Avoiding Diagnostic Imaging, Not Low-Dose Radiation, Is the Real Health Risk

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Diagnostic imaging with low-dose ionizing radiation helps physicians save lives and assist in prolonging good health. Numerous publications[1-5] based on clinical, epidemiological, and ecological studies have claimed increased cancer risk associated with low radiation doses such as received from diagnostic imaging and other sources (e.g., nuclear worker exposures, some Chernobyl accident victims among the public).

The increased risk is often evaluated based on the linear-no-threshold (LNT) model, which assigns absolute or relative risk with any radiation exposure, including natural background radiation exposure. An important question addressed in this paper is how reliable are cancer risk estimates derived from such studies, especially when based on the LNT model.

Results provided in Tables 1 and 2, as explained below, can be used to evaluate the plausibility of epidemiological study results claimed to indicate an increase in cancer or cancer mortality risk from exposure to low radiation doses, such as are received from an X-ray-computed tomography (CT) scan or chest X-ray. Such doses are very much less than 100 mGy (milligray). Thus, the absence of convincing evidence for harm (increased cancer risk) from 100 mGy would imply the lack of convincing evidence for harm from smaller doses associated with diagnostic imaging with single or multiple CT scans and chest X-rays.

Some background information on different risk models and terminology used in epidemiological studies is provided in the following two sections.

LNT, Threshold, and Hormetic Models

Hypothetical examples of LNT, hormetic, and threshold dose-response relationships for cancer relative risk (RR) for a population as a function of radiation dose are provided in Figure 1. The hypothetical examples relate to a source of low linear-energy-transfer (LET) radiation such as diagnostic X-rays. The focus here is on the low-dose region (0 to 100 mGy). Low-LET radiation is sparsely ionizing, unlike high-LET radiation such as alpha particles, which produce lots of ionizations.

With the LNT model as illustrated in Figure 1, cancer RR increases linearly from a value of 1 (no-effect level) as radiation dose increases, so that any small dose (e.g., from diagnostic imaging using X-rays) could in theory lead to a cancer induction in someone. However, usually the increase in cancer RR at low doses is extrapolated from high doses, as it is unlikely that such increases can be demonstrated to be scientifically credible using only low-dose data.[6]

Table 1. Percentiles (2.5%, 5%, 95%, and 97.5%) values for cancer (incidence or mortality) derived relative risk (DRR) distribution under the null hypothesis of no radiation effect when the variability in the derived baseline risk (DBR) is uniform from the minimum (DBR_{min}) to maximum value (DBR_{max}).[a]

Fold change from DBR_{min} to DBR_{max}	2.5%	5%	95%	97.5%
1.25	0.842	0.859	1.17	1.19
1.5	0.732	0.760	1.32	1.37
1.75	0.650	0.685	1.46	1.54
2.0	0.588	0.626	1.60	1.71
2.25	0.538	0.579	1.73	1.86
2.5	0.497	0.540	1.86	2.02
2.75	0.463	0.507	1.98	2.17
3.0	0.433	0.480	2.09	2.31
4.0	0.351	0.401	2.49	2.86
5.0	0.298	0.349	2.87	3.34

[a]Results are based on Monte Carlo evaluations with WinBUGS[10] using 10,000 realizations (iterations) per DBR-fold-change category. Separate samples from the DBR distribution were taken for a radiation-exposed group and a control group with DRR calculated for each set of values. Sampling from the same distribution applies under the null hypothesis of no radiation effect.

