenomenon has been observed in studies of the Japanese survivors of atomic bombs detonated over Hiroshima, August 6, 1945, and over Nagasaki, August 9, 1945 (Manhattan Engineer District 1946). These Japanese survivors were exposed instantaneously to a large acute pulse of external gamma radiation (and some neutrons) delivered in about one minute. Many of these acute absorbed doses were several hundred times the normal annual radiation exposure from background radiation. All of the cells of the body were exposed to this large ionizing radiation pulse and those cells and body tissues were all affected in some way. Years later some of the highly exposed survivors developed cancer of the same types as occurred in the control population but somewhat earlier and at somewhat higher rates. In addition, the increases in these cancer cases were proportional to that one-minute whole-body absorbed radiation dose. This linear relationship is in sharp contrast with cancer induction observed in the protracted and repeated exposures described above. Except for some early cases of myeloid leukemia caused by acute radiation damage to the blood forming tissues of the body from the higher exposures, there were no apparent radiation induced cancer cases among the atomic bomb survivors (Raabe, 2011).

There has been a long-standing scientific disagreement concerning cancer induction associated with protracted and repeated exposures to ionizing radiation and the

carcinogenic effects of the atomic bomb acute instantaneous exposures. The reason for this conflict is readily apparent from the data themselves. It 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 in the Japanese people rather than actual de-novo cancer induction.

The Japanese survivor studies are very important since they have been extremely well done and represent a significant body of human data about the possible effects of acute exposure to ionizing radiation (RERF, 2008). Also, the currently accepted methodology for estimation of solid cancer risk associated with human exposure to ionizing radiation is based primarily on the detailed studies of the Japanese atomic-bomb survivors (ICRP-26, 1977; ICRP-60, 1991; BEIR VII Phase 2, 2006; NCRP 136, 2001; ICRP 103, 2007). The prevailing models of human ionizing radiation exposure risk and relative organ sensitivities (ICRP tissue weighting factors, W_T) are based primarily on those studies. Specifically, the concept that cancer risk as a linear function of cumulative dose and follows a linear no-threshold cancer risk model is based primarily on the acute high dose rate exposures received by the Japanese atomic bomb survivors.

7.2 Radiation promoted cancer from acute exposures

The Radiation Effects Research Foundation (RERF) and its predecessor Atomic Bomb Casualty Commission (ABCC) studied the development of solid malignant tumors in about 80,000 of the Japanese atomic bomb survivors (Pierce and Preston, 2000; Preston et al., 2003; Preston et al., 2004; Preston et al., 2007). The main study considered 79,972 survivors for which there were available calculated radiation doses. Of these, 44,636 survivors had calculated doses that exceeded 5 mSv. Those with less than 5 mSv doses were used as the control group (Preston et al., 2007). These about one-minute acute exposures involved very high-energy gamma radiation and some neutrons. Myeloid leukemia from high dose 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 malignant tumors are the result of simple stochastic (isolated and random) initiating events in individual cells that occurred during that about one-minute exposure. This simplistic stochastic model of ionizing-radiation-induced cancer is based on the 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 random event then ultimately leads to a clone of similar pre-malignant cells. Later, usually much later, a second random DNA alteration occurs in one of the clonal pre-malignant cells that produces a malignant cell that develops into a monoclonal malignant tumor. This process began with the single random (stochastic) cellular event. This process can be advanced by promoter agents including other ionizing radiation that presumably affect the clonal development, quantity, and maturation of the pre-malignant clonal cells (Heidenreich et al., 2007) . 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 (Casarett, 1968). Mathematical models are readily constructed with unknown parameters and hypothetical modifying factors and process lag times designed to fit the data associated with acute ionizing radiation exposures (Heidenreich et al., 1997).

The internal emitter studies discussed above strongly suggest that double strand DNA damage or a related phenomenon is 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 remarkably linear pattern as a function of absorbed ionizing radiation dose. Deterministic cancer promotion of those types found in the exposed population rather than simple isolated stochastic cancer induction better explains the increase of solid cancers in the atomic bomb survivor studies.

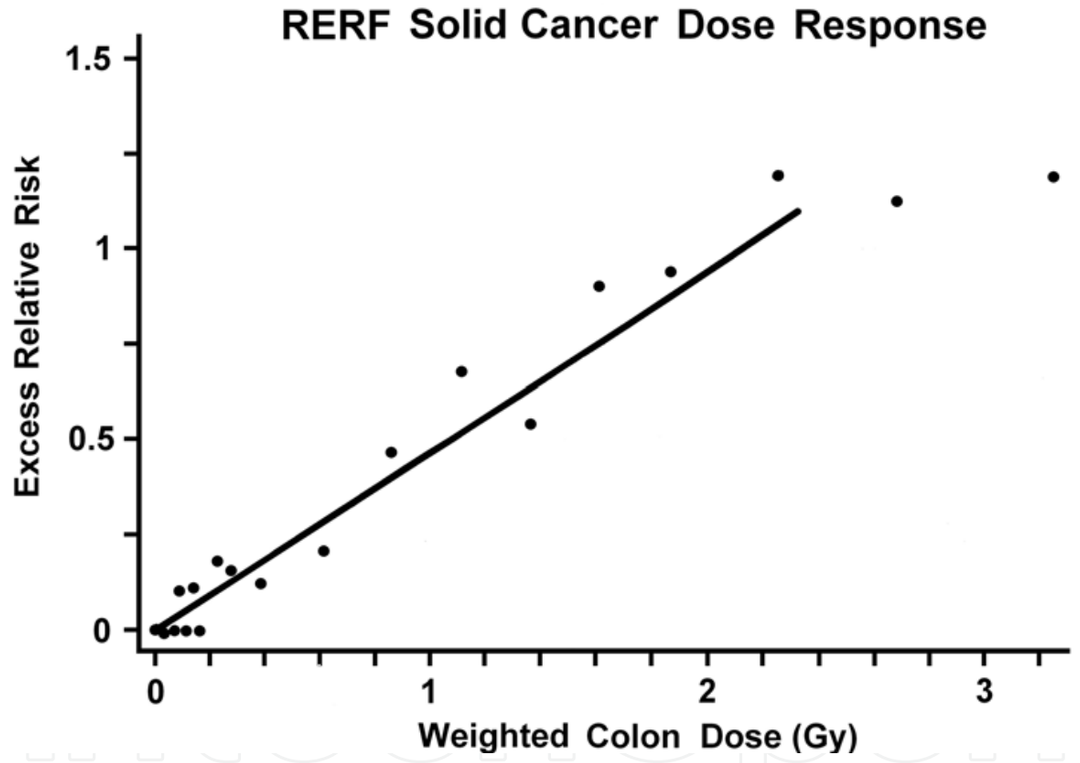


Fig. 25. Linear dose-response relationship of Excess Relative Risk for the promotion of solid cancer in Japanese survivors of the atomic bomb detonations at Hiroshima and Nagasaki in 1945 with respect to survivors who received low radiation exposures as reported by the Radiation Effects Research Foundation [RERF](Preston et al. 2007).

