From radiation dose to cancer risk

D. M. Wood, November 2017

Contents

- *Relating dose and risk* 1
  - *Confounding effects* 3
  - *Most reliable recent data on cancer rates vs. dose* 4
- *A quick analogy* 6
- *Radiation dose and cancer risk modeling* 7
  - *Why should such modeling software be trusted?* 8
- *Takeaway messages* 9

To some extent this document can be read without having read other documents. But the document A crash course in radiation biology and health physics may be useful to understand the status of leukemia as a 'canary in the mine' indicator of radiation exposure.

Relating dose and risk

Since the 1940s the working assumption in relating radiation dose to the risk (once again, the probability for an 'average' person) of developing cancer is that the number of cancers produced by a given form of radiation (e.g., a particular radioactive isotope whose 'decay products' like α particles or γ rays and their energies) is *linearly proportional* to the 'external' dose. In the literature this is known as the 'linear no threshold' (LNT) model. ('No threshold'?: this is assumed to hold right down to zero dose.)

Note: It is very important to note that this assumption has been strongly questioned for the last 15 years or so in the limits of *low dose*. Recent developments are discussed in the document Recent developments in low-dose radiation response elsewhere on this web site. The translation of radiation dose into cancer risk for a population typically uses direct observation over a long period of a large

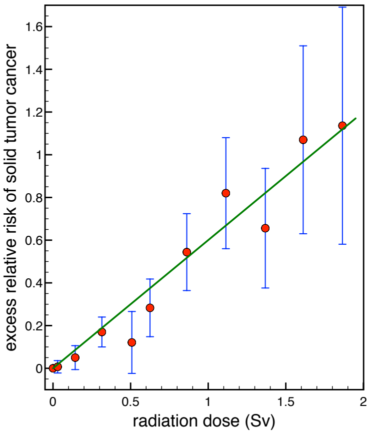


Figure 1: Solid cancer excess relative risk for atomic bomb survivors, from the BEIR VII Phase 2 report, from S. D. Williams' Wikipedia replot. The error bars indicate '90% confidence intervals'. Note that the error bars are due to statistical uncertainty: many fewer survivors were exposed to high radiation doses than to low doses, so the common $1/\sqrt{N}$ relative error (for a sample size N) are large.

number of people exposed to the same dose of radiation. (Bomb survivors from Hiroshima and Nagasaki provided the first such group.)

In radiation epidemiology it is extremely common to quantify this risk via the *excess relative risk* (ERR), defined by

$$\begin{aligned} \text{ERR} &= \frac{\text{radiation exposure risk}}{\text{background exposure risk}} \\ &= \frac{\text{radiation dose}}{\text{background dose}} \end{aligned}$$

where in the second line we have used the linear no-threshold assumption. It is worth noting that the ERR is 1 if the radiation dose (considered apart from background) when its value is the same as what the same population has received from background radiation. Useful discussions of the ERR and calculators [2] for computing it from radiation exposure are at the National Cancer Institute's web site [3].

Example 1: Using Fig. 1, in order for the ERR to be 1 (that is, the risk of a solid tumor cancer due to atomic weapon exposure to be the same as that due to pre-existing background radiation), we would require an external radiation dose of about 1.6 Sv.

The 50-year dose due to background radiation (a world average of about 3 mSv/year (Wikipedia) is about $3.\times 50$ mSv = 0.15 Sv. The factor 1.6/0.15 = 10.7 (from Example 1) is surprisingly large: one might have expected an additional external radiation dose of 0.15 mSv would have caused a doubling of the risk. There are two ways to view this: (i) external radiation is surprisingly ineffective at producing cancers, or (ii) something is very wrong with the linear no-threshold description at low doses (comparable to background). In fact, both are true. We will revisit this issue in the document Recent developments in low-dose radiation response elsewhere on this web site.

Part of a PowerPoint presentation by D. E. Jose from

For example: suppose the incubation time for liver cancer is 16 years. If you watch a large population exposed to a radiation dose of 3 Gy, and 20% have developed after, say, 50 years, then—given the LNT assumption—the lifetime cancer risk is 20%/3 = 16.7 percent per Gy of exposure.

