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A Critique of Recent Epidemiologic Studies of Cancer Mortality Among Nuclear Workers

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Abstract

Current justification by linear no-threshold (LNT) cancer risk model advocates for its use in low-dose radiation risk assessment is now mainly based on results from flawed and unreliable epidemiologic studies that manufacture small risk increases (ie, phantom risks). Four such studies of nuclear workers, essentially carried out by the same group of epidemiologists, are critiqued in this article. Three of the studies that forcibly applied the LNT model (inappropriate null hypothesis) to cancer mortality data and implicated increased mortality risk from any radiation exposure, no matter how small the dose, are demonstrated to manufacture risk increases for doses up to 100 mSv (or 100 mGy). In a study where risk reduction (hormetic effect/adaptive response) was implicated for nuclear workers, it was assumed by the researchers to relate to a "strong healthy worker effect" with no consideration of the possibility that low radiation doses may help prevent cancer mortality (which is consistent with findings from basic radiobiological research). It was found with basic research that while large radiation doses suppress our multiple natural defenses (barriers) against cancer, these barriers are enhanced by low radiation doses, thereby decreasing cancer risk, essentially rendering the LNT model to be inconsistent with the data.

Keywords

cancer, dose response, hormesis, LNT, radiation, risk assessment

Introduction

Epidemiologic studies (eg, case–control and cohort) of cancer or cancer mortality risk, if any, associated with low radiation doses (<100 mSv) are seriously flawed and in many cases unlikely to distinguish between alternative risk models (eg, threshold, hormetic, linear no-threshold [LNT], etc) when key sources of uncertainty are addressed and only low-dose data are used.[1] Data manipulations (adjustments) and descriptive (empirical) multivariate models used hide nonlinearity in the dose–response relationships and can create phantom risk (ie, manufactured risk) that increases at low doses.[1] Uncertainty about confounder influences is usually neglected,[2] and no consideration is usually given to biological mechanisms of cancer induction and mechanisms of cancer prevention via the body's powerful natural defenses (barriers) that can be enhanced by low-dose radiation.[1]

The following (A-G) are approaches used in epidemiologic studies that can distort the shape of the dose–response relationship for radiation-induced cancer and can create phantom (manufactured) risk increases at low radiation doses:

A. *Ignoring missing dose*: In some instances, important dose contributions cannot be accounted for, so the contributions are missing from the reported doses, thereby blaming any claimed harm on smaller doses than were actually incurred.
B. *Dose lagging*: An adjustment is used where a part of the radiation dose (a large amount in some cases[3-5]) is simply thrown away, which allows blaming harm (cancer) on a smaller radiation dose irrespective of the cause of the harm. Dose lagging supposedly corrects for dose wasting, irrespective of whether radiation

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exposure is responsible for the observed cancer. However, the thrown-away dose may have contributed to reducing the cancer latent period for those who develop cancer. For those who do not develop cancer, the thrown-away dose may have stimulated the body's natural defenses and if so may have led to preventing the cancer that would otherwise have occurred for other reasons (eg, environmental, dietary, etc). No dose is wasted in either case.

C. *Forced application of the LNT model*: In many studies, the LNT model is applied, irrespective of the data considered. This effectively makes LNT outcome the null hypothesis. This misleading null hypothesis, which along with other procedures employed (eg, intercept locking, negative slope constraint[3-5] but not positive slope constraint) can lead to phantom (ie, imaginary) risks for low doses. Such phantom risks would be far less likely under the more appropriate null hypothesis of no radiation effect when the data analysis is restricted to low doses and addresses variability with repeated measurements (replications).

D. *Intercept locking of the LNT line*: When LNT outcome is the implied null hypothesis, usually the intercept (at assigned dose 0; for controls or baseline consideration) is locked (ie, not treated as a free parameter), so that the intercept location does not reflect the variability in the dose–response data near the origin. Only one free parameter (LNT line slope, not the intercept) related to radiation exposure is used. The intercept locking procedure is mainly used with relative risk (RR) or excess RR (ERR) characterization (or similar measures) as a function of radiation dose or lagged dose.