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. 25). These processes involve years of cellular division, clonal 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. 26). This promotional effect was observed to advance cancer rates not only relatively soon after exposure but throughout the lives of the exposed individuals (Fig. 27). 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.

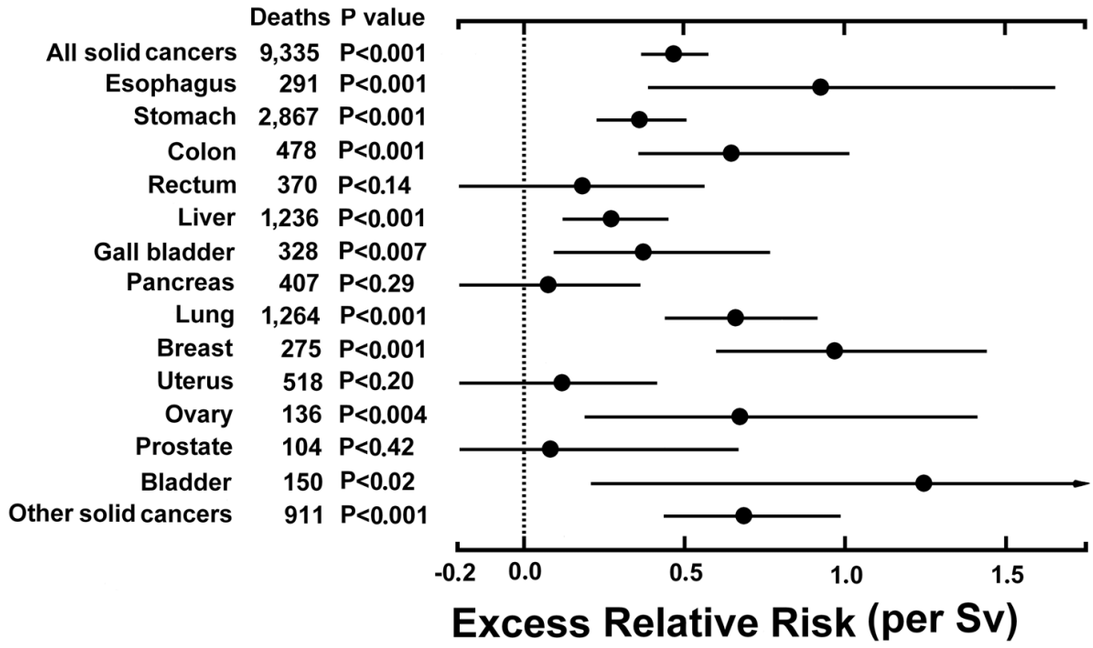


Fig. 26. Observed Excess Relative Risk by body organ for promoted solid cancer observed for one Sv of equivalent ionizing radiation dose in highly irradiated Japanese atomic bomb survivors compared to survivors who received low radiation exposure as reported by the Radiation Effects Research Foundation [RERF] (Preston et al. 2003).

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?" Fig. 27 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 single event 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. The cells of the tissue communicate among themselves as a result of the exposure in a process called bystander effect with various responses evoked even among the cells in these tissues that were not directly impacted (Hall 2003). Tissues respond to sudden ionizing radiation exposure with up-regulation of various genes and down-regulation of others (Snyder and Morgan, 2004; Coleman et al. 2005). This imprint is apparently not lost and

carries forward throughout life promoting the existing biological processes that may lead to cancer in the exposed atomic bomb survivor population. This complex process suggests a systems biology phenomenon rather than a unique stochastic response (Barcellos-Hoff, 2008).

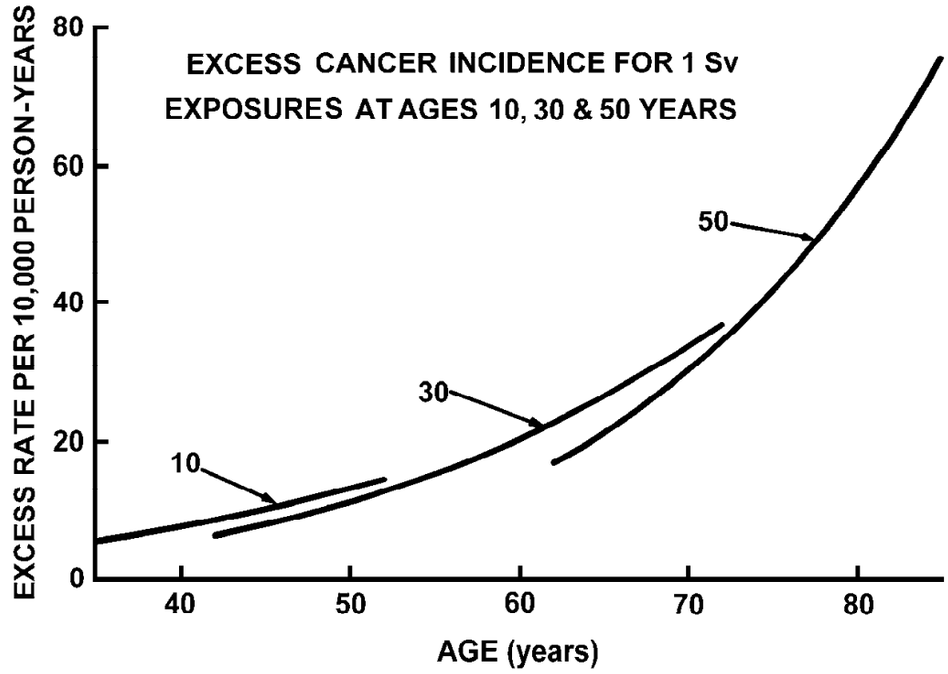


Fig. 27. Observed gender-averaged age-specific excess incidence rates at 1 Sv for most major solid cancers over the 1958-1987 follow-up period for ages at exposure 10 y, 30 y, and 50 for the Japanese atomic bomb survivors (Pierce and Mendelsohn, 1999). The excess rates appear to depend only on age and 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.