For use of the ERR in non-radiation contexts, see [1]. One also occasionally sees simply the 'relative risk' (RR), in the form of

$$\text{RR} = \frac{\text{total radiation exposure risk}}{\text{background exposure risk}} = 1 + \text{ERR}$$

As remarked by some nameless author of the 1996 Harvard Report on Cancer Prevention, "While radiation is considered a universal carcinogen, it is a relatively weak one, in part because it is such an effective cell killer."

the Health Physics Society reviews the 2001 legal status of legal ‘fair compensation’ for radiation injury. In words, the criterion for compensation requires that it is “more likely than not” that cancer was caused by radiation exposure (not “beyond a reasonable doubt”).

$$\text{Criterion for compensation: RR} > 2.0$$

Example 2: Q: For what doses would Hiroshima/Nagasaki survivors be eligible for compensation? *A:* the ERR must exceed 1: doses above 1.6 Sv.

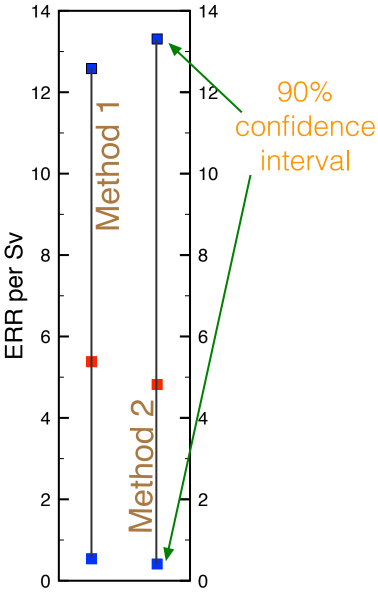


Figure 2: ERR of non-leukemia cancers per Sv of radiation exposure for ORNL population

Depending on the context, despite the clear definition of the ERR, uncertainties in results can be very large because of the need to group large numbers of people (with individual radiation sensitivities, histories, etc) into a much smaller number of groups (e.g., based on similar jobs or plants) to simplify analysis. As an example, Fig. 2 shows how the same data [4] (of non-leukemia cancer mortality rates among workers (accounting for 137,673 person-years of exposure since 1943 at Oak Ridge National Laboratory) can be analyzed in two different but legitimate ways, resulting in similar ‘mean’ ERRs and (typically) very large 90% confidence intervals. Note that the ERR per Sv unit—provided the LNT assumption holds—is sufficient to describe the whole dose range. (For more, see Wikipedia.)

Confidence intervals are discussed in the math appendix document on statistics

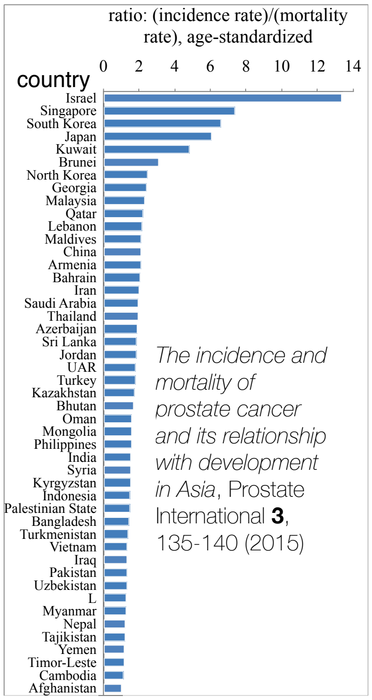
Provided we use the LNT description, the contributions to the ERR from distinct radiation sources can be simply *added*. This assumption is deeply embedded in all but recent radiation/cancer epidemiology. For instance, it underlies all of the cancer rate estimates made by the Department of Energy in the context of low-level radiation exposure from contaminated sites such as Rocky Flats.