Table 2. Percentiles (90%, 95%, and 97.5%) for the bias adjustment factor (BAF) for correcting bias in estimates of DRR (> 1) obtained directly using the DOR value from a case-control study.[a]

Ratio of controls to cases	Reference baseline frequency	90%	95%	97.5%
1 to 1	0.5	2.134	2.537	2.933
1.5 to 1	0.4	1.285	1.362	1.422
2 to 1	0.3333	1.205	1.259	1.301
3 to 1	0.25	1.132	1.165	1.191
4 to 1	0.2	1.098	1.121	1.14
5 to 1	0.1667	1.077	1.096	1.11

[a]Results are based on Monte Carlo evaluations with WinBUGS[10] using 10,000 realizations per controls/cases ratio category with reference baseline frequency ranging from [reference frequency – (reference frequency/3)] to [reference frequency + (reference frequency/3)], which is a plausible and conservative 2-fold range from minimum to maximum. Separate samples from the reference frequency distribution were taken for a radiation-exposed group and a control group with DOR and DRR calculated for each set of values and BAF evaluated as BAF=DOR/DRR. Sampling from the same reference frequency distribution applies under the null hypothesis of no radiation effect.

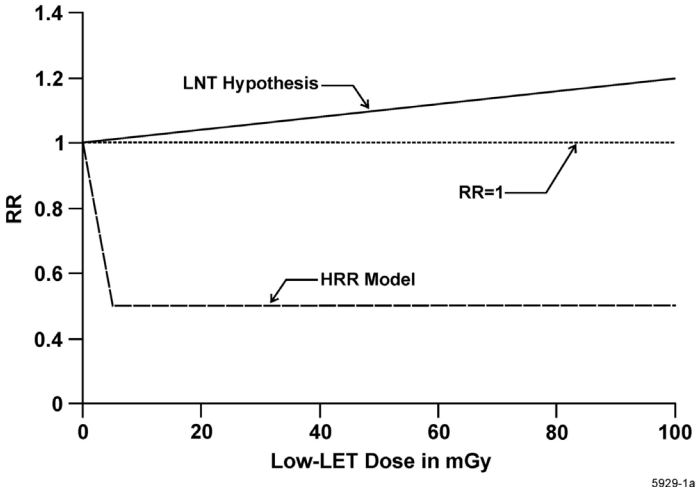

Figure 1. Different dose-response relationships (hypothetical) for cancer relative risk (RR) at the population level based on the linear-no-threshold hypothesis (LNT model), the hormetic relative risk (HRR) model, and threshold model (RR =1 in this example because doses are below the threshold for harm). The three dose-response relationships are not based on real data and are used only for illustrative purposes. The low-LET (radiation) dose range is typical of multiple applications of diagnostic imaging (e.g., several CT scans).

With the hormetic relative risk (HRR) model, low doses can stimulate the body's natural defenses (e.g., anti-cancer immunity), which can prevent cancers caused by other agents (e.g., lung cancer from cigarette smoke carcinogens), rather than causing harm.[7] Because of the stimulated natural protection (i.e., hormetic effect), RR drops to below 1 with the HRR model as illustrated in Figure 1. Unlike with the LNT model, hormetic effects (cancer incidence reduction) have been demonstrated to be scientifically credible using only low-dose data.[8]

With the threshold model, no increase in RR, and no harm, occurs for doses below a threshold. In Figure 1 the threshold is greater than 100 mGy (and thus not shown) so that for this model RR stays at 1 for the dose-range considered.

While regulatory agencies such as the Environmental Protection Agency (EPA) and Nuclear Regulatory Commission (NRC) rely on the LNT model for assessing cancer risk from low radiation doses such as received from diagnostic imaging, the validity of the LNT model has been seriously challenged as the model is inconsistent with findings from mechanistic and toxicological studies using cells and laboratory animals.[6-9]

Epidemiological Studies and Related Terminology

Epidemiological studies of cancer risk related to radiation exposure are usually of two types: cohort and case-control. The cohort study selects a group of individuals who were exposed to radiation (e.g., one or more CT scan exposures). A comparison group (for baseline risk evaluation) is made up of individuals who are thought to have had little or no radiation exposure other than natural background radiation, but otherwise considered similar. Also, subgroups (e.g., unexposed, low-dose, moderate-dose, and high-dose groups) can be compared with each other, in order to generate dose-response relationships. Cancer RR is a common outcome of cohort studies, and RR > 1 is suggestive of (but not proof of) radiation-induced cancer.