The Japanese atomic 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. In fact, 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 (Raabe 2011). The resulting cancer promotion phenomena in the atomic bomb survivors 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.

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 26, 1977; ICRP 30, 1979; ICRP 60, 1991; ICRP 103, 2007). Cancers that were somewhat rare in this Japanese population, such as bone cancer, were assigned relatively

low tissue weighting factors relative to the 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 the whole body cancer or genetic 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 based on the atomic bomb survivor studies is inappropriate for protracted or fractionated exposures.

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).

7.3 Acute medical exposures

7.3.1 Medical exposure concerns

Among the most common instantaneous exposures of people to ionizing radiation are those associated with diagnostic medical radiographs (X-rays). Modern computed tomography (CT) scans using x rays with higher radiation doses can provide precise three-dimensional images and are of great medical value. Fluoroscopic images that use nearly continuous irradiation are also valuable in certain medical procedures. The question as to whether these acute diagnostic medical exposures result in an increased cancer risk has been considered and even assumed in various studies. The promotion of cancer observed among the Japanese atomic bomb survivors is a reasonable basis for considering the possible cancer promotion associated with medical exposures to ionizing radiation, but protracted exposures do not seem to involve cancer risk at small doses and sometimes appear beneficial.

7.3.2 Neonatal medical exposures

Among the earliest studies of possible effects of medical exposures of patients associated with diagnostic X-rays are those associated with the Oxford Survey of Childhood Cancer (OSCC) of deaths in England, Wales, and Scotland from childhood cancer. These case-control studies were initiated and advanced by Alice Stewart, a British physician (Stewart et al., 1956; Stewart et al., 1958). The basic hypothesis of these studies is that childhood cancer was caused in part by fetal exposures from medical X-rays associated with diagnostic radiology of the pregnant mothers. Healthy control children were matched by sex, by birth location and, as closely as readily possible, by birth date. A comprehensive summary and statistical evaluation has been published (Mole 1990). The overall study considered a majority of the cancer deaths in of children in Britian under the age of 16 primarily spanning

the years 1953 to 1978. Most of the major findings were based on children who were born between 1940 and 1969. The initial studies inquired from the mothers about X-ray films that might have been made during pregnancy. Later studies involved verification by review of medical records, but not all cases could be verified. There was no direct ionizing radiation dosimetry associated with these studies. Overall, there was a strong trend to a higher fraction of diagnostic radiology among the mothers of children who died of cancer compared to the healthy controls. Typical overall raw values of these ratios were 1.33 for children dying under age 6, 1.38 for children age 6 or older dying under age 10, and 1.27 for children age 10 or older dying under age 16. For births that occurred prior to 1957 the odds ratios were significantly above unity, while for later births they were not. It may have been most difficult to verify the X-ray recollections of the mothers for those earlier years. The odds ratios for X-raying in Britian for the four birth years 1958 to 1961 were 1.27. 1.36 and`1.02 for cancer deaths at ages 0 to 5, 6 to 9, and 10 to15, respectively. The overall odds ratio for all ages 0 to 15 years was 1.23 with a 95% confidence interval from 1.04 to 1.48 and the associated excess lethal tumor rate from in utero x ray exposure was 0.00028 with a confidence interval from 0.48 to 0.00058 (Mole. 1990).

The findings from the Oxford Survey of Childhood Cancer tend to show an important trend, but they may not convincingly prove that in utero X-rays were the cause of childhood cancer. Much of the earlier data were based on patient-reported X-ray exposures. A mother whose child died of cancer is more likely to remember or readily believe that she received X-ray exposures than a mother of a healthy child. Early medical records may have been incomplete or difficult to locate.

In many cases the X-rays may have been associated with some medical complication or abnormality associated with the pregnancy especially in many cases where the mother was X-rayed more than once. Those medical abnormalities, if they existed, may have directly contributed to later development of cancer in the child. Another possibility is that the in utero exposure promoted a pre-cancer process that led to earlier cancer development than would have otherwise occurred, but the low radiation doses involved in these studies was too low to correlate with the atomic bomb survivor studies promotional effects (Preston et al., 2007). Totter and McPherson (1981) point out that differences in population groups in the Oxford Survey and other factors can explain for the observed relationships.

Although no dosimetry was available to accurately estimate the maternal or in utero ionizing radiation doses associated with the X-ray exposures in these studies, Mole (1990) attempted to estimate the risk of childhood cancer per unit of absorbed ionizing radiation to the fetus using estimates made in 1966 by the Adrian Committee of the British Ministry of Health. He assumed that average dose from all obstetric radiography was 0.61 cGy. From his calculated excess lethal tumor rate he calculated and reported a risk coefficient for irradiation in the third trimester for childhood cancer deaths at ages up to 15 years equal to 0.00046 per cGy with a confidence interval from 0.8 to 0.00095 per cGy. This estimate is not valid because the Oxford Survey of Childhood Cancer does not provide any dose-response information for anyone in the study nor for the whole population at risk. More than 95% of the cases of childhood cancer are not explained by neonatal radiography. In 1958 there were 840,196 births in Britian and it was likely that at least 100,000 babies were irradiated in utero based on the estimates (Mole 1990). The number of deaths associated with cancer ages 0-14 born in 1958 was 977 and the data show that about 15% of those or about 150 had been

irradiated in utero. Therefore the fraction of those irradiated that died of cancer in childhood was about 0.15%.

It might be noted, however, that the promotion of cancer observed in the atomic bomb survivor studies is a mechanism that could explain the observed results, but there are no statistically significant radiation promoted cancer risks for acute doses below about 10 cSv among the atomic bomb survivor data. (Preston et al. 2007). Totter and McPherson (1981) point out that differences in population groups can account for the observed misleading relationships since the sub-population of cancer cases does not have the same probability of being X-rayed as the sub-population of controls.