Confounding effects

Great care must be taken to remove or at least account for ‘confounding effects’: the appearance of a causal link that is actually produced by correlation. Wakeford [5] gives as an example how cirrhosis of the liver can be strongly

Correlation does not imply causation is a watchword in statistics correlated with drinking lots of tonic water. However, it is actually the alcohol in the gin-and-tonic that causes the cirrhosis. Another well-known example is that the incidence rate of prostate cancer is higher in wealthy neighborhoods than in poor. Is this due to the lifestyles of the rich and famous, say in [6] Boulder?

No: it reflects the fact that wealthy people typically have much better health care than poor people, so that more tests are given and cancers are diagnosed much earlier. Fig. 3 shows how the *ratio* of the rates of incidence (effectively, diagnosis of cancer) to the mortality rate (at which people die of prostate cancer) depends on countries in the Middle East and Asia. This ratio closely tracks the level of economic development of the country. In a statistical sense, this is effectively the ratio of men diagnosed with prostate cancer to those who die of it. In Israel roughly 13 times as many men are diagnosed with prostate cancer as die of it. In Afghanistan, unfortunately, the ratio is 1: people learn they have prostate cancer when they are dying, or by autopsy.



The incidence and mortality of prostate cancer and its relationship with development in Asia, Prostate International **3**, 135-140 (2015)

Figure 3: Ratio of *diagnosis* rate to *mortality* rate by prostate cancer is much higher in wealthy country in the Middle East and Asia

By far the most important confounding effect in the study of radiation and cancer is cigarette smoking, which is very common among the nuclear plant workers who provide the best study subjects for reasons discussed next. Smoking is so closely correlated with cancer (and it appears to act synergistically and not additively with radiation) that sometimes smokers are excluded from the statistics.

Most reliable recent data on cancer rates vs. dose

An *excellent* introduction and review of radiation exposure epidemiology [5] by Wakeford is so recent that it has not yet been published (as of November 2017). Most data comes *group correlation studies*, which assume that group-averaged radiation exposures apply to individual people. Formally this may not be correct because of the 'ecological fallacy': we cannot actually infer whether an *individual* will develop cancer based on the statistics of the *group* to which he or she belongs. Nonetheless, this is very commonly done.

Virtually all policy on radiation protection is based on precisely this approach.

Among the most reliable estimations of cancer rates vs. (low-dose) radiation exposure comes from data for workers at nuclear power plants or nuclear processing facilities. This is because their radiation exposure is regulated and they are generally required to wear reliable radiation dosimeters. Very large numbers of study participants are needed precisely because *the increased risk of cancer due to exposure is so tiny*, even for nuclear plant workers. Studies (the '15-country study') have included data from Australia, Belgium, Canda, Finland, France, Hungary, Japan, South Korea, Lithuania, the Slovak Republic, Spain, Sweden, Switzerland, the UK, and the USA.

The INWORKS consortium is a cooperative international epidemiology collaboration meant to pool data from nuclear workers in the US, Great Britain, and France to reliably assess the effects of chronic exposure to low doses of ionizing radiation. The aggregate number of workers as of 2015 is 308,297. In order to be included in statistics workers had to have been working in the nuclear industry for at least one year and had to be monitored for external radiation exposure via personal dosimeters. Statistics were available for 8.2 million person years of exposure with an average ('median') follow-up of 26 years per worker and a median employment time of 12 years.

Results from the INWORKS project through 2005 (but published in 2015 because of follow-ups and data analysis) were split into reports for leukemia [7] and non-leukemias [8]. I have merged results from these two publications into the table below. The incubation periods for leukemias and solid cancers are assumed to be 2 years and 10 years respectively.

As stated in the leukemia report in the British medical journal *The Lancet* [7], "We estimated relative risk (RR) by a model of the form RR = 1 + β d, generally used in studies of radiation effects, where d is the dose and β is an estimate of the excess relative risk (ERR = RR - 1)

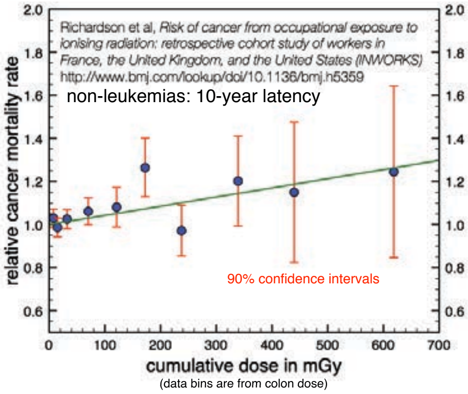


Figure 4: INWORKS relative mortality rates for non-leukemias [8]

per unit dose". This is of course the 'linear, no threshold' model.