A case-control study compares persons who have cancer (cases) with those that do not have cancer (controls) and looks retrospectively to see how frequently radiation exposure is present in each group. Comparing the frequencies of radiation exposure for the two groups allows for indirect inference about the relationship between radiation exposure and cancer risk. With case-control studies one evaluates odds ratio (OR) for cancer among irradiated persons vs. non-irradiated persons. The OR is used as an estimate of cancer RR, as RR cannot be directly evaluated in case-control studies.

Generally replication of cohort and case-control studies is not feasible due to the prohibitive costs involved. Also, RR values generated in cohort and case-control studies are only rough estimates of the corresponding values for the much larger population of interest. Such rough estimates would be expected to vary over replicate studies if they were carried out. Unfortunately, there is no distinction between RR values obtained using the subset of the population studied (i.e., study group) and the entire population of interest. Further, using the terminology "RR" instead of "RR estimate" is misleadingly suggestive of a population response (i.e., RR) rather than a study-group response (i.e., RR estimate, or DRR as defined below).

New Terminology for Characterizing Epidemiological Study Results

New terminology is introduced here to distinguish between population-related concepts [baseline risk (BR) for cancer or cancer mortality, RR, and OR] and *study-related estimates* of the population-related endpoints. Where results are based on a study of a subset of the population of interest (which is always the case), the terminology "derived" is used in this paper, and the letter D is used to point this out.

A study-derived estimate of the population BR (for cancer incidence or mortality) is referred to here as the *derived BR* and is indicated as *DBR*. While the population BR is fixed but unknown, the DBR would be expected to vary over replicate studies were they carried out. It is impractical to conduct actual replicate epidemiological studies related to a population of interest, so simulated studies will be described. These can be very informative.

A study-derived estimate of the population RR (relative risk) is referred to as the *derived RR* and is indicated as *DRR*. While the population RR is fixed but unknown for a given radiation dose, the DRR would be expected to vary over replicate studies.

A study-derived estimate of the population excess relative risk (ERR) is referred to as the *derived ERR* and is indicated as *DERR*. While the population ERR (which equals RR-1) is fixed but unknown for a given radiation dose, the DERR (which equals DRR-1) would be expected to vary over replicate studies.

A study-derived estimate of the population OR is referred to as a *derived OR* and is indicated as *DOR*. While the population OR is fixed but unknown for a given radiation dose, the DOR would also be expected to vary over replicate studies.

These new terms are more in line with current thinking related to distinguishing between a specific population-related variable and an estimate (derived value) of that variable using a small subset of the population. Because derived values vary over replicate studies, they have a distribution. Importantly, ***a value from the distribution of the DBR (derived baseline risk) can easily be mistaken for a radiation effect*** (e.g., representing DRR > 1) when comparing a control and irradiated group (e.g., persons undergoing diagnostic X-ray exposures).

Generally, assessment studies of cancer or cancer mortality risk in humans associated with low radiation doses do not consider variability in the DBR and how this impacts conclusions about DRR and DOR, and it is possible, and perhaps likely, for invalid conclusions to be derived related to increased (or decreased) risk.

Limitations of Epidemiological Studies of Low-Dose-Radiation Health Effects

Epidemiological studies of cancer or cancer mortality risk from low radiation doses, such as are associated with diagnostic imaging, can be seriously flawed due to the studies' severe limitations. Limitations include: 1) having insufficient power to distinguish between alternative risk models; 2) using data-adjustment procedures whose validity and reliability have not been proven; 3) unaccounted-for uncertainties in the influences of co-variates; and 4) omission of key sources of radiation exposure.

Because of large errors (acknowledged and unacknowledged) associated with risk estimates generated in epidemiological studies, such studies usually have insufficient power for distinguishing between alternative risk models (threshold, LNT, hormetic, etc.). Generally only the LNT model is considered,[1-3] and other possibilities are not addressed.