7.3.3 Medical diagnostic X-ray risks

Medical diagnostic radiology has become one of the highest sources of exposure to ionizing radiation in many countries of the world. This is largely associated with the increasing use of computed tomography (CT) images using x rays which involve much higher radiation doses than conventional X-ray images. Since these doses are delivered almost instantaneously, they can be expected to present similar cancer promotion risks as observed in the atomic bomb survivor studies discussed above. However, the radiation doses involved in the use of CT examination are typically well below the approximately 10 cSv dose above which the cancer promotion risk is statistically significant in the Japanese atomic bomb survivor studies (Preston et al 2007). Hence, attempt to extrapolate the cancer promotion risk associated with these small doses involves considerable imprecision and uncertainty. No one can be sure that the same linear no-threshold model applies precisely to individual organ exposures in radiology as applies to whole body exposures as occurred for the Japanese atomic bomb survivors. In addition, biological processes that affect the behavior of cells and tissues at lower doses may alter or cancel the promotional phenomena. For example, low acute doses may stimulate cellular DNA repair mechanisms.

Some investigators have created somewhat precise models of what may be occurring at low doses to predict lifetime cancer risks from the acute x ray exposures that may be associated with diagnostic radiology using linear no-threshold models based on the atomic bomb survivor studies of cancer promotion. These studies of diagnostic medical exposure to ionizing radiation usually refer to their studies as estimates of risk of radiation induced cancer, but in this chapter the acute exposure dose phenomenon has been be more correctly shown to be cancer promotion. In addition, some of these studies report their results as cancer risks, but they are not measured risks but calculated estimates subject to the theoretical use of the linear model and the approximate parameters of that model obtained from the atomic bomb survivor studies.

Brenner and associates (Brenner et al., 2000; Brenner, 2002; Brenner and Hall, 2007; Hall and Brenner, 2008) have published a series of papers providing estimates of lifetime fatal cancer as a function of dose from CT scans of various organs of the body as a function of exposure age utilizing data from the atomic bomb survivor studies and the risk models developed from those data by the United States National Research Council (BEIR V, 1990) and the International Commission on Radiological Protection (ICRP-60, 1991).

The calculated cancer risk depends on the organ irradiated and the sex and age of the irradiated person. The calculated overall lifetime attributable risk tends to be higher for children than for adults since children have many more years of life during which cancer might develop. Representative values for lifetime attributable risk in these studies are from

0.14% for babies to 0.02% for adults. These are typical calculated values using linear no-threshold models following from the separate organ exposure results at high doses from the atomic bomb survivor studies.

Based on BEIR V (1990), Brenner et al. (2000) summarizes 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. 28). 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 if about 9.5% over 60 years = 0.16% per year. For a 45 year old man the risk per year of life if about 6.5% over 40 years = 0.16% per year. The total cancer 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.

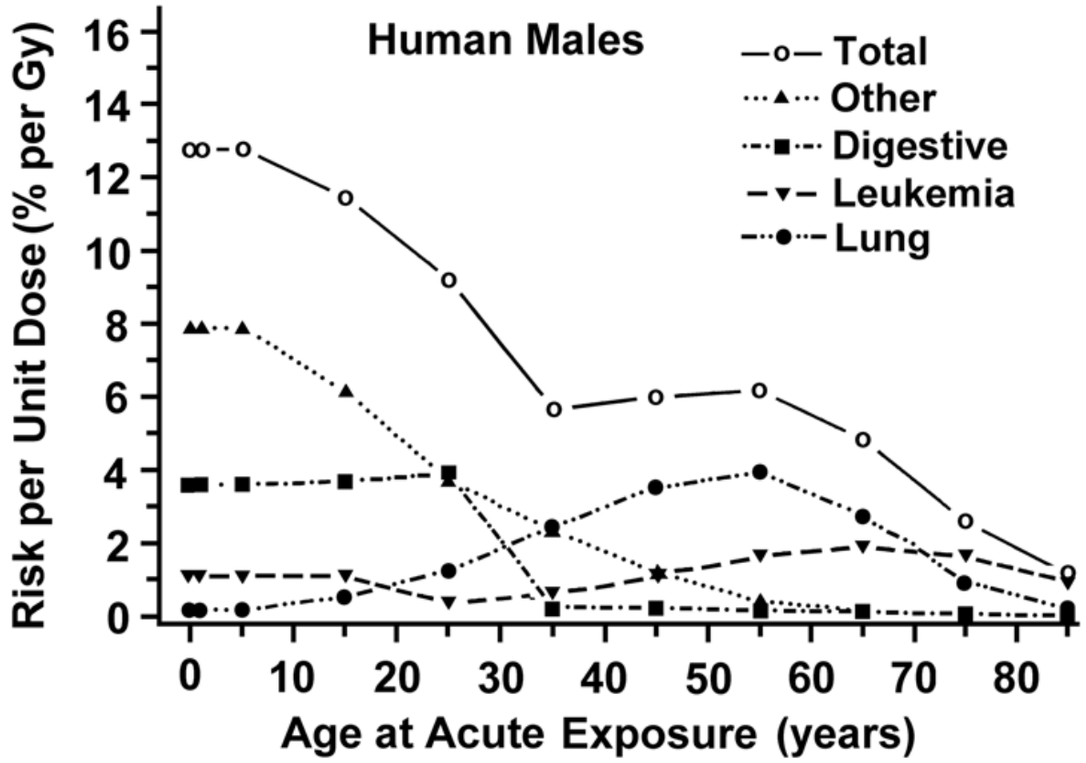


Fig. 28. Lifetime attributable cancer mortality risks for males by cancer type as a function of age at a single acute exposure of one Gy of γ radiation based on BEIR V (Brenner et al., 2000).

Addition evidence for promotion is seen in the lung cancer rates shown in Figure 28. Lung cancer in these males may be related to smoking history. For young boys up to age 15 there is no apparent promotion of lung cancer (total lifetime risk about 0.5%). For these non-

smokers there was no ongoing lung cancer development to promote. But lung cancer risk per year climbs for older males many of whom are likely to have been smokers with a peak risk at age 55.