I have also included (for former Rocky Flats workers) a second table for cancer mortality rates (through 2005, published in 2015 [9] from a survey of pooled US nuclear workers at the Hanford site, Idaho National Laboratory, Oak Ridge National Laboratory, the Savannah River site, and the Portsmouth Naval Shipyard. We see once again that leukemias are the 'canary in the coal mine' with respect to radiation exposure—a fairly rapidly emerging and much more likely to occur cancer.

Cancer	ERR (per Gy)	90% CI
All cancers	0.51	0.23-0.82
Leukemias	2.96	1.17-5.21
Non-leukemias	0.48	0.20-0.79
Solid cancers	0.47	0.18-0.79

Table 1: Summary of cancer mortality through 2005 for INWORKS cohort, from [7] and [8]

Cancer	ERR	95% CI
Non-leukemias	0.14% per 10 mSv	-0.17%-0.48%
Leukemias	1.7% per 10 mSv	-0.22%-4.7%

Table 2: Summary of cancer mortality through 2005 for US nuclear workers [9]

A quick analogy

We all have a reasonable grasp of what "taking a risk" means. We hear "there's a 30% chance of showers between 5 and 7 PM" and think, "OK, I'll grill out on the patio". This is really a form of risk analysis where the worst-case outcome is simple inconvenience, but, as with all risks, they range between 0 (no risk) and 1 (there is a 100% probability the 'risk' will occur).

Underlying this prediction is a vast wad o' calculations, beginning days earlier with what was measured by multi-national cooperating meteorological satellites which can track temperature and water vapor distributions around the Earth and in its atmosphere on a spatial scale (sometimes) of meters and a time scale of hours. This data is augmented by ground-based weather stations

All of this information is fed into extraordinarily large computer codes running on immense computer networks which use this input and the equations of hydrodynamics for fluid flow (the flow of a very non-uniform atmosphere and the water vapor it contains, driven by differences in temperature, pressure, altitude, water distributions, from point to point on the surface of the earth) to make predictions.

(more or less continuously logging and transmitting temperature, pressure, relative humidity, wind direction and wind speed) around the world. Given what is predicted by weather codes for a given region at a given time, probabilities between 0 and 1 for a variety of outcomes (thunderstorms, hail, snowstorms) can be determined. Leavened by the experience of meteorologists, these probabilities are distributed around the world as weather forecasts.

Radiation dose and cancer risk modeling

We can all feel temperature, humidity, winds and eyeball the horizon for a guess about what will happen to the weather. We are not so lucky with the subatomic particles you know are associated with nuclear radiation. Nonetheless, an analogous process to what is used for the weather can be used to assess the risks associated with exposure to radiation. Just as weather forecasts deal with probabilities between 0 and 1, so too do the probabilities for particular outcomes related to radiation.

Once the sources of radiation and their spatial distribution are identified, they can be used as input to elaborate modeling computer codes to predict radiation exposure and cancer risk. Analogous to the weather codes mentioned above, these can be used to estimate radiation doses to populations, and probabilities of various cancers depending on the isotopes present and their concentrations. One example of such a 'weather forecasting' program for cancer is named RESRAD-ONSITE (`http://resrad.evs.anl.gov/codes/resrad-onsite/`). Developed at Argonne National Laboratory, it is used by the Department of Energy (and in fact, by the Nuclear Regulatory Commission and by other countries) to "…estimate radiation doses and cancer risks to an individual located on top of radioactively contaminated soils and to derive radionuclide soil guideline levels corresponding to a specific dose criterion".