Data manipulations (called adjustments) and multi-variate descriptive models (i.e., models not related to biological mechanisms that include multiple variables such as radiation dose, age, gender, smoking habits, alcohol consumption, etc.) are employed in data analyses. Uncertainties about influences of multi-variate model co-variates (e.g., smoking habits, alcohol consumption, etc.) are generally neglected, and influences of unrecognized confounders cannot be addressed. For example, life histories of carcinogen exposure (for all carcinogens encountered) for each member of a study group may have the most important impact on the DBR, and this exposure history is not known for any member of a study population. Thus, carcinogen exposure histories are unlikely to be reliably accounted for when evaluating risk metrics (e.g., DOR in case-control studies or DRR in cohort studies).

Epidemiological studies of effects of low radiation doses may exclude important dose contributions from natural background radiation (e.g., radon) and medical exposures (e.g., from diagnostic imaging), and may introduce systematic errors related to methods employed to analyze the data. Thus, actual errors (random and systematic) are likely greater than reported.

Unfortunately, many members of the scientific community, the press, and general public are not aware of the severe limitations of epidemiological and ecological studies of low-dose-radiation risks. In fact, ***there are currently no credible epidemiologic studies that document cancer arising directly from radiologic medical studies or procedures involving low radiation doses.***

Studies attempt to adjust for known and potential confounder influences, but usually do not mention the uncertainty in confounder effects (known or presumed), or of the possible existence of unknown but influential confounders. They also neglect to discuss collinearity issues. (Collinearity is a phenomenon in which two or more variables are highly correlated.) In addition, data-adjustment methods can be error-prone (e.g., bias producing[4]) and at least in some circumstances may have no theoretical foundation. A calculated DRR > 2 may be arrived at solely by confounder (e.g., unknown) influences in combination with variation in the DBR (demonstrated below). This is not the case for a DRR > 10 for example, which may be reported for a high-dose group.[4]

Numerous epidemiological studies (e.g., case control) rely on DOR as an estimate of cancer DRR. However, DOR is not a reliable estimate of DRR,[10] and LNT outcomes for DRR as estimated by using DOR may not be defensible for low radiation doses such as are associated with diagnostic imaging or exposure to natural background radiation.

Epidemiologists, e.g. Leuraud et al.,[2] often use the inappropriate null hypothesis that the DRR is an LNT function of radiation dose. This greatly favors finding the LNT model to be consistent with epidemiological study data, simply because the null hypothesis was not properly formulated. The proper null hypothesis is that there is no radiation effect.

Davies et al.[10] evaluated the reliability of DOR as an estimate of DRR, and the following points are based on their findings:

- The DOR will always overestimate DRR.
- The degree of overestimation of DRR increases as both the DBR and DOR increases.
- In studies that show increases in DOR with dose (e.g., LNT

function), the DRR can be up to a factor of 2 smaller than the DOR. This bias may be even greater because of DBR variability.

The discussion below addresses potential influences of neglected sampling-associated variability in the DBR on DRR estimates in epidemiological studies. A bias adjustment factor (BAF) is introduced, and an assigned conservative value based on percentiles of a derived BAF distribution is used to obtain biased-adjusted DRR values.

The baseline risk of cancer or cancer mortality is likely influenced by the variable responses of different individuals to environmental and other carcinogenic stress. These are affected by genetic susceptibility, DNA damage-response capability, and variable immune response. Study group selection for epidemiological studies therefore likely influences the DBR. In addition, unknown confounders and collinearity as well as error-prone data adjustments contribute unaccounted-for error in risk estimates. Even if it were possible to have the same carcinogen exposure history, for all carcinogens encountered for each member of a study group, outcomes of replicate studies of baseline cancer risk would vary, possibly by a large amount, depending on the variable abilities of different individuals in the study replicate to mount anti-cancer defenses.