Berrington de Gonzalez and Darby (2004) estimated the hypothetical overall population cancer risks from diagnostic X-rays in the UK and 14 other countries based on frequency of diagnostic X-ray use, doses to different body organs, and linear no-threshold risk models based on the Japanese atomic bomb survival data. Their results led them to report that the cumulative risk of cancer for people up to age 75 from diagnostic X-ray exposures was indicated to be in the range from 0.6% to 1.8%.

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 et al., 2002).

Overall, the attributable risk values estimated in these reports from individual X-rays and CT scans are hypothetical and unproved since the doses involved are much smaller than those for which statistically significant elevations in cancer rates have been observed in the atomic bomb survivors. The calculations depend on the unproved assumption that the promotion risk for acute exposures is perfectly linear down to a dose near zero, the linear no-threshold hypothesis. Various biological processes could compete with or nullify the ionizing radiation promotion process for these relatively small individual acute exposures. There seems to be considerable evidence there is no significant risk at very low acute doses, and some possible beneficial effects.

8. Discussion

An important observation is that the dose-response relationships for protracted exposures to internally deposited radionuclides are quite different from the observed effects of a single high dose rate exposure as experienced by the atomic bomb survivors in temporal manifestation and preciseness of the effect. In the internal emitter studies the time to cancer development depends on the lifetime average dose rate and the cases are not randomly distributed with respect to time but rather are tightly grouped over a predictable and narrow range of times. At low lifetime average dose rate the time required to develop cancer may exceed the natural life span yielding a virtual threshold for cancer induction.

Bone cancer and lung cancer are equally sensitive in the internal emitter studies with beagles, but there is no apparent induction of bone cancer in the atomic bomb survivors while there is a considerable increase in lung cancer. The main data are the relative increase that suggests radiation promotion was more effective than radiation induction.

Based on the linear relative risk relationship observed for acute exposure in the RERF studies of the atomic bomb survivors, the ICRP developed an absolute risk model for radiation-induced cancer as a function of absorbed cumulative ionizing radiation dose that was believed to apply to all forms of exposures to ionizing radiation. It is assumed that the linear model can predict cancer induction risk but needs a hypothetical dose and dose-rate effectiveness correction factor (DDREF) for protracted, fractionated, or low dose exposures.

In recognition that protracted or fractionated exposures have been observed to be less carcinogenic than the RERF data directly suggest, the ICRP reduced the calculated risk using a DDREFof 2, but still assumed lifetime LNT linearity of cancer induction was maintained (ICRP 103, 2007). This approach has led to simplistic linear cancer induction risk factors such as " 5% per Sv" (ICRP 60, 1991; ICRP 103, 2007).

The idea that such a risk factor is valid rests on the assumption that each ionizing-radiation-induced malignancy is the result of a simple isolated random or "stochastic" initial event that is equally probable in any exposed person. Although each malignant tumor is monoclonal, the biological processes that lead to that first tumor (and successive tumors) are apparently deterministic systemic processes.

Others have also adopted similar linear cancer induction risk models as a function of person-sievert based on the RERF studies. However, as discussed above, these cancer inductions models do not apply to non-acute exposures that depend on lifetime average dose rate rather than simply on cumulative dose.

These cancer induction risk models are not valid because of the confusion of cancer promotion associated with brief high dose-rate exposures and cancer induction associated with protracted exposures. Unfortunately, these misleading cancer induction risk values may be used to implement expensive cleanup standards for environmental radioactivity.

The LNT model does not predict the observed effects or lack thereof for protracted exposures to ionizing radiation exposure (Jaworowski 2010). The LNT model does not readily predict the results of a cumulative set of fractionated medical diagnostic x ray exposures of the lung where there was no indication of increased lung cancer with the observed relative risk at a cumulative doses of 1 Sv being 1.00 [95% confidence interval 0.94-1.07] contrasting with the high expected relative risk based on the atomic bomb survivors being 1.60 [95% confidence interval 1.27-1.99] (Howe 1995). Also, the large population exposures to long-term protracted ionizing radiation associated with the 1986 Chernobyl reactor accident in the Ukraine was predicted with LNT to result in a virtual epidemic of long term radiation-induced cancer (Anspaugh et al. 1988). Instead, there was no apparent major effect of this widespread protracted exposure to ionizing radiation except for thyroid disease associated with very high acute radiation doses from short-lived ^{131}I in milk (WHO, 2006; Jaworowski, 2010).

Failure to realize the fundamental differences between cancer promotion and cancer induction has been the source of scientific misunderstandings and risk estimate disagreements. A logical barrier 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 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 protracted exposures to ionizing radiation.

The underlying assumption in these current recommendations is that risk of radiation-induced cancer is proportional to cumulative dose without threshold. This assumption obviously conflicts with the induction of cancer observed in the cases of lifetime protracted and repeated exposures to ionizing radiation. An understanding of the source of this conflict of data interpretation is essential for sound estimates of cancer risk associated with exposures to ionizing radiation.

Radiation cancer induction is not a simple stochastic process in the sense that it is not the result of a random radiation event in a single cell that converts it into some kind of pre-malignant neoplastic cell. In reality, both radiation promoted and radiation-induced cancers are the result of complex biological processes involving multiple cellular events. These events include but are not limited to intercellular communication in irradiated tissues, up-regulation and down-regulation of genes, DNA mutations, cell division rates, clonal expansion of altered cells, and various responses to numerous specific radiation events such as DNA double-strand breaks. Induced cancer risk from protracted radiation exposures of body organs depends on the lifetime average dose rate to the irradiated organs rather than on some function of cumulative dose. The middle Twentieth Century radiation protection standards promulgated by the ICRP were properly focused on minimizing dose rate (ICRP 2, 1959).

9. Conclusion

Clearly the development of a radiation-induced malignant tumor from either protracted ionizing radiation exposures or acute exposures is not the result of a single random interaction of the ionizing radiation with an isolated cell. Hence, the term stochastic as used by the ICRP is not appropriate. The following conclusions indicate that major revisions of methodology and standards are needed and other currently accepted ionizing radiation risk models should be improved to provide more meaningful and realistic estimates of ionizing radiation cancer risk:

(1) Cancer induction risk associated with protracted or fractionated ionizing radiation exposure is a non-linear function of lifetime average dose rate to the affected tissues and exhibits a virtual threshold at low lifetime average dose rates. (2) Cumulative radiation dose is neither an accurate nor an appropriate measure of cancer induction risk for protracted or fractionated ionizing radiation exposure except for describing the virtual threshold for various exposures. (3) Cancer promotion risk for ongoing lifetime biological processes is a relative process as seen in the RERF studies of the Japanese atomic bomb survivors for brief high dose-rate exposures to ionizing radiation. It cannot be used to estimate cancer induction risk from protracted or fractionated ionizing radiation exposures over long times and at low dose rates.