According to the software description,

> The calculation of dose and cancer risk by the RESRAD-ONSITE code is scenario driven, with the use of parameter values specified by the user. Nine exposure pathways are provided which can be selected or suppressed to reflect the land use and receptor scenario under consideration. These nine exposure pathways are: (1) direct external radiation from radionuclides in soil, (2) inhalation of airborne radionuclides resuspended or volatilizing (H-3 and C-14) from soil, (3) incidental ingestion of soil, (4) ingestion of plant foods grown in contaminated soil and irrigated with contaminated water, (5) ingestion of meat and (6) ingestion of milk produced by livestock fed with contaminated fodder and water, (7) ingestion of drinking water from a well or pond adjacent to the contaminated area, (8) ingestion of aquatic foods from the pond, and (9) inhalation of radon emitted from contaminated soil. Input information needed for the calculation include characteristics of the contamination, properties of surface, sub-surface, and saturated soil strata, site-specific meteorological, hydraulic, and hydrogeological data, as well as exposure pattern of the receptor.

This software has been under development since 1993 and is in use by foreign countries and European environmental modeling groups; you will find references to its use in the Fourth Five-Year Review Report for the Rocky Flats Site Jefferson County, Colorado submitted by the DOE to the Rocky Flats/Legacy Management Site Manager Scott Surovchak on August 2, 2017.

A very good overview [11] overview surveys the capabilities of RESRAD, although it has been revised considerably since 2012. (see also the slightly older International Atomic Energy Agency presentation [12] The RESRAD-BIOTA suite can be used to assess radiation exposure to 'flora and fauna in a terrestrial or aquatic ecosystem'.

Why should such modeling software be trusted?

As might be expected because it is used in a regulatory capacity, RESRAD has been thoroughly vetted both in the US and by foreign regulatory agencies. This occurs in the form of verification (internal mathematical consistency and accuracy) and validation (comparison of the underlying mathematical model with accurately observed field or lab observations). It has been used in international code-comparison exercises using other codes developed abroad. It has by now been used on more than 300 sites in the US and abroad. An example of a comparison with

EPA-developed calculation tools (for a non-Rocky Flats site) is shown in Fig. 5 for a 'resident' scenario. Note that because RESRAD includes the results of long-lived radioactive decay products, it yields a higher lifetime cancer risk, a Good Thing in a tool used to set permissible contamination levels.

We will revisit RESRAD in the context of the region around Rocky Flats.

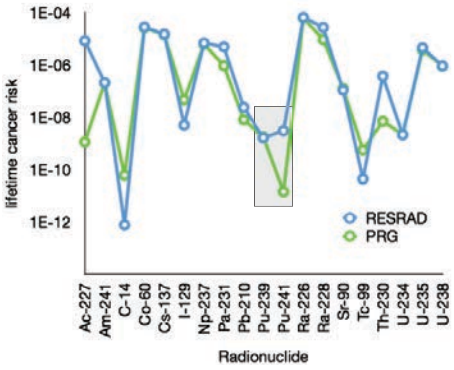


Figure 5: Sample comparison of RESRAD and EPA calculator tool results for a variety of radionuclides, from [13] the 'resident' scenario data of Table 3.2.7

Takeaway messages

- The 'linear no threshold' assumption is made in cancer epidemiology: the cancer risk is linearly proportion to the radiation dose. Recently this assumption has been reconsidered for low doses—the very ones to which Rocky Flats Wildlife Refuge and those living in new developments around Rocky Flats—are subjected.
- Although there remain large 'error bars' to encompass statistical uncertainty, in later documents we will use data from an international collaboration which pools data from workers at nuclear facilities, since their exposure is carefully monitored using reliable 'dosimeters'.
- Elaborate, exhaustive computer codes exist to translate a spatial distribution of radioactive contamination into cancer risk for a variety of land use scenarios.
- We will examine results from one of these (RESRAD-ONSITE) for the area around Rocky Flats.

References

[1] Wen Chung Lee. "Excess relative risk as an effect measure in case-control studies of rare diseases". In: *PLoS ONE* 10.4 (2015), pp. 1–9. ISSN: 19326203. DOI: `10.1371/journal.pone.0121141`.