E. *Averaging over a wide dose interval*: For a radiation dose group considered, doses differ for each individual so that the average dose for the group is used, with no consideration of the dose distribution for the group. Often the doses within a dose group span a wide range. The within-dose-group averaging makes it more difficult to detect a nonlinear dose–response relationship. Such nonlinearity has been revealed when individual-specific rather than group-averaged dose has been used.[6] Modern computational methods allow for individual-specific doses to be used.[6]

F. *Ignoring key uncertainties*: Uncertainty about key covariates (eg, measurement-error related) is often not addressed in epidemiologic studies. Radiation dose errors (random and systematic) are often not addressed and can be quite important for the low-dose region.

G. *Disregarding of biological mechanisms*: The LNT model is not supported by currently known biological mechanisms of cancer development and cancer prevention. Thus, its use requires ignoring the indicated currently known, biological mechanisms both for cancer occurrence and prevention, as is done in many epidemiologic studies.

The hallmarks of cancer (development) include the following[7]: (1) genome instability and mutations, (2) resisting cell death, (3) deregulating cellular energetics, (4) sustaining proliferative signaling, (5) evading growth suppressors, (6) avoiding immune destruction, (7) enabling replicative immortality, (8) tumor-promoting inflammation, (9) activating invasion and metastasis, and (10) inducing angiogenesis. That such complex processes can be jointly caused by a single radiation ionization event (a single radiation hit can cause cancer) is highly implausible. Further, there is a hierarchy of natural defenses[8-11] that are differentially stimulated by low radiation doses that must be overcome for cancer to occur, which are the bases for the hallmarks of cancer suppression.[12]

The hallmarks of cancer suppression include the following: (1) epigenetically regulated DNA damage repair and antioxidant production, (2) p53-independent selective apoptosis (ie, selective removal) of aberrant cells including neoplastically transformed cells, (3) reducing cancer promoting inflammation, and (4) anticancer immunity.[12]

Epidemiologic studies (eg, cohort, case–control) are seriously limited as far as informing about low-dose-radiation-related cancer risks, if any. The limitations in part relate to unaddressed sampling variability,[1] confounding (known and unknown), collinearity of potential covariates, and other issues.[2]

The problem of unaddressed sampling variability (for the baseline cancer risk estimate), although quite important, has been largely ignored for low-dose radiation carcinogenic effects studies.[1] Sampling variation means the changes in results over replication, if replications were to be carried out. However, replications are generally not carried out in epidemiologic studies since it is impractical to do so. Indeed, a claimed increased (or decreased) risk after a low radiation dose may instead relate to variability in the estimated cancer risk (baseline risk estimate) in the absence of a radiation influence or to an invalid extrapolation from high to low doses, yielding hypothetical results.

A cohort study (but not a case–control study) provides an estimate of the population-level baseline cancer risk (BR), and the estimate is used as a reference point for evaluating radiation effects (eg, increased cancer risk). An epidemiologic–study–related estimate of the population-level BR has been called the derived BR (DBR). An epidemiologic–study–related estimation of the population-level cancer RR has been called the derived RR (DRR). Similarly, the estimated ERR has been called the derived ERR (DERR). The definitions of DBR, DRR, and DERR were recently introduced to facilitate addressing variability in outcomes of epidemiologic studies under circumstances where replicate results would be available.[1]

Case–control studies provide estimates of the population-level odds ratio (OR) for cancer. An epidemiologic–study–related estimation of the population-level cancer OR has been called the derived OR (DOR).[1] The DOR for cancer (or cancer mortality) is used by some researchers as an estimate of the DRR. However, the DOR always overestimates the DRR, and

the overestimation increases as both the DOR and the DBR increase.[13]

Case–control studies cannot produce a DBR (for cancer incidence or mortality) and are particularly prone to serious selection bias for a given control group. In fact, selecting controls to adequately match for lifelong exposure to carcinogens (a likely major influence on the DBR) and for unknown confounders (eg, carcinogenic bacteria[14]) is essentially impractical, as such information is not known for controls or cases. In fact, a DRR considered greater than 1 for low radiation doses (which may be reported for case–control studies) may be a phantom increase.[1]