10. References

Anspaugh, L.R.; Catlin R.J. & Goldman M. (1988). The Global Impact of the Chernobyl Reactor Accident. *Science* 242:1513–1519.

Barcellos-Hoff, M.H. (2008). Cancer as an Emergent Phenomenon in Systems Radiation Biology. *Radiat. Environ. Biophys.* 47: 33-38.

BEIR IV. (1988). *Health Risks of Radon and Other Internally Deposited Alpha-Emitters.* National Research Council, Washington DC: The National Academy Press.

BEIR V. (1990). *Health Effects of Exposure to Low Levels of Ionizing Radiation.* National Research Council, Washington DC: The National Academy Press.

BEIR VI (1999). *Health Effects of Exposure to Radon.* National Research Council, Washington DC: The National Academies Press.

BEIR VII Phase 2. (2006). *Health Risks From Exposure to Low Levels of Ionizing Radiation.* National Research Council, Washington DC: The National Academies Press.

Berrington de Gonzalez A. & Darby S. (2004). Risk of Cancer from Diagnostic X-rays: Estimates for the UK and 14 other countries. *Lancet* 363:345-51.

Boecker, B.B. (1969). Comparison of ^{137}Cs Metabolism in the Beagle Dog Following Inhalation and Intravenous Injection. *Health Phys.* 16: 785-788.

Brenner, D.J. (2002). Estimating Cancer Risks From Pediatric CT: Going From the Qualitative to the Quantitative. *Pediatr. Radiol.* 32:228-231.

Brenner, D.J.; Elliston. C.D.; Hall, E.J. & Berdon, W.E. (2000). Estimated Risks of Radiation-Induced Fatal Cancer From Pediatric CT. *American J. Radiology* 176:289-296.

Brenner, D.J. & Hall, E.J. (2007). Computed Tomography - An Increasing Source of Radiation Exposure. *N. Engl. J. Med.* 357:2277-2284.

Cardis, E. & International Agency for Research on Cancer Study Group on Cancer Risk Among Nuclear Industry Workers. (1994). Direct Estimates of Cancer Mortality Due to Low Doses of Ionising Radiation: An International Study. *Lancet* 344:1039-1043.

Cardis, E.; Gilbert, E.S.; Carpenter, L.; Howe, G.; Kato, I.; Armstrong, B.K.; Beral, V.; Cowper G.; Douglas, A.; Fix, J.; Kaldor, J.; Lave, C.; Salmon, L.; Smith, P.G.; Voelz, G.L. & Wiggs, L.D. (1995). Effects of Low Doses and Low Dose Rates on External Ionizing Radiation: Cancer Mortality Among Nuclear Industry Workers in Three Countries. *Radiat. Res.* 142:117-132.

Cardis, E.; Vrijheid, M.; Blettner, M.; Gilbert, E.; Hakama, M.; Hill, C,; Howe, G.; Kaldor, J.; Muirhead, C.R.; Schubauer-Berigan, M.;Yoshimura, T. & International Study Group.(2005). Risk of Cancer After Low Doses of Ionizing Radiation: Retrospective Cohort Study in 15 Countries. *British Med. J.* 331:77-80.

Casarett, A.P. (1968). *Radiation Biology*. Prentice-Hall, Englewood Cliffs, New Jersey.

Cohen, B.L. (1995). Test of the Linear-no Threshold Theory of Radiation Carcinogenesis for Inhaled Radon Decay Products. *Health Phys.* 68:157-174.

Coleman, M.A.; Yin, E.; Peterson, L.E.; Nelson,D.; Sorensen, K.;Tucker, J.D.; Wyrobek, A.J. Low-dose irradiation alters the transcript profiles of human lymphoblastoid cells including genes associated with cytogenetic radioadaptive response. (2005). *Radiat. Res.* 164:369-382.

Eisenbud, M. & Gesell, T.F. (1997) *Environmental Radioactivity From Natural, Industrial, and Military Sources*, Fourth Edition, Academic Press, San Diego, California.

Evans, R.D. (1955). *The Atomic Nucleus*. McGraw-Hill Book Company, New York.

Evans, R.D. (1943). Protection of Radium Dial Workers and Radiologists from Injury by Radium. *Journal of Industrial Hygiene and Toxicology* 25: 253-269.

Evans, R.D.; Keane, A.T. & Shanahan, M.M. (1972). Radiogenic Effects In Man of Long-term Skeletal Alpha-irradiation. In: Stover BJ, Jee WSS, eds. *Radiobiology of Plutonium.* Salt Lake City, UT: The J.W. Press; 431-468.

Evans, R.D. (1974). Radium In Man. *Health Phys.* 27: 497-510.

Finkel, M.P.; Biskis, B.P. & Jinkins. P.B. (1969) Toxicity of radium-226 in mice. In: *Radium Induced Cancer.* Vienna: International Atomic Energy Agency [IAEA-SM-118/11]; 369-391.

Feinendegen, L.E. (2005). Evidence For Beneficial Low Level Radiation Effects and Radiation Hormesis. *Br. J. Radiology* 78:3-7.

Fornalski, K.W. & Dobrzynski, L. (2011). Pooled Bayesian Analysis of Twenty-eight Studies on Radon Induced Lung Cancers. *Health Phys.* 101:265-273.

Ghiassi, M.; Mortazavi, S.M.J.; Cameron, J.R.; Niroomand-rad, A. & Karam, P.A. (2002). Very High Background Radiation Areas of Ramsar, Iran: Preliminary Biological Studies. *Health Phys.* 81:87-93.

Hall, E.J. (2003). The Bystander Effect. *Health Phys.* 85:31-35.

Hall, E.J. & Brenner, D.J. (2008). Cancer risks from diagnostic radiology. *Br. J. Radiology* 81:362-378.

Heidenreich, W.F.; Luebeck, E.G.; Moolgavkar, S.H. (1997). Some properties of the Hazard Function of the Two-Mutation Clonal Expansion Model. *Risk Anal.* 17:391-399.