[2] National Cancer Institute. *Interactive RadioEpidemiological Program*. URL: `https://radiationcalculators.cancer.gov/irep/model/` (visited on 03/05/2018).

[3] National Cancer Institute Division of Cancer Epidemiology and Genetics. *Radiation Risk Analysis Tools*. URL: `https://radiationcalculators.cancer.gov/` (visited on 03/05/2018).

[4] Leslie Stayner et al. “A Monte Carlo maximum likelihood method for estimating uncertainty arising from shared errors in exposures in epidemiological studies of nuclear workers.” In: *Radiation research* 168.6 (2007), pp. 757–763. ISSN: 0033-7587. DOI: `10.1667/RR0677.1`.

[5] Richard Wakeford. *Human Risk Assessment âĹŠ Radiation Epidemiology*. Tech. rep. June. 2017, p. 257. URL: `https://www.nmbu.no/download/file/fid/26686`.

[6] Alex Burness. *Study: Cancer rates not notably higher near Rocky Flats, but Boulder sees uptick in prostate cases - Boulder Daily Camera*. 2017. URL: `http://www.dailycamera.com/news/boulder/ci_30706193/report-cancer-rates-not-notably-higher-near-rocky`.

[7] Klervi Leuraud et al. “Ionising radiation and risk of death from leukaemia and lymphoma in radiation-monitored workers (INWORKS): An international cohort study”. In: *The Lancet Haematology* 2.7 (2015), e276–e281. ISSN: 23523026. DOI: `10.1016/S2352-3026(15)00094-0`. URL: `http://dx.doi.org/10.1016/S2352-3026(15)00094-0`.

[8] David B Richardson et al. “Risk of cancer from occupational exposure to ionising radiation: retrospective cohort study of workers in France, the United Kingdom, and the United States (INWORKS)”. In: *BMJ* (2015), h5359. ISSN: 1756-1833. DOI: `10.1136/bmj.h5359`. URL: `http://www.bmj.com/lookup/doi/10.1136/bmj.h5359`.

[9] Mary K Schubauer-Berigan et al. “Cancer Mortality through 2005 among a Pooled Cohort of U.S. Nuclear Workers Exposed to External Ionizing Radiation”. In: *Source: Radiation Research RADIATION RESEARCH* 183.6 (2015), pp. 620–631. DOI: `10.1667/RR13988.1`. URL: `http://www.bioone.org/doi/full/10.1667/RR13988.1`.

[10] *Fourth Five-Year Review Report for the Rocky Flats Site Jefferson County, Colorado*. Tech. rep. Department of Energy, Legacy Management, 2017. URL: `https://www.lm.doe.gov/Rocky_Flats/Regulations.aspx`.

[11] Charley Yu. “RESRAD Family of Codes âĂŤ A Suite of Tools for Environmental Radiological Dose Assessment”. In: *Environmental Radiological Assistance Directory Web Conference*. 2012.

URL: https://www.energy.gov/sites/prod/files/2014/03/f14/resrad_codes_erad_june_2012-CharlieYu.pdf.

[12] Charley Yu and David Lepoire. "Dose and Risk Assessment". In: 2010. URL: https://www.iaea.org/OurWork/ST/NE/NEFW/documents/ENVIRONET/TM_ER_Radiologically_Contaminate_Sites_ANL/D3/Dose_and_Risk_Assessment.pdf.

[13] C. Yu, J. J. Cheng, and S. Kamboj. *RESRAD for Radiological Risk Assessment. Comparison with EPA CERCLA Tools - PRG and DCC Calculators*. Tech. rep. Argonne, IL (United States): Argonne National Laboratory (ANL), 2015. DOI: 10.2172/1203604. URL: http://www.osti.gov/servlets/purl/1203604/.

Reminders: (i) Just click on a reference in the text to reposition the cursor in the bibliography; (ii) generally by simply clicking on the URL field or the DOI field in a bibliographic entry will fire up our Web browser and take you to where the original file is available.