To mitigate carcinogen-induced damage (e.g., DNA damage), cells mount complex responses that rely on changes in gene expression. These gene expressions differ greatly between individuals,[11,12] and variable gene expression among different individuals likely influence the DBR for a given study group and endpoint. Because of such large variation in DNA damage responses among different individuals, as well as expected additional variability related to anti-cancer immunity and other defense mechanisms for different humans, the DBR for cancer or cancer mortality obtained from replicates in epidemiological studies (if they were somehow carried out) would be expected to vary considerably, possibly by more than threefold, as has been observed in animal studies using more homogeneous groups of mice.[13]

Addressing the Impact of Derived Baseline Risk (DBR) Variability

Without replicate epidemiologic studies, there is a high risk of claiming that a DRR is increased or decreased when the apparent change actually relates to a sampling variation in the DBR. Because replicate epidemiological studies are unlikely to be carried out, it is necessary to conduct simulation studies that can be repeated many times using computer calculations.

In conducting the simulated multiple studies, one first has to assign a plausible distribution for the DBR. If there is no radiation effect for a low-dose-radiation-exposed group, the derived cancer risk (DRR) for an irradiated group will have the same distribution as the DBR for the unexposed controls.

Thus, one first takes a random value from the DBR distribution and assigns it to the controls. Then one takes a second value from the same distribution and assigns it to the irradiated group. The ratio of the DBR assigned to the irradiated group to the DBR assigned to the control group (DBR irradiated divided by DBR controls) gives the simulated DRR corresponding to a single study.

This can be repeated many times, simulating use of a large number of replicate studies. This allows for evaluating percentiles of the DRR distribution when there is no radiation effect. The percentiles can then be used to evaluate the plausibility of any claimed increase (or decrease) in cancer risk associated with low radiation doses from diagnostic imaging or other radiation sources. This is what has been done to obtain results presented in Table 1.

Table 1 provides percentile values (2.5%, 5%, 95%, and 97.5%) for the DRR for cancer (of a specific type) induction or cancer mortality from low-dose radiation exposure under the null hypothesis of no radiation effect, when the DBR varies uniformly from a minimum (DBR_{min}) to maximum (DBR_{max}) value. The uniform distribution is a conservative assumption. Results are presented for different fold variations (where fold variation = DBR_{max}/DBR_{min}) in the DBR. While results depend on the fold variation of the DBR they do not depend on the magnitude of the DBR. This can be seen from the fact that the maximum value for the DRR is DBR_{max}/DBR_{min} and the minimum value for the DRR is DBR_{min}/DBR_{max}. For a twofold variation in the DBR, the maximum value for the DRR is 2 and the minimum is 0.5.

To obtain the results in Table 1, the random sampling discussed above was repeated 10,000 times, yielding 10,000 separate estimates of the DRR, allowing for accurate estimates of the DRR distribution percentiles. The computations were achieved using what is called Monte Carlo evaluations, carried out with WinBUGS software.[14] The software allows for repeated sampling from assigned distributions and repeatedly carrying out computations (e.g., for DRR or DOR) using the sampled values.

Regarding findings in Table 1, a more than threefold variation in the DBR might be expected for heterogeneous groups of mixed gender and variable ages used in epidemiological studies. The table shows the fallacy of accepting a DRR = 1.5 in a cohort study as indicating a 50% increase in cancer risk as a result of low-dose radiation exposure. For twofold variability in the DBR, there would be no convincing evidence for such an increase. A DRR > 1.6 is needed for a significant increase at $P < 0.05$.

For case-control studies, there is a further complication. If DOR is used to approximate DRR, the DRR may be overestimated by as much as a factor or 2.[10] Thus, for a case-control study, the DOR should be divided by a bias adjustment factor (BAF) as can be derived from values presented in Table 2 to arrive at the estimated DRR.

It is possible for a DRR < 1, representing a possible hormetic or beneficial effect, to be found in epidemiological

studies, but such findings are not discussed here, as the focus is on claimed increases in cancer risk after low radiation doses. However, some claimed hormetic effects (decreased cancer risk) may be invalid and instead explainable based on a sampling variability in the DBR. The 2.5% and 5% values in Table 1 can be used when evaluating plausibility of claimed hormetic responses. DRR values observed would need to be less than the values in the table for hormetic responses to be considered plausible.