Heidenreich, W.F.; Cullings, H.M.; Funamoto, S. & Paretske, H.G. (2007). Promoting action of radiation in the atomic bomb survivor Carcinogenesis Data? *Radiat. Res.* 168: 750-756.

Howe, G.R. (1995) Lung Cancer Mortality between 1950 and 1987 after Exposure to Fractionated Moderate-Dose-Rate Ionizing Radiation in the Canadian Fluoroscopy Cohort Study and a Comparison with Lung Cancer Mortality in the Atomic Bomb Survivors Study. *Radiat. Res.* 142: 295-304.

ICRP 2. (1959) *Report of Committee II on Permissible Dose for Internal Radiation.* The International Commission on Radiological Protection Publication 2. Pergamon Press, Headington Hill Hall, Oxford, UK.

ICRP 20. (1973) *Alkaline earth metabolism in adult man.* International Commission on Radiological Protection Publication 20. Pergamon Press, Elmsford, NY.

ICRP 26. (1977). *Recommendations of the International Commission on Radiological Protection.* International Commission on Radiological Protection Publication 26. *Annals of the ICRP* 1:3. Pergamon Press, Oxford.

ICRP 30. (1979). *Limits for Intakes of Radionuclides by Workers.* International Commission on Radiological Protection Publication 30 Part 1. *Annals of the ICRP* 2: 3-4. Pergamon Press, Oxford, UK.

ICRP 60. (1991). *1990 Recommendations of the International Commission on Radiological Protection.* International Commission on Radiological Protection Publication 60. *Annals of the ICRP* 21: 1-3. Pergamon Press, Elmsford, NY.

ICRP 66. (1994). *Human Respiratory Tract Model for Radiological Protection.* International Commission on Radiological Protection Pub. 66. Elsevier Science Ltd., Oxford.

ICRP 103. (2007). *The 2007 Recommendations of the International Commission on Radiological Protection.* Exeter, International Commission on Radiological Protection. Publication 103. Annals of the ICRP 37: 2-4. Elsevier, UK.

Jaworowski, Z. (2010). Observations on the Chernobyl Disaster and LNT. *Dose Response* 8: 148–171.

Lloyd, R.D.; Miller, S.C.; Taylor, G.N.; Bruenger, F.W.; Jee, W.S.S. & Angus, W. (1994). Relative Effectiveness of ^{239}Pu and Some Other Internal Emitters for Bone Cancer Induction in Beagles. *Health Phys. 67*: 346-353.

Lubin, J.H.; Boice, J.D.; Edling, C.; Horning, R.W.; Howe, G.; Kunz, E.; Kusiak, R.A.; Morrison, H.I.; Radford, E.P.; Samet, J.M.; Tirmarche, M.; Woodward, A.; Yao, S.X. & Pierce, D.A. (1994). *Radon and Lung Cancer Risk: A Joint Analysis of 11 Underground Miner Studies*, National Institutes of Health Publication No. 94-3644, United States Department of Health and Human Services, Washington, DC.

Lubin, J.H.; Boice, J.D.; Edling, C.; Horning, R.W.; Howe, G.R.; Kunz, E.; Kusiak, R.A.; Morrison, H.I.; Radford, E.P.; Samet, J.M.; Tirmarche, M.; Woodward, A.; Yao, S.X. & Pierce, D.A. (1995). Lung Cancer In Radon-Exposed Miners and Estimation of Risk From Indoor Exposure. *J. Natl. Cancer Inst*. 87: 817-827.

Manhattan Engineering District. (1946). *The Atomic Bombings of Hiroshima and Nagasaki.* Manhatten Engineer District, United States Army, Washington, DC.

Mauderly, J.L. & Daynes, R.A. (1994). *Biennial Report on Long-term Dose-response Studies of Inhaled or Injected Radionuclides 1991-93.* Inhalation Toxicology Research Institute, Albuquerque, New Mexico. Springfield, VA: National Technical Information Service; ITRI-139.

Mays, C.W. & Lloyd, R.D. (1972). Bone Sarcoma Incidence Versus. Alpha Particle Dose. In: Stover BJ, Jee WSS, eds. *Radiobiology of Plutonium.* Salt Lake City, UT: The J.W. Press, 409-430.

Ministry of Health. (1966). *Radiological Hazards to Patients.* Final Report. HMSO: London, UK.

Mole, R.H. (1990). Childhood Cancer After Prenatal Exposure To Diagnostic X-ray Examinations in Britian. *Br. J. Cancer* 62: 152-168.

Moolgavkar, S.H. Dewanji, A.; & Venzon, D.J. (1988). A Stochastic Two-Stage Model for Cancer Risk Asssessment. I. The Hazard Function and the Probability of Tumor. *Risk Anal.* 8:383-392.

NCRP 136. (2001). *Evaluation of the Linear-Nonthreshold Dose-Response Model for Ionizing Radiation.* National Council on Radiation Protection and Measurements Report No. 136. Bethesda MD.

NCRP 160. (2009). *Ionizing Radiation Exposure of the Population of the United States.* National Council on Radiation Protection and Measurements Report No. 160. Bethesda, MD.

Park, J.F. (1993). *Pacific Northwest Laboratory Annual Report for 1992 to the DOE Office of Energy Research: Part 1: Biomedical Sciences.* Pacific Northwest Laboratory, Richland, Washington. Springfield, VA: National Technical Information Service.

Peto, R.; Pike, M.C.; Day, N.E.; Gray, R.G.; Lee, P.N.; Parish, S.; Peto, J.; Richards, S. & Wahredorf, J. (1980). *Guidelines For Simple, Sensitive Significance Tests for Carcinogenic Effects in Long-Term Animal Experiments, Supplement 2 In: Long-Term and Short-Term Screening Assays for Carcinogens: A Critical Appraisal.* IARC Monographs. Lyon, France: World Health Organization International Agency for Research on Cancer; Sup 2, Annex 311-426.

Pierce, D.A. & Mendelsohn, M.L.(1999). A Model For Radiation-Related Cancer Suggested by Atomic Bomb Survivor Data. *Radiat. Res.* 152: 642-654.

Pierce, D.A. & Preston, D.L. (2000). Radiation-Related Cancer Risks at Low Doses Among Atomic Bomb Survivors. *Radiat. Res.* 154: 178-186.