Often, a misleading null hypothesis is used in epidemiologic studies of cancer or cancer mortality RR (or relative mortality rate [RMR] or standardized mortality rate [SMR]): An assumed LNT function of radiation dose is used as the null hypothesis, which is a departure from the type of null hypothesis used in toxicological research using animals (eg, null hypothesis of no radiation effect). With the LNT as the null hypothesis approach, high-dose data are usually included which essentially guarantees a positive slope to the fitted LNT line with a locked intercept (ie, intercept is not a free parameter). Using the indicated null hypothesis along with LNT-line-intercept locking, and including high-dose data, makes it more likely than not that study findings will be insufficient to reject the null hypothesis. In turn, this allows for misleadingly stating that study findings were consistent with the LNT model, so that it is justifiable to use the model-related findings to implicate harm (hypothetical cancers) from very small radiation doses such as are associated with elevated natural background radiation and medical imaging (eg, computed tomography). In addition to using a misleading null hypothesis (LNT model with locked intercept), some investigators also impose a constraint on negative slopes derived in data fitting but not on positive slopes, thereby favoring risk increases over risk decreases. This was done in 3 cancer mortality–related examples (epidemiologic studies) discussed in this article for irradiated humans, which claim evidence for increase cancer risk at low doses.

The DBR for a given type of cancer (or cancer mortality) evaluated in a radiation effects study is influenced by environmental, dietary, and other carcinogens exposures during life and the variable responses to carcinogenic stresses (eg, different genetic susceptibilities, different adaptive responses [adaptive protection]) of the different individuals used in the study. The adaptive protection relates to molecular-, cellular-, tissue-, and organ-level natural defenses against the indicated carcinogenic stresses.[1,10,15-18]

To prevent harm from mild carcinogenic stresses, cells and tissue in the body mount complex responses that are regulated by changes in adaptive-response-gene expression. The gene expression level can differ by more than a factor of 10 for different individuals.[19,20] Interindividual variability is also associated with the hallmarks of cancer suppression. Thus, much greater than 10-fold variation between individuals in their overall responses to low-level stress (eg, low-dose radiation) is highly plausible. Such large variability likely impacts variability in the DBR from replicate epidemiologic studies, where they carried out. Thus, it is important to address variability in the baseline cancer risk estimates in epidemiologic studies of cancer or cancer mortality DRR and related concepts. Not doing so favors obtaining the wrong results for a population of interest, especially for low radiation doses. For example, if the minimum and maximum value for the DBR for a given type of cancer (or cancer mortality) varies by a factor of 2 (ie, 2-fold) over replicate studies directed at a specific population, then a cancer (or cancer mortality) DRR as high as 2 or as low as 0.5 for a study could arise (although with low probability) without any radiation-induced harm or benefit (eg, hormetic effect). Methods described in the next section allow addressing the issue of DBR variation and are applied to show evidence for phantom cancer risk generation in 3 epidemiologic studies and evidence for hormesis/adaptive response in another study of cancer mortality among nuclear workers.

Generating DRR Distributions Under the Null Hypothesis of No Radiation Effect

Using modern computational tools, distributions of the DRR can be generated under the null hypothesis of no radiation effect for an irradiated group. The distribution percentiles obtained (based on sampling from the DBR distribution only) can be used in testing for a plausible increase or decrease in the DRR for a given study. To consider radiation-caused cancer (or cancer mortality) to be plausible for an irradiated group, the DRR obtained in an actual epidemiologic study needs to exceed a criterion value (eg, 95% [percentile] or 97.5% value) based on the distribution of the DRR under the null hypothesis of no radiation effect.

To address the issue of variability in the baseline risk estimate for replicate cohorts of heterogeneous humans with differing life histories, a simulation study was previously conducted[1] where the same uniform distribution for the DBR (for cancer or cancer mortality) was repeatedly sampled (one risk value for controls [baseline] and one paired risk value for the irradiated group per each sampling round) in order to obtain a phantom risk distribution for the DRR under the null hypothesis of no radiation effect. Using the uniform distribution of the DBR is a conservative approach.[1] WinBUGS software[21] was used to generate the phantom risk distribution for DRR.[1]

Percentiles of 2.5% and 97.5% of the phantom DRR distribution were used to evaluate the plausibility of claimed LNT cancer risk increases reported in epidemiologic studies of populations of nuclear workers. Linear no-threshold lines and their 90% or 95% confidence intervals (CIs) reported from the epidemiologic studies were evaluated for their credibility for the low-dose region (doses up to 100 mSv or mGy). Where RMR or SMR was evaluated rather than RR, the same approach was used.

Not considering at least a 2-fold variation (minimum to maximum) in the DBR for a cohort study could lead to accepting a DRR of 1.5 as indicating a 50% increase in cancer risk as

Table 1. Percentiles 2.5% and 97.5% for the Distribution of the Derived Relative Risk (DRR) or Derived Relative Mortality Rate (DRMR) for a Heterogeneous Population of Humans Under the Null Hypothesis of No Radiation Effect When the Derived Baseline Cancer Risk (DBR) or Derived Baseline Cancer Mortality Rate (DBMR) Is Uniformly Distributed (Conservative Assumption) From the Minimum to Maximum Value.

Fold Change From Minimum to Maximum Value of DBR or DBMR	2.5% (Percentile) Value for DRR or DRMR Distribution[a]	97.5% (Percentile) Value for DRR or DRMR Distribution[a]
1.25	0.842	1.19
1.5	0.732	1.37
1.75	0.650	1.54
2	0.588	1.71
2.5	0.497	2.02
3	0.433	2.31

[a]Results for the percentile values are based on Monte Carlo evaluations with WinBUGS software[21] using 10 000 iterations per fold-change category as reported elsewhere.[1] Each iteration represented a study replicate.

a result of low-dose radiation exposure, when there may be no credible evidence for such an increase.[1] Thus, evaluations carried out in this article were based on a 2-fold variation, even though a higher variation could easily be justified.

For case–control studies for which the DOR is used without adjustment as an estimate of RR, the DRR obtained may be overestimated by as much as a factor or 2.[13] This relates to fundamental differences between population OR and population RR. When logistic regression is used in a cohort study (and presumably also for a case–control study), an additional bias (for DRR overestimation) as large as a factor of 2 may occur.[22] Thus, claims of elevated cancer or cancer mortality risk based on logistic regression–related, case–control studies with DOR <3 may be registering phantom-elevated risk.[1]

Results previously[1] obtained using WinBUGS[21] software for the 2.5% (percentile) and 97.5% (percentile) values for the phantom DRR distribution are presented in Table 1 for a 1.25-, 1.5-, 1.75-, 2-, 2.5-, and 3-fold variation in the DBR. Ten thousand iterations were used for each fold-change category. Each iteration simulated the outcome of a study replicate under the null hypothesis of no radiation effect. Table 1 can be used to assess the plausibility of a risk increase or decrease (hormetic effect/adaptive response) after low radiation doses.

In using Table 1, it is important to consider that DBR and similar concepts are not based on the total population (eg, total population of the United States) but rather a relatively small group (eg, nuclear workers in the United States) as used in cohort studies. Thus, larger variability in DBR (which is based on a relatively small group) is more likely than for the total population as reflected by annual changes. The variability reflected in Table 1 is based on a very conservative approach (assumed uniform distribution). Other distributions could also be considered, but this is beyond the scope of this publication.

Results of Recent Epidemiologic Studies of Nuclear Workers and Why They Are Unreliable

Evidence of Manufactured (Phantom) Risks From a 2007 Cancer Mortality Study

A 15-country collaborative cohort study was conducted by researchers[3] to supposedly provide direct estimates of cancer risk following protracted low doses of ionizing radiation. Their analyses were based on 407 391 nuclear industry workers monitored individually for external radiation exposure and 5.2 million person-years of follow-up. What the researchers referred to as ERR is here referred to as DERR (which varies over replicate studies should they be carried out). The researchers reported that a significant association was seen between radiation dose and increased cancer mortality (DERR/lagged- Sievert (Sv): 0.97, 90% CI: 0.28-1.77; 5233 deaths) for all cancer deaths. Lagged radiation dose in Sv (10 years of dose thrown away) was used by the researchers. Poisson regression was employed along with the default LNT model (misleading and inappropriate null hypothesis) to look for associations between lagged radiation dose and cancer mortality. The intercept for the LNT line was locked at DERR = 0, and a constraint was placed on the value of a negative slope (could not be more negative than −1/maximum dose), but no constraint was imposed on positive slope values (another misleading LNT-model-linked procedure used in epidemiologic studies). The study was indicated to be the largest analytical epidemiologic study of the effects of low-dose protracted exposures to ionizing radiation at the time it was conducted and implicated increase cancer risk from radiation doses <100 mSv.

Throwing away radiation dose is common for the indicated group as well as for some others. Throwing away dose artificially inflates the DERR per unit dose. Taking at face value, the DERR per unit dose of 0.97/lagged-Sv and related 90% CI yields corresponding values of 0.00097/lagged-mSv (90% CI: 0.00028/lagged-mSv to 0.00177/lagged-mSv). For a dose of 100 mSv, the calculated upper 90% CI value on the DRR would be 1.177 which according to Table 1 (for a reference 2-fold variation in the DBR for mortality and uniform distribution) is nowhere close to being a plausible increase as the value is well within the phantom risk increase region. The upper risk estimate needs to be larger than the percentile 97.5% value of 1.71 to be considered as a plausible increase. The corresponding percentile 95% value (not shown in the table) for phantom risk increases is 1.60 which is clearly larger than 1.177. There is no evidence for harm from radiation doses up to 100 mSv (low-dose region).

Evidence of Manufactured (Phantom) Risks From a 2015 Cancer Mortality Study

Epidemiologists[5] carried out another cohort study related to nuclear workers to evaluate associations between protracted low-dose radiation exposures and cancer mortality (excluding

leukemia mortality). Excess relative mortality rate (ERMR) was evaluated and here is referred to as derived ERMR (DERMR) to be consistent with other terminology used related to subsets of a total population of interest in that variability in study outcome would be expected with replication. The DERMR per Gy (ie, LNT line slope) for mortality from cancer (excluding leukemia) is the focus in their paper which inappropriately used LNT as the null hypothesis. Both LNT-line-intercept locking and constraints on negative (but not positive) slopes were used. Follow-up encompassed 8.2 million person years. Of 66 632 known deaths by the end of follow-up, 17 957 were due to solid cancers. The reported DERMR per Gray of lagged radiation dose for cancer mortality was 0.48/lagged-Gy (90% CI: 0.20/lagged-Gy to 0.79/lagged-Gy; 10 years of dose accumulation was thrown away). With 10 years of radiation dose being thrown away (ie, lagged), monitored radiation-exposed persons working for 10 years or less were apparently assigned no radiation dose. In addition, the cumulative doses from natural background radiation sources and from diagnostic imaging during medical examinations were excluded. Importantly, the zero-dose group does not actually represent no radiation exposure since natural background radiation and medical exposure were not accounted for and assigning a dose of 0 impacts the slope of the LNT line.[23]

Taking the above-derived risk coefficients of the researchers[5] at face value gives 0.00048/lagged-mGy (90% CI: 0.0002/lagged-mGy to 0.00079/lagged-mGy) for the DERMR per lagged-mGy. For a dose of 100 mGy, the calculated upper 90% CI value on the derived relative mortality rate (DRMR) would be 1.079, which, according to Table 1 and for a reference[1] 2-fold variation in the DBR for mortality and uniform distribution, is also nowhere close to being a plausible increase as the value is well within the phantom risk increase region (upper risk value needs to exceed the percentile 97.5% value of 1.71). The corresponding percentile 95% value is 1.60 (not shown in the table). There is no evidence for harm from radiation doses up to 100 mGy (low-dose region).

Evidence of Manufactured (Phantom) Risks From a 2015 Leukemia Mortality Study

Epidemiologists[4] conducted a cohort study which quantified possible associations between protracted low-dose radiation exposures and leukemia mortality among radiation-monitored (for external radiation) adult nuclear workers employed in France, the United Kingdom, and the United States. A cohort of 308 297 radiation-monitored workers employed for at least 1 year by the nuclear industry was used. The cohort comprised 8.22 million-person-years of follow-up with a focus on deaths from leukemia, lymphoma, and multiple myeloma. Some workers may have had internal contamination by various radionuclides (isotopes of uranium, plutonium, etc), but doses from such exposures could not be evaluated and therefore are not accounted for in the assigned radiation doses.

Regression based on an assumed Poisson distribution of outcomes was used, along with the default LNT model (an inappropriate null hypothesis as previously indicated) to investigate possible associations between assigned red bone marrow absorbed radiation dose (estimates) and leukemia mortality. The DERR was evaluated with stratification by country, calendar period, sex, and age. The researchers reported DERR per unit lagged dose for leukemia mortality, excluding chronic lymphocytic leukemia. The reported value for the DERR was 2.96/lagged-Gy (90% CI: 1.17/lagged-Gy to 5.21/lagged-Gy), with 2 years of dose accumulation thrown away. This corresponds to 0.00296/lagged-mGy (90% CI: 0.0017/lagged-mGy to 0.00521/lagged-mGy). For a dose of 100 mGy, the calculated upper 90% CI value on the DRR would be 1.521 which also according to Table 1 (for a reference[1] 2-fold variation in the DBR and uniform distribution) is an implausible increase as the value is within the phantom risk increase region (upper risk value needs to exceed percentile 97.5% value of 1.71 to be considered plausible). The corresponding percentile 95% value is 1.60 (not shown in the table) for phantom risk which is also greater than the upper risk estimate of 1.521. There is no evidence for harm from radiation doses up to 100 mGy (low-dose region).

Evidence for Possible Hormetic Effects in a 2017 Cancer Mortality Study

Another epidemiologic study focused on a cohort of French nuclear workers that were badge-monitored for external radiation exposure.[24] Annual exposure to external ionizing radiation (mainly γ rays) expressed in Sv was assessed for each worker and expressed as personal penetrating photon dose equivalents in soft tissue at a depth of 10 mm (Hp(10)). Some workers were exposed to neutrons and some may have had internal contamination from radionuclides (isotopes of plutonium, uranium, and others), but radiation doses were not known so were not included in their dose estimates. The average cumulative photon dose equivalent (Hp(10)) for exposed workers was 25.7 mSv.

The mortality of 59 004 nuclear workers was followed-up between 1968 and 2004, with the average follow-up being 25 years. At the end of the follow-up, workers average age was 56 years and 6310 workers had died. Using national mortality rates as a reference, SMR was calculated. The SMRs were stratified by calendar period in 7 categories (1968/1973/1978/1983/1988/1993/1998+), sex, and attained age in 5-year intervals (<20/25/30/ . . . /75/80/85+). Byar approximation was used to estimate 95% CI for the SMRs.

Use of this cohort allowed for comparing the mortality of irradiated nuclear workers to that of the French general population. The focus was on cancer and circulatory disease mortality. Interestingly, the derived SMRs (DSMRs) were less than 1 (suggestive of hormetic effect/adaptive response) for death from all causes, death from solid cancers, death from tumors of the lymphatic and hematopoietic tissue, death from circulatory diseases, and death from digestive diseases as shown in Table 2. For these causes of death, the DSMR ranged from 0.37 (digestive diseases) to 0.81 (tumors of the lymphatic and

Table 2. Mortality in a French Nuclear Worker Cohort Compared to That of the French Population, 1968 to 2004 Based on 2017 Publication.[24]

Cause of Death	Observed Deaths	Derived Standardized Mortality Ratios (DSMR)	95% Confidence Interval (CI)
All causes	6310	0.60	0.59-0.62
Solid cancers	2356	0.68	0.65-0.71
Tumors of lymphatic and hematopoietic tissue	196	0.81	0.70-0.94
Circulatory diseases	1483	0.62	0.59-0.65
Respiratory diseases	200	0.41	0.36-0.47
Digestive diseases	270	0.37	0.32-0.41

hematopoietic tissue) with the upper 95% CI value ranging from 0.41 (digestive diseases) to 0.94 (tumors of the lymphatic and hematopoietic tissue) and the lower 95% CI value ranging from 0.32 (digestive diseases) to 0.7 (tumors of the lymphatic and hematopoietic tissue).

The DRMR results in Table 1 can be used to assess the importance of these findings for DSMR because they also apply to DSMR under the null hypothesis of no radiation effect. Results for mortality from respiratory diseases and from digestive diseases are clearly consistent with the possibility that the nuclear workers radiation exposures may have helped to protect them (hormetic effect/adaptive response) from the indicated diseases. As demonstrated for residential radon exposure, chronic low-level irradiation can reduce the occurrence of lung cancer mortality.[6,25] However, the researchers did not consider the possibility the results in Table 2 may be due to hormesis/radiation adaptive response. Rather they claimed the results to demonstrate strong healthy worker effects.

Because of the results presented in Table 2, it makes no sense to forcibly apply the LNT model to such data. Even so, the researcher applied the LNT model anyway and in most cases LNT line slopes were not significantly positive, as should be expected.

Implications of Findings Presented

The indicated findings reported in this article point to the unreliability of epidemiologic studies, such as carried out by a highly influential group,[3-5,24] so far as informing about cancer risks, if any, associated with low radiation doses. Even so, some group members[5] misleadingly concluded regarding one of their studies that "The study provides a direct estimate of the association between protracted low-dose exposure to ionizing radiation and solid cancer mortality." Equally of concern, the World Health Organization issued a press release[26] related to the indicated study that states "This study strengthens the evidence of a causal relationship between solid cancers and exposure to low doses of ionizing radiation." This is quite unfortunate, given the serious flaws in many epidemiologic studies and the unreliability of the research findings as also pointed out elsewhere.[1,23]

In trying to implicate a causal relationship between cancer mortality and occupational exposure to low doses and dose rates of ionizing radiation, the indicated group of epidemiologists[3-5,24] not only ignored major sources of radiation exposure (medical and natural background radiation exposure, neutrons, and internal α and other forms of radiation) but also failed to recognize that cumulative occupational radiation dose over years for nuclear workers is correlated with cumulative exposure to many other carcinogens (dietary, airborne, carcinogenic bacteria, etc) by a given age. Thus, there is no way to convincingly prove a causal relationship between cancer mortality and cumulative occupational radiation exposure to low doses (eg, <100 mGy or 100 mSv) delivered at low rates.

Because usage of the LNT model for low-dose radiation risk assessment for cancer induction (or cancer mortality) is now mainly justified based on epidemiologic studies, it is important to be aware of the following, which can strongly bias study findings:

A. Radiation dose uncertainties should be well characterized. However, this is most often not the case including studies of A-bomb survivors where radiation doses from black rain–related radioactive fallout[27] have been disregarded and may represent a large part of the total dose for some individuals.
B. Epidemiologists (but not toxicologists) in many cases throw away a large part of the radiation dose (ie, they use lagged dose) when evaluating radiation risks. There is no validity to arbitrarily throwing away radiation dose, since for a given cancer victim, the cancer may not be related to radiation exposure. Even for instances where radiation is responsible for the cancer as may occur after a high dose, the thrown-away dose may have reduced the latent period and thus was not wasted. Also, for those not developing cancer, the dose that is thrown away may have helped to prevent (ie, via enhancing the body's multiple natural cancer barriers[11,12]) cancer induction by other carcinogens, in which case would not be wasted but rather beneficial. Indeed, natural cancer barriers are enhanced by low but not high radiation doses.[12]

Researchers[2] previously assessed limitations of epidemiologic studies so far as demonstrating causality for cancer. They discussed challenges related to addressing the following: (1) selecting the appropriate cancer risk model, (2) errored covariate (confounders) assignments (eg, wrong or missing covariates), (3) accounting for different genetic backgrounds, (4) variable coding and multiple selection, (5) measurement errors for independent variables, (6) diagnostic suspicion and recall biases, and (7) classification errors. A main finding of their

work was that statistical modeling alone may be unreliable for establishing causal links. This is indeed the case for the low-dose and dose-rate results[3-5,24] reported by epidemiologists for nuclear workers.

A misleading procedure often used by LNT advocates is to use the LNT model (related to radiation dose) as the null hypothesis. As might be expected given the indicated complexities of epidemiologic data analyses, LNT as the null hypothesis is unlikely to be rejected in cases where high-dose data are included and the intercept is locked rather than being a free parameter.[1] This was the case for a number of studies,[3-5,24,28-30] some of which received wide news media and other coverage related to claiming harm (cancer) from low radiation doses and dose rates, with supporting statements by the World Health Organization[26] for one such study.

Importantly, it appears that methods used in epidemiologic studies have not been rigorously tested for reliability and accuracy so far as generating reliable radiation dose–response relationships. Now there is a way to unmask any serious flaws (should they exist) in the epidemiologic study methods for studies of low-dose radiation carcinogenic effects as discussed below.

Modern computational methods (random-variable-based) allow for generating simulated epidemiologic data sets using stochastic-multivariate models that allow for covariate errors (eg, radiation dose error, smoking history error, dietary carcinogen intake error, etc) and for stochastic cancer (or cancer death) occurrence or for loss to a competing risk. Different data sets for use in epidemiologic studies generated by modelers using a set of plausible hidden, stochastic, multivariate models (known only to those who generate the data) could be provided to different epidemiologists who would then use their preferred data analysis methods (for covariates such as radiation dose, age at exposure, gender, smoking history, alcohol consumption, etc) and models to analyze the data set (or sets) they were provided.

The indicated approach would allow for assessing the reliability of the epidemiologic methods employed in cohort, case–control, and other studies of populations exposed to low radiation doses and dose rates in addition to other risk factors. For example, if the hidden model for the population RR for cancer of a specific type was of the radiation-dose-threshold or hormetic or other nonlinear type and the epidemiologic study using the simulated data (for a cohort rather than the total population, with some high-dose data included) and preferred data analysis methods concluded that the DRR (or corresponding derived absolute risk or DERR) as a function of radiation dose was consistent with the LNT model, then this would reveal the study methods used as being unreliable.

Rigorously revealing serious flaws in the epidemiologic study methods, should this occur, may promote interest in making improvements in the methods. Without such improvements, then it would be in the best interest of the world community to rely less on findings from epidemiologic studies of health effects of low radiation doses and dose rates. An international effort (with stochastic modelers, epidemiologists, and other specialists as needed) could be mounted to address the study methodology reliability issue and could perhaps be sponsored by organizations such as the Department of Energy, the Environmental Protection Agency, the Nuclear Regulatory Commission, and the National Institutes of Health.

A major finding of this research and supported by research findings elsewhere[6,23,25,31-35] is that cancer risk estimates derived for low radiation doses with forced use of the LNT model in epidemiologic studies should be seriously questioned. In addition, they appear to be phantom risks. Further, such risk projections are radiation phobic and the phobia has been proven to cost thousands of lives related to the Chernobyl (abortions) and Fukushima (overly stressed fragile elderly evacuees) nuclear accidents.[1] The scientific, medical, and regulatory communities need to be made aware of LNT misuse (eg, used as null hypothesis and employed with locked intercept and constraining negative but not positive slopes and including high-dose data to force a positive slope) by LNT advocates among the epidemiological community, the serious harm LNT has caused and is likely to cause in the future if the misuse problem is not addressed.

Alternative approaches for conducting epidemiologic studies not requiring forcibly applying the LNT or any other model to cancer data are now recognized and should be considered.[6,25,35]

Findings reported in this commentary related to large variation in the baseline risk estimate (ie, DBR) are based on the conservative assumption of a uniform distribution (from minimum to maximum) by as much as a factor or 2 or more. The assumed large variation is supported by combined DRR data from multiple epidemiologic studies (ecological and case–control) of lung cancer morbidity related to residential radon exposure that were analyzed by Dobrzyński et al[36] in their recent publication. The reported large variation in DRR (more than a factor of 3) at low annual equivalent doses (<10 mSv) can be explained on the basis of large variation in the baseline risk estimate since there was no correlation between lung cancer morbidity DRR and annual equivalent dose to the lung.

Conclusions

Seriously flawed epidemiologic studies of cancer or cancer mortality risk, if any, associated with low radiation doses and dose rates are the main bases for the current use of the radiation phobia–promoting, biological mechanisms–devoid, LNT model. The promoted fear of even small, harmless radiation doses has led to thousands of lives being lost related to the Chernobyl and Fukushima nuclear power plant accidents and to many avoidances of potentially lifesaving diagnostic imaging with low radiation doses. Basic radiobiological research has revealed that low doses of radiation enhance our body's natural cancer barriers, while high doses reduced the barriers, rendering the LNT model inconsistent with the data. Risk of cancer from low radiation doses should not be based on epidemiologic studies that forcibly apply the LNT model as the default model (null hypothesis) and use data analysis

procedures that greatly favor an LNT outcome, irrespective of the cancer data, as was done in studies critiqued in this article.

Authors' Note

The views and conclusions contained herein are those of the author and should not be interpreted as necessarily representing policies or endorsement of his affiliated institution.

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