How does one arrive at a BAF to adjust for bias in cancer or cancer mortality DRR values obtained from case-control studies that yield DOR as a direct estimate of DRR? Table 2 was developed to assist in making such adjustments. Because DRR depends on the DBR and the baseline risk is not estimated (evaluated) in case-control studies, *a reference baseline frequency*, based on the ratio of controls to cases, was used. For example, for a two-to-one controls-to-cases ratio, the reference baseline frequency = 1/(2+1) = 0.3333 (rounded). To evaluate the influence of variation in the DBR on DRR and DOR under the null hypothesis of no radiation effect, the reference baseline frequency was allowed to vary uniformly by a plausible factor of 2 from [reference frequency - (reference frequency/3)] to [reference frequency + (reference frequency/3)]. This allowed generating the percentiles in the BAF (= DOR/DRR), where DOR and DRR were separately evaluated for each Monte Carlo iteration (see Table 2 footnote).

Some Applications of Tables 1 and 2

In this section, examples are provided on how Tables 1 and 2 can be used to evaluate the plausibility of elevated cancer risk claims based on epidemiological studies involving low radiation dose rates and low doses. The examples relate to leukemia among chronically irradiated nuclear workers, and breast cancer among patients receiving medical radiation exposures.

Plausibility of Leukemia Cohort Study Results

Leuraud et al.[2] carried out a cohort study to quantify associations between protracted low-dose radiation exposures and leukemia, lymphoma, and multiple myeloma mortality among radiation-monitored adult nuclear workers employed in France, the UK, and the U.S. The researchers assembled a cohort of 308,297 radiation-monitored workers employed for at least 1 year by the nuclear industry. The cohort was followed-up for 8.22 million person-years. Deaths caused by leukemia, lymphoma, and multiple myeloma were assessed.

Regression based on an assumed Poisson distribution of outcomes was used, along with the default LNT model (an inappropriate null hypothesis) to look for associations between estimated red bone marrow absorbed radiation dose and leukemia and lymphoma mortality. The researchers reported DERR (derived excess relative risk) per unit lagged dose for leukemia mortality, excluding chronic lymphocytic leukemia. Dose lagging involves throwing away some of the radiation dose, thereby assigning blame for any implied harm to a smaller dose than was actually received. The reported value for the DERR was 2.96/lagged-Gy (90% CI: 1.17–5.21), with 2 years of dose accumulation thrown away. The biggest contributor was the claimed association between radiation dose and mortality from chronic myeloid leukemia (DERR/lagged-Gy 10.45, 90% CI: 4.48–19·65).

Throwing away radiation dose (i.e., lagging), supposedly because of "dose wasting," is common in some research groups that apparently are not aware that the thrown-away dose may have stimulated the body's natural defenses[7] and thereby protected some members of the population from leukemia induction by other leukemogens. In such cases the dose is not wasted! Throwing away dose also inflates the DERR per unit dose (e.g., 10.45 per lagged-Gy). Taking the DERR value of 2.96/lagged-Gy at face value yields a corresponding value of 0.00296/lagged-mGy. Since diagnostic radiation doses are usually < 100 mGy (e.g., for CT and chest X-ray), it is informative to calculate the leukemia (excluding chronic lymphocytic leukemia) DRR value for a 100 mGy dose, which is 1 + DERR = 1+0.296 = 1.296. From Table 1 it can be seen that this value can be explained based on a 1.25-to1.5-fold variation in the DBR, with occupational radiation exposure playing no role in leukemia occurrence.

Carrying out the corresponding calculation for a 100 mGy dose using the upper 90% CI point for DERR/lagged-mGy gives 1 + DERR = 1 + 0.521 = 1.521, which based on Table 1 (95th percentile values) is consistent with a 1.75-to twofold variation in the DBR, without there being any occupational radiation exposure effect. Thus, there is no convincing evidence for radiation-induced leukemia for doses up to 100 mGy.

Carrying out the corresponding calculation for a 100 mGy dose using the upper 90% CI point for DERR/lagged-mGy for mortality from chronic myeloid leukemia gives 1 + DERR = 1 + 1.97 = 2.97 (likely an overestimate because of dose lagging and forced fitting of the intercept at DERR=0), which would require a fivefold variation in the DBR to explain the chronic myeloid leukemia results on that basis. However, there were other problems: The researchers introduced biases and ignored other radiation sources. Leuraud et al.[2] ignored the fact that the workers received medical exposures to ionizing radiation as well as being exposed to natural background radiation (both internal and external sources). Thus, dose misclassification errors (individuals placed in the wrong dose groups), dose underestimation, and dose-response-modeling-related bias introduction all likely influenced their research findings, making their reported DERR values potentially seriously flawed.

To see the possible influence of dose lagging, consider for example a hypothetical cohort study where the true DERR per unit dose (correct dose) was 0.01/mGy and the

cohort study conducted arrived at the DERR value 0.015/mGy without dose lagging, and then decided to re-analyze the data with 90% dose lagging (i.e., throwing away 90% of the dose) yielding a DERR of 0.15/lagged-mGy. Without dose lagging the calculated DRR for a 100 mGy dose would be DRR = 1+100 mGy*(0.015/mGy) = 2.5, which could possibly be explained based on variability in the DBR and confounder influences, while with 90% dose lagging one gets DRR = 1+100 mGy*(0.15/lagged-mGy) = 16, a greater-than-sixfold larger value introduced by being allowed to throw away part of the radiation dose. Since low-dose radiation is a weak carcinogen, cancer cases incorporated in epidemiological studies of groups exposed to low-dose radiation are more likely caused by something other than radiation.

The practice of dose lagging needs to be critically reviewed by a team of experts for its validity and reliability. This is especially important because throwing away some of the radiation dose can make low radiation doses appear quite harmful even when no harm has occurred, thereby promoting radiation phobia, which in turn, has led to the tragic loss of thousands of lives of aborted babies[15,16] following the Chernobyl accident, and more than 1,000 premature deaths among highly stressed, fragile Fukushima evacuees.[17]

Plausibility of Breast Cancer Case-Control Study Results

Applying Table 2 to results of a published breast cancer case-control study shows that when the bias associated with use of DOR as an estimate of DRR along with the impact of variability in the DBR are considered, results obtained are consistent with the possibility of no radiation-associated breast cancers.

John et al.,[1] using a case-control study design, analyzed data from the Breast Cancer Family Registry to investigate a possible association between low-dose medical radiation exposure and breast cancer risk. Self-reported data on therapeutic and diagnostic radiation exposures to the chest were acquired for 2,254 breast cancer cases and 3,431 controls (1,556 unaffected sisters and 1,875 unrelated population controls). As part of the study, they evaluated DOR for breast cancer and 95% CI associated with diagnostic radiation exposure, after supposedly adjusting for age, study center, country of birth, and education. Such adjustments may be error-prone and produce bias, as it appears that some adjustment methods used in epidemiological studies may have never been rigorously tested for validity and reliability.

Increased DORs for breast cancer were reported by John et al.[1] for women for diagnostic chest X-rays for tuberculosis (DOR = 2.49, 95% CI = 1.82–3.40). DOR was evaluated to be highest for women who reported a large number of exposures at a young age or who reported exposures in earlier calendar years. There was no evidence found for increased DOR associated with other diagnostic chest X-rays (not including tuberculosis or pneumonia), both in women with and without indicators of increased genetic risk (i.e., diagnosis at age <40 years or family history of breast cancer).

Since DOR likely over-estimates DRR (when DOR>1), it is prudent to make an adjustment. The reference baseline frequency is given by 2254/(2254+3431) = 0.4. Using the derived 95th percentile value for the BAF (= 1.362 in Table 2), the bias-adjusted DRR (central estimate) for the tuberculosis patients is 2.49/1.362 = 1.83, which can be explained based on a 2.25 to 2.5-fold variation in the DBR and unrecognized sources of bias (one is identified below). A similar calculation for the upper 95% CI point for DOR yields 3.40/1.362 = 2.5, which would require between threefold and fourfold variations in the DBR to explain, assuming no radiation effect and no other source of significant bias. However, data analysis methods employed need to be closely examined, as unaccounted-for bias can be introduced by the logistic regression analysis used, as has been found for cohort studies using simulated data.[18]

Indeed, McNutt et al.,[18] using simulated data, derived a non-conservative BAF of 2.16. This would mean that a DRR estimate of 4.328 would be obtained from a logistic-regression method as used by John et al., when the correct simulated value was 2. Risk factor (co-variate) interactions were not addressed, so that a conservative estimate of the bias would be > 2.16, assuming that similar bias occurs in case-control and cohort study designs that employ logistic regression. Correcting for this additional, logistic-regression-related bias using the indicated factor gives the biases-adjusted values of 1.83/2.16 = 0.874 and 2.5/2.16 = 1.56, both which are consistent with a less-than-twofold variation in the DBR, and with no radiation-induced breast cancer, contrary to the implication by John et al.[1]

Discussion

All results presented in Tables 1 and 2 are based on assumed uniform distributions for DBR (Table 1) and the reference baseline frequency (Table 2). Similar tables could be constructed based on a different distribution in which reliable information is presented that favors the other distribution. In the absence of such information, the uniform distribution may be more conservative and therefore may be preferred.

Findings reported here are supported by other publications reviewed elsewhere.[6,9,19] These papers point out the lack of any solid evidence for cancer induction by low radiation doses (< 100 mGy) such as are received from single or several applications of CT or chest X-rays. Sacks et al.[19] summarize their findings about LNT-based claims in epidemiological studies of evidence for cancer induction by low radiation doses as follows:

"The appearance of validity in these studies rests on circular reasoning, cherry picking, faulty experimental design, and/or misleading inferences from weak statistical evidence."

Particularly disturbing is the application of the LNT model where moderate- and/or high-dose data are included and

there is forced model fitting with only one free parameter (slope) while the intercept is forced to take on a specific value (1 for DRR and 0 for DERR). This misleading procedure hides the impact of variability in the DBR. In some cases there is even a constraint imposed on negative slope values, but not on positive slope values,[2] another misleading procedure, thereby greatly favoring an LNT outcome. Allowing the intercept to be a free parameter (basic linear model) and testing for significant departure of the derived intercept from its hypothesized value (1 for DRR and 0 for DERR) could lead to additional evidence against the validity of the LNT model.

The notion that multiple uses of diagnostic imaging, when separated by weeks or months or longer, is cumulative with respect to damage induction, is not supported by the fact that lifetime exposure to ionizing radiation in regions of elevated background radiation does not increase cancer risk.[20-23]

Notably, current concerns of the public related to potential harm from repeated diagnostic imaging (e.g., via CT) has led to imaging avoidance at a time when there are growing pressures related to reducing the usage of ionizing-radiation-based imaging in order to control costs.[24]

Conclusions

There is no credible evidence for cancer induction by a low radiation dose such as is received from single or several applications of CT or chest X-rays. The claims of harm from such exposures are based mainly on seriously flawed epidemiological studies that usually rely on the unscientific and forced LNT default model with a locked intercept. DOR > 1 and DRR > 1 for cancer incidence or cancer mortality, associated with low radiation doses (e.g., < 100 mGy of diagnostic X-rays), may reflect phantom risk due to failure to consider variability in the DBR, inadequate accounting for confounding, model-fitting-introduced biases (including those related to intercept-value locking), and inappropriate application of dose lagging.

Phantom DRR values as large as 2 and possibly larger could arise as a result of these influences and lead to continued promotion of phobia about likely harmless radiation doses from diagnostic imaging and other sources. Such unwarranted phobia has already led to many refusals of potentially lifesaving diagnostic imaging at medical facilities, and to the loss of thousands of lives related to Chernobyl (abortions[15,16]) and Fukushima (deaths of chronically-stressed fragile evacuees.[17])

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