Preston, D.L.; Shimizu, Y.; Pierce, D.A.; Suyama, A. & Mabuchi, K. (2003). Studies of Mortality of Atomic Bomb Survivors. Report 13: Solid Cancer and Noncancer Disease Mortality: 1950-1997. *Radiat. Res.* 160:381-407.

Preston, D.L.; Pierce, D.A.; Shimizu, Y.; Cullings, H.M.; Fujita, S.; Funamoto, S. & Kodama, K. (2004). Effect of Recent Changes in Atomic Bomb Sutvivor Dosimetry on Cancer Mortality Risk Estimates. *Radiat. Res.* 162:377-389.

Preston, D.L.; Ron, E.; Tokuoka, S.; Funamoto, S.; Nishi, N.; Soda. M.; Mabuchi, K. & Kodama, K. (2007). Solid Cancer Incidence in Atomic Bomb Survivors: 1958-1998. *Radiat. Res.* 168:1-64;

Raabe, O.G. (1987). Three-dimensional Dose-Response Models of Competing Risks and Natural Life Span. *Fundam. Appl. Toxicology* 8:465-473.

Raabe, O.G. (1989). Extrapolation and Scaling of Animal Data to Humans: Scaling of Fatal Cancer Risks From Laboratory Animals to Man. *Health Phys.* 57, Sup. 1:419-432.

Raabe, O.G. (1994). Cancer and Injury Risks From Internally Deposited Radionuclides. In: *Actualités sur le Césium,* Comité de Radioprotection, Electricité de France, Publication Numéro 8: 39-48.

Raabe, O.G.. (2010). Concerning the Health Effects of Internally Deposited Radionuclides. *Health Phys.* 98: 515-536.

Raabe, O.G. (2011). Toward Improved Ionizing Radiation Safety Standards. *Health Phys.* 101: 84-93.

Raabe, O.G.; Book, S.A. & Parks, N.J. (1980). Bone cancer from radium: Canine dose response explains data for mice and humans. *Science* 208:61-64.

Raabe, O.G. & Abell, D.L. (1990). *Laboratory for Energy-Related Health Research Final Annual Report, Fiscal Year 1989*, UCD 472-13. University of California, Davis, CA. Springfield VA: National Technical Information Service.

Raabe, O.G.; Rosenblatt, L.S. & Schlenker, R.A. (1990). Interspecies Scaling of Risk for Radiation-induced Bone Cancer. *Int. J. Radiat. Biol.* 57: 1047-1061.

Raabe, O.G. & Parks, N.J. (1993). Skeletal uptake and lifetime retention of ^{90}Sr and ^{226} Ra in beagles. *Radiat. Res.* 133:204-218.

RERF. (2008). 60-year Anniversary of ABCC/RERF, Annual Report 1 April 2007-31 March 2008 Radiation Effects Research Foundation Hiroshima, Japan.

Rowland, R.E. (1994). *Radium in Humans, A Review of U.S. Studies.* ANL/ER-3, Argonne, IL: Argonne National Laboratory.

Saccomanno, G; Huth, G.C.; Auerbach, O. & Kuschner, M. (1988). Relationship of Radioactive Radon Daughters and Cigarette Smoking in the Genesis of Lung Cancer in Uranium Miners. *Cancer* 62:1402-1408.

Snyder, A.R. & Morgan, W.F. (2004). Gene Expression Profiling After Irradiation: Clues To Understanding Acute and Persistent Responses? *Cancer Metastasis Reviews* 23:259-268.

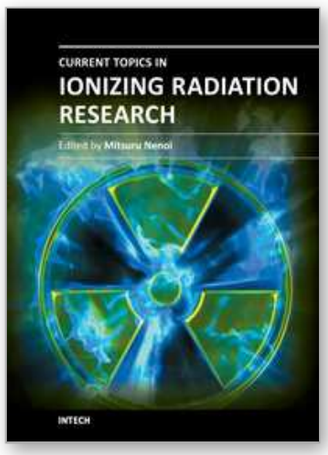
Stewart, A., Webb, J., Giles, D. & Hewitt, D. (1956). Malignant Disease in Childhood and Diagnostic Irradiation In Utero, *Lancet* ii:447-448.

Stewart, A. , Webb, J., Hewitt, D. (1958). A Survey of Childhood Malignancies. *Br. Med. J.* 1:1495-1508.

Totter, J.R. & MacPherson, H.G. (1981). Do Childhood Cancers Result From Prenatal X-rays. *Health Phys.* 40:511-524.

Wing, S.; Shy, C.M.; Wood, J.L.; Wolf, S.; Cragle, D.L. & Frome, E.L. (1991). Mortality Among Workers at Oak Ridge National Laboratory. *J. American Med. Assoc.* 265:1397-2402.

WHO. (2006) *Health Effects of the Chernobyl Accident and Special Health Care Programmes.* World Health Organizion, Geneva, Switzerland.



Current Topics in Ionizing Radiation Research
Edited by Dr. Mitsuru Nenoi

ISBN 978-953-51-0196-3
Hard cover, 840 pages
Publisher InTech
Published online 12, February, 2012
Published in print edition February, 2012

Since the discovery of X rays by Roentgen in 1895, the ionizing radiation has been extensively utilized in a variety of medical and industrial applications. However people have shortly recognized its harmful aspects through inadvertent uses. Subsequently people experienced nuclear power plant accidents in Chernobyl and Fukushima, which taught us that the risk of ionizing radiation is closely and seriously involved in the modern society. In this circumstance, it becomes increasingly important that more scientists, engineers and students get familiar with ionizing radiation research regardless of the research field they are working. Based on this idea, the book "Current Topics in Ionizing Radiation Research" was designed to overview the recent achievements in ionizing radiation research including biological effects, medical uses and principles of radiation measurement.

How to reference
In order to correctly reference this scholarly work, feel free to copy and paste the following:

Otto G. Raabe (2012). Ionizing Radiation Carcinogenesis, Current Topics in Ionizing Radiation Research, Dr. Mitsuru Nenoi (Ed.), ISBN: 978-953-51-0196-3, InTech, Available from: http://www.intechopen.com/books/current-topics-in-ionizing-radiation-research/ionizing-radiation-carcinogenesis

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen