CHAIRMAN Resource

From:	Mark Miller <marklmiller20@gmail.com>
Sent:	Tuesday, February 12, 2019 11:50 AM
To:	Mark Miller
Cc:	CMRBurns Resource; CMRBARAN Resource; CHAIRMAN Resource; CMRCaputo Resource; CMRWright Resource
Subject:	[External_Sender] Re: Two papers rebutting NCRP Commentary 27
Attachments:	LNT-NCRP Commentary 27 of little value (Doss JNM 2018).pdf; Ulsh Environ Res 2018 - NCRP Critique.pdf; As Published- LNT a Failed Fiction, CWP & JAS 1559325818824200.pdf; Low Dose from A-Bomb Prolonged Life - Sotou.pdf

Dear Commissioners:

The two attached files are published papers refuting the scientific value of NCRP Commentary 27, a Commentary which NRC commissioned from the NCRP after my Petition to revise the basis of Radiation Protection Regulations was submitted. The NCRP has not rebutted either of these papers. These two were also submitted by Carol Marcus.

I have also submitted a few others that help illustrate that the Linear No-Threshold (LNT) model has no scientific basis at low doses and low-dose-rates if radiation.

There is growing momentum to replace the unscientific LNT with an alternative that has sound scientific basis. There have been many recent meetings where this challenging task has been discussed, such as sessions at the HPS and the ANS (among others). Here is a link to a 3-day Low Dose Joint ANS/HPS meeting that was held last fall in Pasco Washington. This meeting was attended by an International audience of highly respected scientists, who examined all aspects of the issue. Dr. Cynthia Jones from the NRC was in attendance.

http://hps.org/newsandevents/feature_article.html
http://www.lowdoserad.org/

Sincerely,
Mark Miller, Certified Health Physicist

On Sun, Feb 10, 2019 at 5:58 PM Carol Marcus <csmarcus@ucla.edu> wrote:

> Feb. 10, 2019
>
> Dear Commissioners:
>
> The two attached files are published papers refuting the scientific value of NCRP Commentary 27, a Commentary which NRC commissioned from the NCRP after my Petition was submitted. It is very telling that NCRP

has not rebutted either of these papers. I guess NCRP knows it published very bad science.

These papers have been added to my Petition.

Thank you for your attention and consideration.

Sincerely,

Carol S. Marcus, Ph.D., M.D.

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Are We Approaching the End of the Linear No-Threshold Era?

Mohan Doss

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The linear no-threshold (LNT) model for radiation-induced cancer was adopted by national and international advisory bodies in the 1950s and has guided radiation protection policies worldwide since then. The resulting strict regulations have increased the compliance costs for the various uses of radiation, including nuclear medicine. The concerns about low levels of radiation due to the absence of a threshold have also resulted in adverse consequences. Justification of the LNT model was based on the concept that low levels of radiation increase mutations and that increased mutations imply increased cancers. This concept may not be valid. Low-dose radiation boosts defenses such as antioxidants and DNA repair enzymes. The boosted defenses would reduce the endogenous DNA damage that would have occurred in the subsequent period, and so the result would be reduced DNA damage and mutations. Whereas mutations are necessary for causing cancer, they are not sufficient since the immune system eliminates cancer cells or keeps them under control. The immune system plays an extremely important role in preventing cancer, as indicated by the substantially increased cancer risk in immune-suppressed patients. Hence, since low-dose radiation enhances the immune system, it would reduce cancers, resulting in a phenomenon known as radiation hormesis. There is considerable evidence for radiation hormesis and against the LNT model, including studies of atomic bomb survivors, background radiation, environmental radiation, cancer patients, medical radiation, and occupational exposures. Though Commentary 27 published by the National Council on Radiation Protection and Measurements concluded that recent epidemiologic studies broadly support the LNT model, a critical examination of the studies has shown that they do not. Another deficiency of Commentary 27 is that it did not consider the vast available evidence for radiation hormesis. Other advisory body reports that have supported the LNT model have similar deficiencies. Advisory bodies are urged to critically evaluate the evidence supporting both sides and arrive at an objective conclusion on the validity of the LNT model. Considering the strength of the evidence against the LNT model and the weakness of the evidence for it, the present analysis indicates that advisory bodies would be compelled to reject the LNT model. Hence, we may be approaching the end of the LNT model era.

Key Words: LNT model; radiation hormesis; NCRP commentary no. 27; BEIR VII report

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The cancer risk attributable to radiation is known to increase linearly with radiation dose for high levels of radiation, as observed, for example, in a study of the atomic bomb survivors (*1*). However, there has long been disagreement in the scientific community about the carcinogenicity of low levels of radiation (*2*). The prevailing view, supported almost unanimously by national and international advisory bodies since the 1950s, is the linear no-threshold (LNT) model for radiation-induced cancers (*3*). Justification of the LNT model was based on the concept that even a small amount of radiation increases DNA damage and mutations and that increased mutations imply increased cancers (*4*). The atomic bomb survivor data, which are generally regarded as the most important for estimating the health effects of radiation, were consistent with the LNT model until recently (*1*) and were used to justify the continuing use of the LNT model by advisory bodies (*5*).

A contradictory point of view on the health effects of low-dose radiation is that it has benefits. This concept, known as radiation hormesis, was proposed by Luckey in 1980 (*6*). Justification of radiation hormesis is based on the concept that low radiation doses stimulate bodily defenses, resulting in beneficial health effects including reduction of cancers (*7*). However, most advisory bodies have not accepted this view and continue to support the LNT model (*5*).

The LNT model and the consequent concerns about the smallest amounts of radiation have resulted in strict radiation safety regulations that have increased the compliance costs for all uses of radiation, including nuclear medicine. The concerns about low radiation doses have also resulted in adverse consequences in many areas, including diagnostic imaging (*8–10*). Hence, it is important that we periodically evaluate the validity of the LNT model.

Whereas many studies have supported the LNT model over the years, others have supported radiation hormesis, and the controversy over low-dose radiation carcinogenicity remains unresolved. In fact, in contemporaneous reports, 2 advisory bodies took opposite stances on the LNT model, with Biologic Effects of Ionizing Radiation report VII (BEIR VII) by the National Academies of Sciences (*5*) supporting its use and a report by the French Academy of Sciences (*11*) opposing it.

BEIR VII concluded that the LNT model is consistent with available evidence, quoting the cancer data from the atomic bomb survivors (*1*) and a 15-country study of radiation workers (*12*). However, the shape of the dose–response curve in a subsequent update to the cancer mortality data for the atomic bomb survivors (*13*) was inconsistent with the LNT model because of the significant curvature in the 0- to 2-Gy dose range. When a correction

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was applied for the likely negative bias in the baseline cancer rates used in processing the data, these data become consistent with radiation hormesis (*14*). In addition, because of a reanalysis of the Canadian data, the 15-country study of radiation workers no longer shows significantly increased cancer risk in the irradiated workers (*15*). Hence, the main studies quoted by BEIR VII to support the LNT model do not support it any longer.

Since the time of BEIR VII, several studies have supported the LNT model (*16,17*). However, major deficiencies have been identified in such studies, making their conclusions not credible (*9,18,19*). On the other hand, several studies have supported radiation hormesis (*20,21*), and such studies have not been refuted. Thus, a resolution of the controversy over low-dose radiation carcinogenicity appears to be imminent. In view of this situation, it was surprising that the National Council on Radiation Protection and Measurements (NCRP), in its Commentary 27, reviewing 29 epidemiologic studies, concluded that it supports the continued use of the LNT model (*22*). In this article, I will review the current state of knowledge in this field and discuss whether the NCRP is justified in its conclusion.

CURRENT STATE OF KNOWLEDGE ON THE CAUSE OF CANCER AND THE CARCINOGENICITY OF LOW-DOSE RADIATION

It is now widely accepted that cancer is the result of the gradual accumulation of driver gene mutations that successively increase cell proliferation (*23*). However, such mutations may not be sufficient to cause cancer. For example, though mutations accumulate at the highest rates in the spleen from conception to maturity, there is no increase in lymphomas during that period, as observed in a mouse study (*24*). For humans also, cancers occur at the lowest rates at a young age (*25*), when mutations would be accumulating at the highest rates. Mutations are necessary but may not be sufficient to cause clinical cancer, since the immune system would eliminate or control cancer cells, resulting in covert cancers (*26*). A recent analysis has concluded that clonal expansion of cancer-associated mutations is an extremely common, if not universal, condition in somatic tissues (*27*). It has been estimated that almost everyone develops covert cancers, but only a small percentage of those who have covert cancer develop clinical cancer (*28*). When the immune system is suppressed, such as in organ-transplant patients or AIDS patients, cancer risk increases substantially (*29*). In young organ-transplant patients, the cancer mortality rate is increased by a factor of about 60 (*30*), and in young AIDS patients, cancer incidence is increased by a factor of about 40 (*31*). Such large increases in cancer rates when the immune system is suppressed indicate that the immune system plays a major role in preventing covert cancers from developing into clinical cancers.

Now let us examine the current state of knowledge on the health effects of low-dose radiation. It is well known that exposure to low levels of radiation results in increased DNA damage (*32*). However, even in the absence of radiation, DNA damage does occur from endogenous causes and is much more than the damage caused by low levels of radiation (*33*). Low-dose radiation also boosts defenses such as antioxidants and DNA repair enzymes (*7*). With the boosted defenses, there would be less endogenous DNA damage and mutations in the subsequent period, and the ultimate result would be reduced DNA damage and mutations (*9,33*). This result has been observed in studies of fruit flies (*34*) and mice (*35*). In addition, low-dose radiation enhances the immune system (*36*). Considering the important role played by the immune system in preventing cancers, the boosted immune system would reduce cancers. Evidence against the LNT model or for radiation hormesis has been observed in a variety of human studies. The graphs in Figures 1–3 illustrate some of this evidence in chronologic order of publication date to highlight the availability of the evidence over several decades. The evidence includes studies of atomic bomb survivors (Figs. 1A and 3C) (*14,37*), background radiation (Fig. 2B) (*38*), cancer patients (Figs. 1C and 2C) (*39,40*), environmental radiation (Figs. 2A and 3D) (*19,41*), medical radiation (Figs. 1D and 3B) (*20,42*), and occupational exposure (Figs. 1B, 2D, and 3A) (*21,43,44*).

Notwithstanding the above state of knowledge in this field, NCRP Commentary 27 (*22*) concluded that recent epidemiologic studies support the continued use of the LNT model.

DISCUSSION OF NCRP COMMENTARY 27

NCRP Commentary 27 stated that some studies provided strong support for the LNT model, some provided weak or moderate support, and others provided no support or were inconclusive. The conclusion was that the data are broadly supportive of the LNT model. I will now discuss in some detail the 5 studies that the NCRP claimed provided strong support for the LNT model.

The first is the study of solid cancer incidence among atomic bomb survivors (*45*). The abstract of this publication states: "uncertainties in the shape of the dose response preclude definitive conclusions to confidently guide radiation protection policies." With such an indeterminate conclusion by the authors, this study should not be considered supportive of the LNT model.

One problem with the atomic bomb survivor data, as traditionally reported, is the shape of the dose–response function that the data analysis used to extract excess relative risks (ERRs). Since low radiation doses have resulted in decreased cancers in many studies (Figs. 1–3), and since high radiation doses would increase cancer risk (*1*), a J-shaped dose–response function should have been used while processing the data. However, an LNT dose–response function was used in analyzing the data, and so the resultant ERRs may not be reliable and should not be used to draw conclusions on the dose–response relationship for radiation. Notwithstanding this reasoning, if these ERRs are used, the ERRs as a function of radiation dose show a linear increase for low doses near zero. However, the dose–response function also shows a significant curvature for the dose range of 0–2 Gy, and the significant curvature would be inconsistent with the LNT model because it would imply that cancer risk decreases or remains unchanged as radiation dose increases. For the above reasons, this study does not support the LNT model.

The second study is the International Nuclear Workers (INWORKS) study of nuclear industry workers in France, the United Kingdom, and the United States during 1945–2005 (*46*). The relative rate for solid cancer mortality in the workers was reported to be consistent with a linear dose–response shape (Fig. 4), with ERR/Gy being 0.48 (90% confidence interval [CI], 0.20–0.79). Smoking prevalence declined considerably between the 1940s and 2000s in these countries (*47,48*). Since smoking increases all cancer risk (*49*), and the highest occupational radiation doses were in the earlier years (*50*), considerable confounding of the cancer mortality dose–response data due to smoking is likely. For French nuclear workers, a study reported that lung cancer rate is substantially confounded by smoking (*51*). The INWORKS study stated that contrary to the pattern that

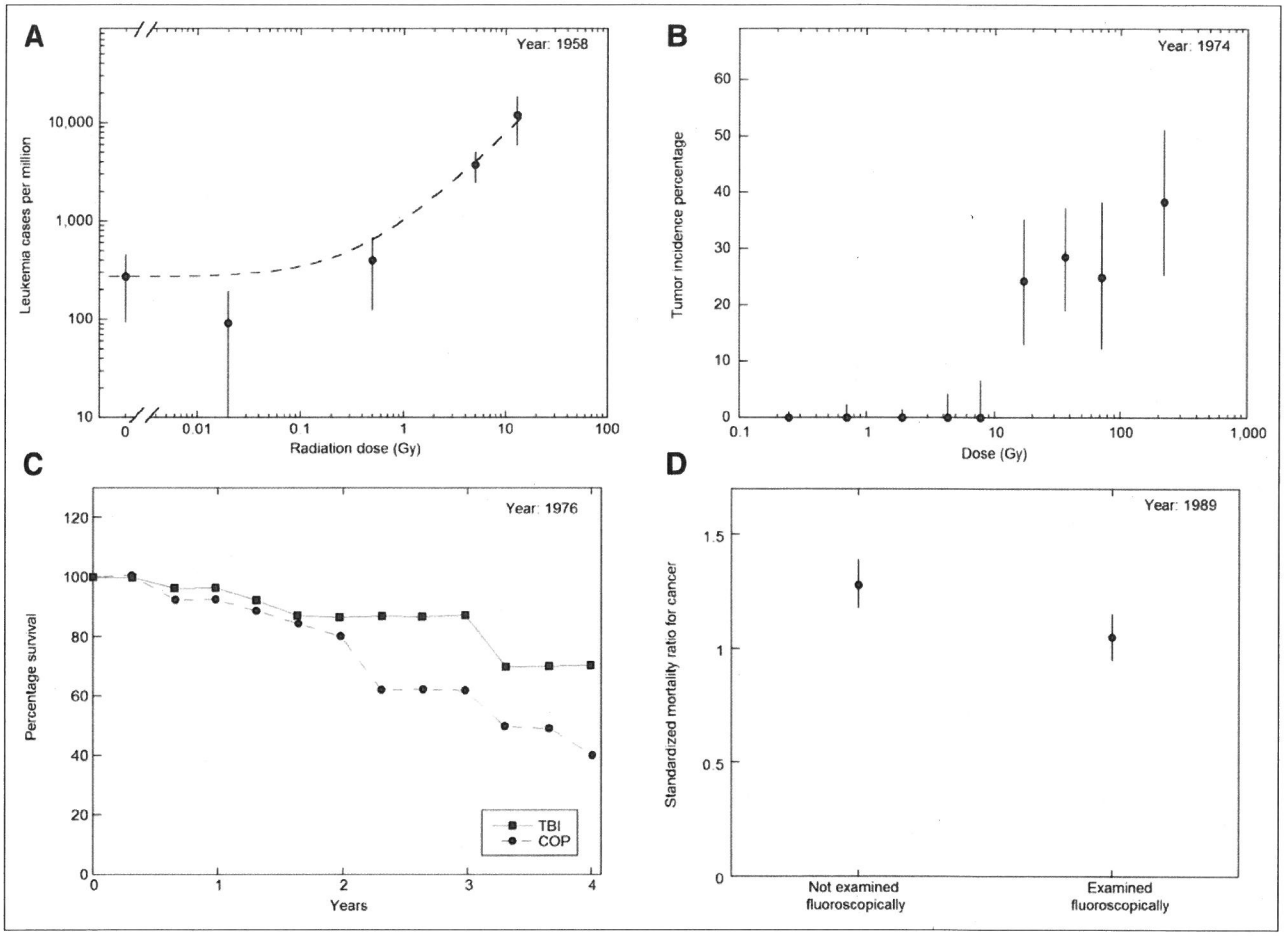

FIGURE 1. Evidence against LNT model or for radiation hormesis from 1950s to 1980s. (A) Leukemia in Hiroshima survivors as function of radiation dose, using data from Table 7, Annex F, of UNSCEAR report (*37*). Dashed line is LNT model fit to high-dose data. Data show reduction in leukemia at low doses with threshold dose exceeding ~0.5 Gy. Error bars are 95% CIs. (B) Bone sarcomas in radium dial painters (*44*). Error bars are SDs. No bone sarcomas were observed for doses below ~10 Gy. (C) Survival of lymphosarcoma patients treated with low-dose total-body irradiation (TBI) (10 cGy 15 times in 5 wk) vs. cyclophosphamide, vincristine, and prednisone (COP) (*39*). Survival curves do not significantly differ. TBI had cancer therapeutic effect equivalent to chemotherapy. (D) SMRs for all cancers in Massachusetts tuberculosis patients who underwent repeated fluoroscopy vs. those who did not (*42*). Error bars are 95% CIs. Patients undergoing fluoroscopy had lower all-cancer risk. (Note: threshold dose in A and B is inconsistent with LNT model. Cancer preventive or therapeutic effect observed in C and D after exposure to low levels of radiation contradicts LNT model and is consistent with radiation hormesis).

would be expected if there was confounding by smoking, the magnitude of the estimated ERR/Gy for solid cancers was essentially unchanged after excluding lung cancer. However, the use of such negative control outcomes to detect confounding also requires the assumption that the exposure of interest does not cause the negative control outcome (*51*). There is evidence that low-dose radiation prevents lung cancer in animal studies (*52*). Also, reduction of lung cancers has been reported in tuberculosis patients who underwent fluoroscopy, in comparison to patients not undergoing fluoroscopy (*42*). Therefore, the use of a negative control to exclude confounding by smoking in the INWORKS study may not be appropriate. The INWORKS study stated that when all smoking-related cancers were excluded, the ERR/Gy for solid cancers was 0.37 (90% CI, −0.14 to 0.95), which is consistent with no increased cancer risk in the irradiated workers. Hence, the INWORKS study does not support the LNT model.

The third is the study of breast cancer risk in Massachusetts tuberculosis patients who underwent repeated fluoroscopic examinations (*53*). In this study, the bin size used for radiation dose in the underlying data (*54*) was large, covering the range of 1–99 cGy, and so included both low and high doses, likely masking any hormetic reduction of breast cancer at low doses. A Canadian study of tuberculosis patients who underwent repeated fluoroscopy (*55*) used a smaller bin size and did observe a reduction in the breast cancer mortality rate for low doses, but a later study (*56*) with a larger bin size masked the hormetic reduction. Another problem with the Massachusetts study (*53*) is that it examined breast cancer only. An earlier study on the same cohort (*42*) stated that for female fluoroscopy patients, standardized mortality ratios (SMRs) for breast cancer were significantly increased, at 1.4 (95% CI, 1.05–1.75), but SMRs for all cancers were not significantly increased, at 1.1 (95% CI, 0.95–1.24), indicating that other cancers had decreased, with no overall increase in cancer mortality. For male and female tuberculosis patients not undergoing fluoroscopy, SMRs for all cancers were significantly elevated, at 1.28 (95% CI, 1.18–1.38), whereas for the patients who underwent fluoroscopy, SMRs

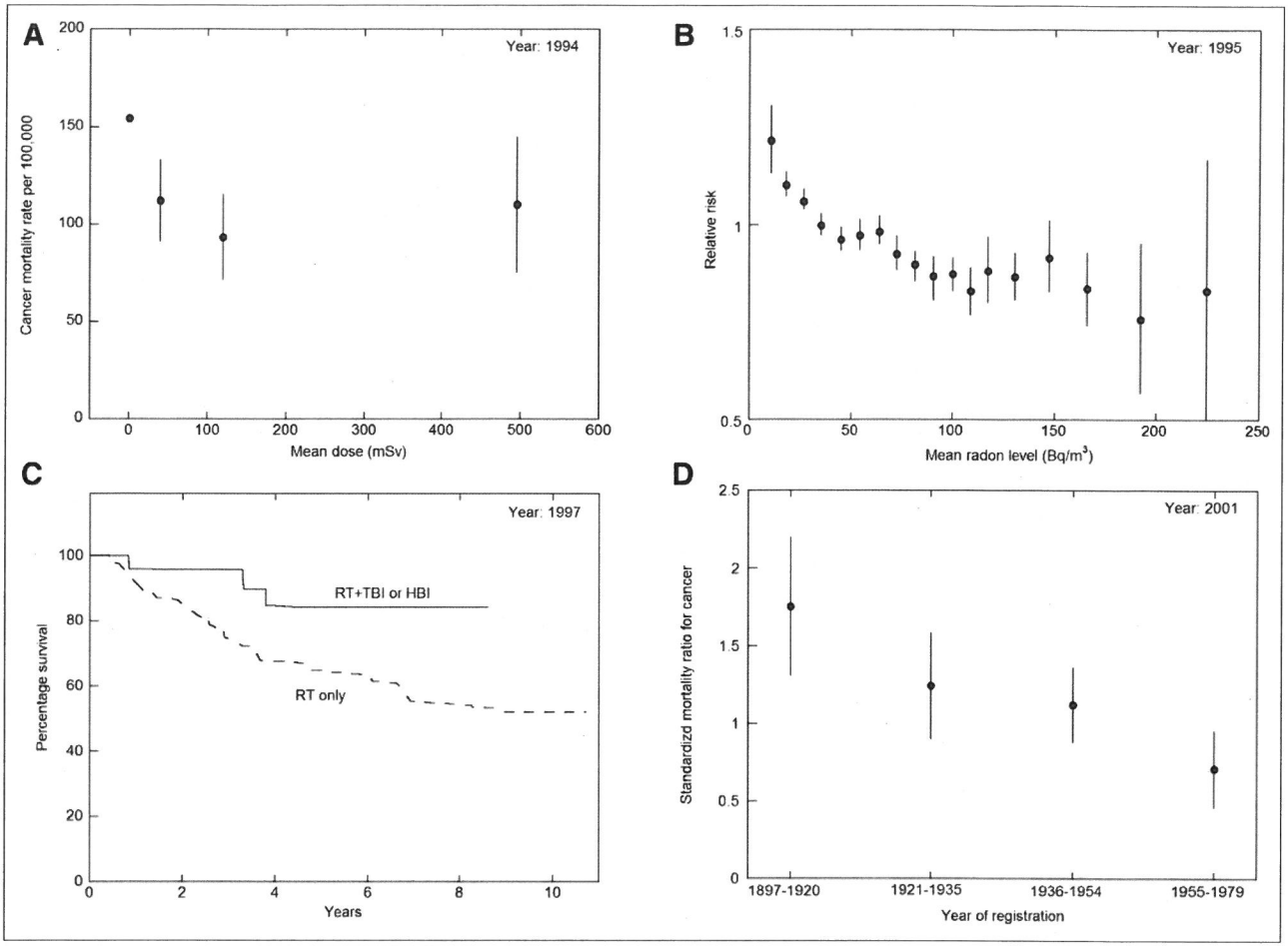

FIGURE 2. Evidence against LNT model or for radiation hormesis from 1990s to 2000s. Error bars are 95% CIs. (A) Cancer mortality rates in residents of evacuated villages near Mayak nuclear weapons facility after accident that released radioactivity into environment, as function of radiation dose (*41*). Data point at zero dose is from control population. (B) Relative risk for lung cancer mortality of males in counties of United States as function of residential radon levels, corrected for smoking (*38*). (C) Survival of non-Hodgkin lymphoma patients having radiation therapy (RT) to tumor compared with patients having interspersed low-dose total-body or half-body irradiation (TBI or HBI) between radiation treatments to tumor (*40*). TBI/HBI had cancer therapeutic effect. (D) SMR for cancer mortality in male British radiologists compared with male physicians, for different periods of registration (*43*). Radiologists who registered during 1955–1979 had exposure to low levels of radiation and were observed to have reduced cancer rates compared with male physicians, consistent with radiation hormesis. (Note: All these data show reduction of cancers after low radiation exposures, contradicting LNT model and consistent with radiation hormesis).

for all cancers showed no increase, at 1.05 (95% CI, 0.95–1.15), indicating a reduction in the all-cancer mortality rate after the fluoroscopy. Radiation hormesis can explain the decrease in all cancers in this cohort. Though the breast received high radiation doses from the fluoroscopic examinations, other parts of the body would have received lower doses resulting in the reduction of other cancers and all cancers. Examining only breast cancer risk would misrepresent the overall health effect of the irradiation by ignoring the reduction of other and all cancers. Therefore, the Massachusetts study does not provide evidence for the LNT model.

The fourth one is the study of solid cancer incidence in the atomic bomb survivors exposed in utero or in childhood (*57*). As discussed earlier, the use of an LNT dose–response shape while extracting ERRs is not justified because of the large observed evidence for radiation hormesis (Figs. 1–3). Therefore, the extracted ERRs would not be reliable for determining the dose–response relationship. Notwithstanding this reasoning, if we use the ERRs as reported, the dose–response shape in this study also shows significant curvature ($P = 0.09$) for the dose range of 0–2 Gy, and significant curvature would be inconsistent with the LNT model, as discussed earlier.

The fifth study is the pooled analysis of thyroid cancer incidence after childhood radiation exposures (*58*). One issue with this study is that thyroid cancer incidence is subject to considerable overdiagnosis. A sign of such overdiagnosis is that despite the large increase in thyroid cancer incidence due to increased imaging and screening over the past few decades, there has been little change in thyroid cancer mortality rates in the United States and South Korea (*59,60*). A recent review has concluded that most thyroid cancers are self-limiting and do not metastasize and, so, has recommended against screening for thyroid cancer (*61*). Hence, the pooled analysis of thyroid cancer incidence would also likely be subject to large overdiagnosis, and conclusions based on such studies would not provide useful information on the shape of the dose–response curve. Therefore, this study also does not support the LNT model.

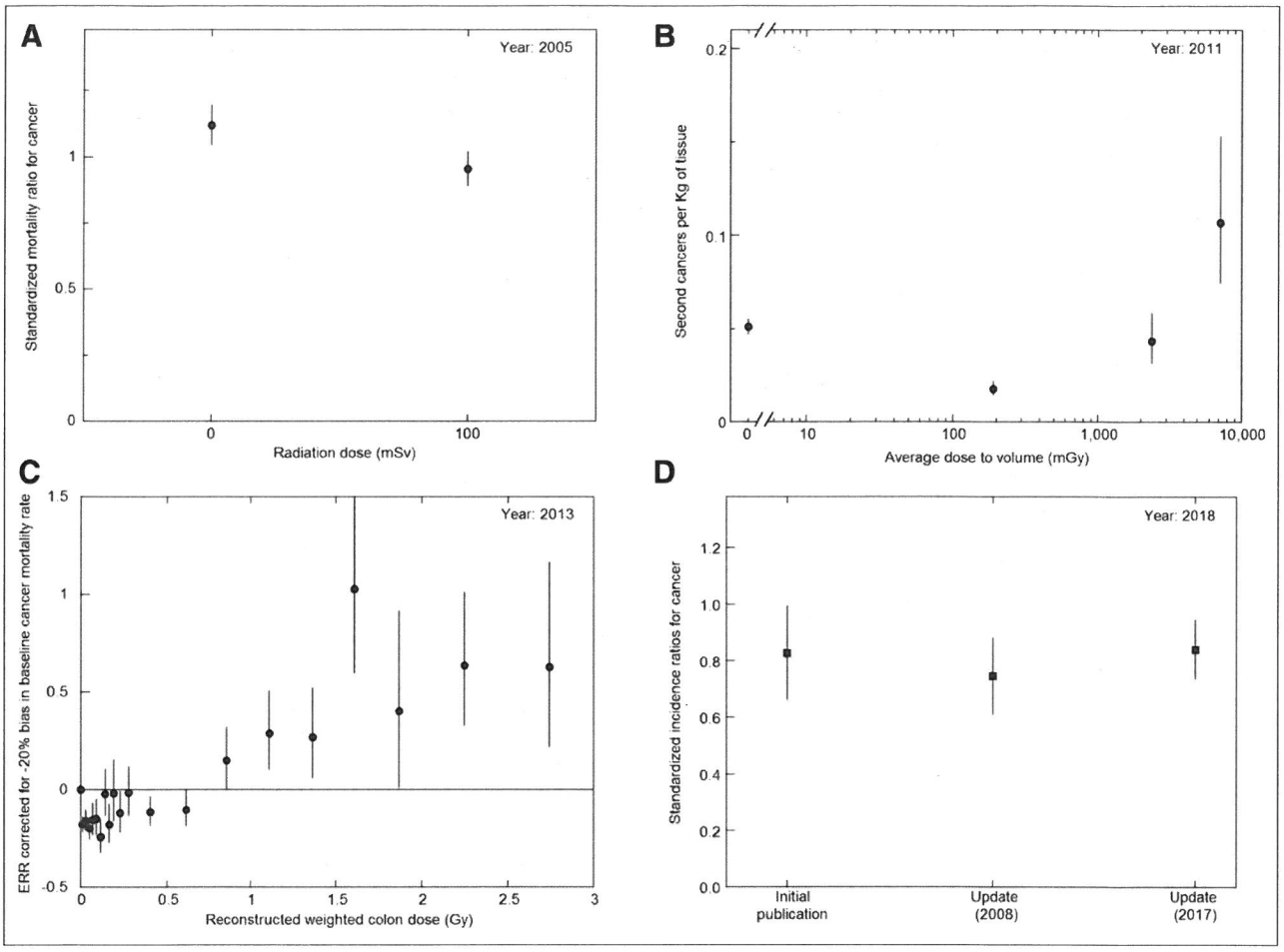

FIGURE 3. Evidence against LNT model or for radiation hormesis from 2000s to 2010s. (A) SMRs for all cancers in nuclear shipyard workers as function of radiation dose (*21*). Error bars are 95% CIs. (B) Second cancers per kilogram of tissue in radiation therapy patients as function of dose to tissue (*20*). Error bars are SDs. (C) ERR for solid cancer mortality in atomic bomb survivors, corrected for likely negative bias in baseline cancer mortality rate used in analyzing data (*14*). Error bars are 95% CIs. (D) Standardized incidence ratios for cancers in irradiated residents of radio-contaminated apartment buildings in Taiwan, from initial study and 2 updates (*19*). Error bars are 95% CIs. (Note: All studies show reduction of cancers after low radiation exposures, contradicting LNT model and consistent with radiation hormesis).

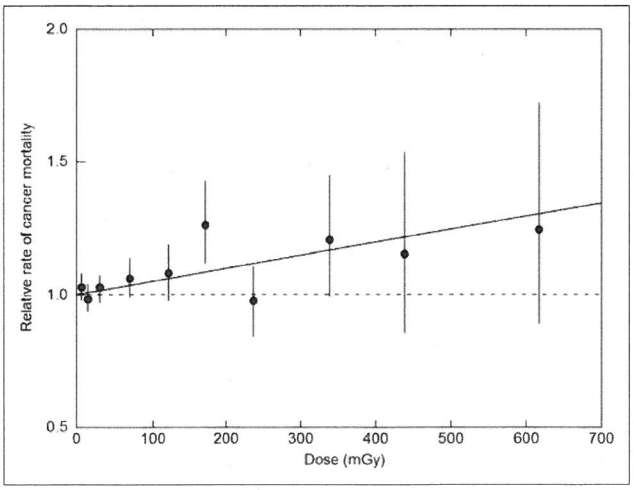

FIGURE 4. Relative risk of cancer mortality as function of radiation dose in nuclear industry workers from INWORKS study (*46*). Error bars indicate 95% CIs. Solid line is linear model fit to data.

The above discussion shows that none of the studies claimed by the NCRP to strongly support the LNT model actually do support the model, nor do the studies claimed to provide moderate support or weak-to-moderate support (Table 1). Therefore, the conclusion of NCRP Commentary 27 that recent epidemiologic studies broadly support the LNT model may not be justifiable.

CONCLUSION

For some issues such as the carcinogenicity of low levels of radiation, a substantial number of publications may reach opposite conclusions, making the issues controversial. It is clear that two studies reaching opposing conclusions cannot both be correct and that the study reaching the wrong conclusion would likely have major shortcomings. Therefore, when advisory bodies consider such controversial issues, they should critically examine the studies supporting both sides so that they can identify the studies with major shortcomings and discard them. This procedure would allow an objective conclusion to be reached. Hence, a major deficiency of NCRP Commentary 27 is that it did not consider the

TABLE 1
Comments on Epidemiologic Studies that NCRP Commentary 27 Claimed to Provide Moderate, or Weak-to-Moderate, Support for LNT Model

Study	Comments
Mayak nuclear workers (*62*)	For radiation doses less than 0.5 Gy, ERR is consistent with no increased cancer risk (Fig. 2 of the publication).
Chernobyl fallout, Ukraine and Belarus thyroid cancer (*63*)	Like Massachusetts tuberculosis study (*53*), this study has flaw of considering thyroid cancer incidence, which is subject to large overdiagnosis, and considering thyroid cancer only.
Breast cancer studies, after childhood exposure (*64*)	According to the publication, 3% of women in whole cohort had breast doses exceeding 1 Gy, and mean dose was 0.18 Gy. Thus, cohort included patients with highly carcinogenic doses, even though average dose was much lower. Increased cancers would occur in patients with high breast doses and should not be attributed to low radiation doses. Dose–response data from earlier publication on same cohort (*65*) show no significantly increased breast cancer risk for breast doses less than 1 Gy (Table 3 of the publication).
In utero exposure, Japan atomic bombs (*57*)	Data shown in Table 4 of the publication indicate no significant increase in relative risk of cancer for low-dose category (0.005–0.2 Sv) for in utero or childhood exposure. Next dose range (>0.2 Sv) shows significantly increased relative risk for a few categories. Because this dose range includes high doses, increased relative risk for this dose range may not be attributable to low radiation doses. A review of a large number of studies (*57,66*) indicated that no definitive conclusion can be drawn on carcinogenic effect of in utero exposure.
Techa River, nearby residents (*67*)	Data in Table 3 of the publication indicate no significant increase in cancer risk for any dose range.
In utero exposure, medical (*68*)	This is a review article. A later review of a large number of studies (*66*) indicated that no definitive conclusion can be drawn on carcinogenic effect of in utero exposure.
Japan nuclear workers (*69*)	The publication stated that data are likely confounded by alcohol drinking. Data in Table 2 of the publication indicate that this study does not show significantly increased cancer risk in radiation workers when alcohol-related cancers are excluded.
Chernobyl cleanup workers, Russia (*70*)	SMR for all cancers is 0.95 (95% CI, 0.92–0.99) (from Fig. 5 of the publication), indicating reduction of cancer in this cohort after radiation exposure.
U.S. radiologic technologists (*71,72*)	Overall cancer mortality rate for radiologic technologists was significantly lower, with SMR of 0.82 (95% CI, 0.80–0.84), as reported in Table A2 of supplementary materials of one publication (*71*). The other publication (*72*) studied breast cancer only. Studying single type of cancer does not provide complete information on carcinogenic effect of low radiation doses, as hormetic reductions of other cancers would not be considered.
Mound nuclear workers (*73*)	Overall cancer mortality rate was significantly lower in radiation workers, with SMR of 0.86 (95% CI, 0.79–0.93).
Rocketdyne nuclear workers (*74*)	Overall cancer mortality rate was significantly lower in radiation workers, with SMR of 0.88 (95% CI, 0.81–0.94), and relative risk for all cancer mortality did not significantly increase.
French uranium processing workers (*75*)	Overall cancer mortality rate was significantly lower in radiation workers, with SMR of 0.79 (95% CI, 0.72–0.87).
Medical x-ray workers, China (*76*)	Data below 0.15 Gy are consistent with no increase in cancer risk (Fig. 2 of the publication). Shape of dose–response curve cannot be determined reliably from these data because of large errors.
Taiwan radiocontaminated buildings, residents (*17*)	As explained in the publication (*19*), Standardized incidence ratios for all cancers, calculated using data in the publication, are significantly reduced in irradiated residents of radiocontaminated buildings.
Background radiation levels and childhood leukemia (*77*)	Breastfeeding and child-care attendance are known to be important factors in childhood leukemia (*78,79*) but were not considered confounding factors in the study. Because relative risk per millisievert for leukemia was 1.07 (95% CI, 1.01–1.13), small changes in these confounding factors could make increase in risk not significant. We should await better studies that account for such major confounding factors.

studies that supported radiation hormesis. If the NCRP had considered such studies and had critically evaluated publications supporting both sides, it would not have reached its present conclusion. Previous advisory body reports that have supported the LNT model, such as BEIR VII, have the same deficiency of not considering publications that support radiation hormesis and not critically examining the publications. Hence, notwithstanding the almost unanimous support of the advisory bodies for the LNT model, their recommendations are questionable. The advisory bodies are urged to critically evaluate the available evidence on both sides to draw an objective conclusion. Considering the strength of the evidence against the LNT model (Figs. 1–3) and the weakness of the evidence for it (Fig. 4), the present analysis indicates advisory bodies would be compelled to reject the LNT model. Hence, we may be approaching the end of the LNT model era.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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Are We Approaching the End of the Linear No-Threshold Era?

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Review article

A critical evaluation of the NCRP COMMENTARY 27 endorsement of the linear no-threshold model of radiation effects

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ABSTRACT

Regulatory policy to protect the public and the environment from radiation is universally based on the linear, no-threshold model (LNT) of radiation effects. This model has been controversial since its inception over nine decades ago, and remains so to this day, but it has proved remarkably resistant to challenge from the scientific community. The LNT model has been repeatedly endorsed by expert advisory bodies, and regulatory agencies in turn adopt policies that reflect this advice. Unfortunately, these endorsements rest on a foundation of institutional inertia and numerous logical fallacies. These include most significantly setting the LNT as the null hypothesis, and shifting the burden of proof onto LNT skeptics. Other examples include arbitrary exclusion of alternative hypotheses, ignoring criticisms of the LNT, cherry-picking evidence, and making policy judgements without foundation. This paper presents an evaluation of the National Council on Radiation Protection and Measurements' (NCRP) Commentary 27, which concluded that recent epidemiological studies are compatible with the continued use of the LNT model for radiation protection. While this report will likely provide political cover for regulators' continued reliance on the LNT, it is a missed opportunity to advance the scientific discussion of the effects of low dose, low dose-rate radiation exposure. Due to its Congressionally chartered mission, no organization is better positioned than the NCRP to move this debate forward, and recommendations for doing so in future reviews are provided.

> "A scientist, having selected some challenging field which interests him, tries to read all of the literature pertinent to his problem, carefully identifying those portions which are theory or postulation and those which are strongly or weakly supported by experimental evidence or facts. Upon digesting this, he then maps out a course of action, but *one thing a scientist never does is to start out with a preconceived idea of what the final results will be*" (Taylor, 1980).

Lauriston S. Taylor, the first Chairman of the National Council on Radiation Protection and Measurements

1. Introduction

This paper examines the longevity of the linear, no-threshold (LNT) model as applied to low dose, low dose-rate (LDDR) radiation effects on human health and the environment, and considers the question of why, over nine decades after its introduction, the LNT model continues to divide the radiation sciences community. The LNT model has been controversial from its earliest days but has so far survived significant challenge. Factors contributing to the longevity of the LDDR radiation effects debate are identified and illustrated by a detailed examination in this paper of the most recent commentary on the topic by the National Commission on Radiation Protection and Measurements (NCRP). In its Commentary 27 (NCRP, 2018), the

> "NCRP concludes that, based on current epidemiologic data, the LNT model [perhaps with excess risk estimates reduced by a dose and dose-rate effectiveness factor (DDREF) or a DREF] should continue to be used for radiation protection purposes. This is in accord with judgments by other national and international scientific committees, based on somewhat older data than in the present Commentary (ICRP, 2007; NA/NRC, 2006; UNSCEAR, 2008), that no alternative dose-response relationship appears more pragmatic or prudent for radiation protection purposes than the LNT model".

I was asked by the American Academy of Health Physics (AAHP) to review a draft of the NCRP's commentary, and I submitted 117 critical comments (plus a few complimentary comments that suggested no changes). The AAHP requested that the NCRP provide a written disposition of these comments, however this request was declined. The NCRP's unresponsiveness to this request seems to contradict recent guidance by the International Commission on Radiological Protection on the ethical foundations of radiation protection (ICRP, 2018), which

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recommends transparency in radiation protection decisions. In the absence of an explanation of the NCRP's disposition of these comments, I compared the draft report to the final commentary and determined that the NCRP addressed four of my submitted comments, partially addressed five comments, and did not address 108 of them in any obvious way. This also seems to contradict the ICRP's advice, which recommended seriously considering the concerns of stakeholders (ICRP, 2018). This paper was constructed in large part from my comments on the draft NCRP commentary. It reflects my own opinions and not necessarily those of the AAHP.

The NCRP plays a unique and influential role in radiation protection in the United States. Since its organization in 1929 as the Advisory Committee on X-Ray and Radium Protection (Taylor, 1971), the NCRP has served as the preeminent American national advisory body on radiation protection matters (Mossman, 2009). In light of the importance of NCRP guidance, and in the belief that the scientific enterprise is best served by transparency and constructive engagement on controversial issues, a main purpose of this paper is to present my evaluation of the latest NCRP commentary in a peer-reviewed forum, for consideration and discussion by the larger radiation sciences community.

2. The LNT model as the basis for radiation protection: from murky origins to current inertia

The origin of the LNT model has been traced by (Calabrese, 2013) back at least as far as 1928, when A.R. Olson and G.N. Lewis proposed genetic mutations induced by naturally occurring radiation as the engine of evolution (Olson and Lewis, 1928). Since this paper deals with the NCRP's views of the evidence on LDDR radiation effects, the writings of Lauriston Taylor, the first Chairman of the NCRP, are considered especially relevant from a historical perspective. Dr. Taylor noted,

> "In a report to the League of Nations in 1930, Wintz and Rump (1931) enunciated the first philosophical concepts of radiation effects, which were agreed to by both the ICRP and the NCRP at that time. In discussing the amount of radiation which tissue would be able to tolerate, the report said:
>
> "The above observations show that the tolerance dose is never a harmless one and that tolerance doses can in no case be readministered indefinitely to any particular piece of tissue after the visible effects have disappeared on each occasion.... We thus reach the conclusion that a really harmless dose of radiation can only be said to be given if it is incapable either of destroying or damaging the cells or of exercising any stimulating action... " (pp. 1 and 8)"

This has been the guiding tenet for both the NCRP and ICRP since 1930. It explicitly states the lack of belief in the concept of a threshold of dose effect, yet it does not use the word threshold; nor was such a word used until the NCRP did so in the late I940s" (Taylor, 1988).

A pivotal moment in the history of the LNT model was the National Academy of Science's Biological Effects of Atomic Radiation (BEAR I) Committee's report, released on 12 June 1956, which recommended the abandonment of a threshold model, and the adoption the LNT model as the basis for radiation protection (Calabrese, 2015). The BEAR I Committee's recommendations were met with initial acceptance by the radiation protection community. For example, just two years after the BEAR I report was released, Taylor explained,

> "But before a maximum permissible dose of radiation can be set for man, there must be an unequivocal answer to one question: "what amount of radiation may man receive in either chronic or acute exposure without any harm to himself or his progeny?" At present the only answer to this question is: "none". There is today little or no direct, positive proof that there does or does not, exist some level of exposure below which harm will not result" (Taylor, 1958).

The BEAR I Committee was dominated by geneticists, so it is not surprising that its recommendation to adopt the LNT model was based on concern about genetic harm in the human descendants of a population exposed to fallout from radioactive testing. As described by Taylor,

> "...at the time of the study by the National Academy of Sciences on the Biological Effects of Atomic Radiation, the committee making the first report was dominated by geneticists. They convincingly set forth the genetics hazard problem in such a way that the NCRP and the ICRP revised their protection philosophy and recommendations so that for all practical purposes the genetic factor was the controlling factor" (Taylor, 1965).

and

> "In January 1957, the as the controlling factas the controlling factadiation workers was again changed-now to an average value of 5 rems/yr. This value was introduced primarily for reasons then thought to be valid for a reasonable minimization of genetic injury" (Taylor, 1971).

However, it didn't take long for doubts about this policy shift to begin to surface. In 1958, the very year the NCRP recommended the adoption of the LNT model for assessing cancer risk, the work of William and Liane Russell of Oak Ridge National Laboratory using the single locus test in mice was published in *Science* (Russell et al., 1958). Their work revealed the existence of a dose-rate effect in mouse spermatogonia and oocytes, which challenged the LNT model's assertion that mutation rate depended only on total dose (Calabrese, 2017a). The later revelation that the Russells had significantly underestimated the mutation rate in their control animals not only strengthened the finding of a dose-rate effect, but had this error not occurred, it would have revealed the existence of thresholds and hormetic dose-responses in the Russells' mouse data (Calabrese, 2017b), and quite possibly would have changed the course of radiation protection history.

Evidence of genetic harm in humans – the primary justification presented for adoption of the LNT model for radiation protection - has since failed to materialize (Brent, 2015). Indeed, Taylor noted,

> "In the 1940s, it was thought that the genetic effects of irradiation might be the controlling concern. It was, indeed, the controlling concern in 1956, when the National Academy of Sciences proposed lowering the occupational permissible dose level to 5 rem y^{-1}. However, by 1960, the work of William Russell threw considerable doubt on this conclusion and even indicated the existence of some thresholds of effect under certain conditions" (Taylor, 1988).

These doubts proved insufficient to prevent the expansion of the LNT model beyond estimating genetic harm in humans to include estimation of the carcinogenic risk of radiation, as explained by Taylor just two years after the BEAR I report,

> "The new levels have been dictated mainly for reasons of genetic damage, but it must now be recognized that somatic damage possibilities are assuming equivalent importance. As already mentioned, *the direct evidence of genetic damage to man is almost totally lacking, and that of somatic damage is very scant at best*" (Taylor, 1958)(emphasis added).

The justification for continuing to use a radiation protection model undercut by existing and developing scientific evidence was summed up by Taylor 47 years ago,

> "Throughout the decade since 1959, there have been only two or three major developments that might seriously influence the basic protection criteria. One of these was the demonstration by Russell of the dose-rate dependence of certain genetic effects. For the first time this marked a clear deviation from the single, linear dose-effect relationship-no threshold assumptions which all protection bodies had been using for many years...The trends in the genetic information, together with other bits and pieces of information in the somatic area have mostly been in the direction of indicating that radiation exposure at low doses and low dose rates was probably less serious

than assumed in the 1950's. However, in spite of this trend, the magnitude of the differences did not appear to be great enough to warrant any serious consideration of an upward revision of the already existing standards. However in retrospect one might suppose that *if, 10 yr ago, we had had today's knowledge of genetic effects we might not have made some of the changes which we did*" (Taylor, 1971) (emphasis added).

Though Taylor's writings do not indicate that he ever completely repudiated the adoption of the LNT model for radiation protection purposes, his cautious retreat from his initial unqualified acceptance continued over the next decade.

"*Today we know enough about dose-effect relationships to state unequivocally that at least for low LET radiations the relationships cannot be strictly linear over the whole dose range and that even for high doses they are probably not linear.* In general, the deviation from linearity has been such as to make our radiation protection standards more conservative or more restrictive than predicted by the linear relationship alone. The difficulty, of course, is that since we do not know the precise relationship—and perhaps it doesn't make much difference anyway—it is assumed, as a matter of cautious procedure, that the dose-effect relationships are linear throughout the entire dose range. This assumption is constantly being subjected to hard scrutiny because, if taken too literally, it leads to unnecessary and unjustifiable restrictions on the use of ionizing radiations". (Taylor, 1980)(emphasis added)

Despite Taylor's personal qualms, the use of the LNT model for radiation protection has been repeatedly reaffirmed by various advisory committees and regulatory agencies in the intervening years (Jones, 2005; Kathren, 1996), even by the organization he chaired – the NCRP. Today, the Environmental Protection Agency (EPA) is primarily responsible for protecting the American public and the environment from negative effects of radiation exposure, and the EPA has endorsed the use of the LNT to estimate risks from LDDR radiation exposure (USEPA, 2011). The EPA's endorsement and application of LNT has been strongly criticized (Cardarelli and Ulsh, 2018; Miller et al., 2017; Siegel et al., 2017b). Following suit, the use of the LNT model for radiation protection is endorsed by the Nuclear Regulatory Commission (NRC), for which it too has been criticized (Doss et al., 2015b; Marcus, 2015; Miller, 2015), and by the Department of Energy (DOE). The accuracy of the LNT model has also been endorsed by the National Academy of Sciences (NAS) Biological Effects of Ionizing Radiation (BEIR VII) Committee (National Research Council, 2005), but questioned by the French National Academies of Medicine and Sciences (Aurengo et al., 2005), the Health Physics Society (HPS, 2016), the Society for Pediatric Radiology (SPR, 2001), the International Organization for Medical Physics (Pradhan, 2013), the American Academy of Physicists in Medicine (AAPM, 2017), Australasian Radiation Protection Society (ARPS, 2008), and by a majority of scientists who believe a threshold model more accurately describes LDDR effects (Jenkins-Smith et al., 2009; Silva et al., 2007).

Objective criteria have been promulgated to determine when epidemiological evidence is sufficient to infer causality, rather than simply an association, between a putative agent and an observed health effect (Hill, 1965; Weed and Gorelic, 1996). The LNT model has survived despite failing to satisfy these criteria and thereby establish causation between LDDR radiation exposure and increased cancer risk (Ulsh, 2012). This paper argues that the explanation for the longevity of the debate surrounding the LNT model, which has spanned at least nine decades and has significantly fractured the radiation sciences community, is in large part related to what Sacks termed paradigm blindness (Sacks et al., 2016), supported by logically fallacious reasoning by advisory bodies, regulators and policy makers who follow their advice (Sacks and Siegel, 2017). This is amply illustrated in the NCRP's latest commentary on the LNT model (NCRP, 2018), which is examined in depth in the following text.

3. Shifting the burden of proof: setting LNT as null hypothesis

In epidemiological studies, the null hypothesis is defined as, "there is no relationship between the agent under study (*e.g.* radiation exposure) and the effect of interest (*e.g.* cancer)". As explained by Green and colleagues in a report published by the National Research Council,

"Formal procedures for statistical testing begin with the null hypothesis, which posits that there is no true association (*i.e.*, a relative risk of 1.0) between the agent and disease under study. Data are gathered and analyzed to see whether they disprove the null hypothesis. The data are subjected to statistical testing to assess the plausibility that any association found is a result of random error or whether it supports rejection of the null hypothesis". (Green et al., 2011)

The most significant factor in the persistence of the LNT model is the subtle, and logically fallacious practice in radiation epidemiological studies, and reviews of these studies, of setting the LNT as the null hypothesis, instead of the scientifically valid no-effect null, against which an arbitrarily limited set of alternatives (*e.g.* linear quadratic without threshold, and occasionally threshold models, but never hormetic models) are tested (Ulsh, 2012). This is a clear example of the logical fallacy known as is *argumentum ad ignorantiam* – argument from ignorance – also known as shifting the burden of proof (Cardarelli and Ulsh, 2018; Hansen, 2015; Ulsh, 2012; Walton, 1999). In simplistic terms, this argument takes the form:

Proponent: makes claim C, which requires justification;
Skeptic: requests justification for C;
Proponent: demands justification for the opposite of C;
Skeptic: refuses or cannot comply;
Proponent: therefore concludes C is true.

In terms of the LNT debate, this fallacy takes the form:

LNT proponent: There is no safe dose of radiation – even the smallest dose carries some risk!
Skeptic: What's the evidence of that?
LNT proponent: Can you prove there's absolutely zero risk from low doses?
Skeptic: No, epidemiological studies cannot prove an absolute absence of risk because of statistical power limitations, and it is impossible to prove a negative assertion.
LNT proponent: Then there is some risk from even the smallest doses.

Regulatory agencies and advisory bodies rely heavily, if not exclusively, on human epidemiological studies in developing radiation protection standards. While epidemiology studies have the great benefit of directly studying human health risks, they are observational rather than experimental, and they are fundamentally limited by imprecision and lack of statistical power to determine effects at low doses (Brenner et al., 2003; Land, 1980). Indeed, observational studies have been described as "dull scalpels" (Taubes, 1995) because of possible systematic errors (*i.e.* bias and confounders) which can be hard to detect, and can significantly compromise a study's ability to accurately characterize small effects. Many prominent epidemiologists have cautioned against placing too much confidence in observational studies asserting causation between a particular health effect and an environmental factor when observed relative risks (RRs) are less than about three (Taubes, 1995). Even the "gold-standard" of radiation epidemiological studies – the Lifespan Study of the Japanese Atomic Bomb Survivors – observed excess relative risks (ERRs) Gy^{-1} values less than 1.5 [see Figure 3.2 of (NCRP, 2018)]. Since RR = ERR + 1, all of the corresponding RR values for individual cancer sites, and for all solid cancers combined the LSS study [as shown in Figure 3.2 of (NCRP, 2018)] are less than about

2.3. These estimates are reported at 1 Gy – an acute dose on the order of 1000 times higher than typical environmental or occupational doses. Even so, as reported in Table 4.3 of (NCRP, 2018), most of the studies evaluated by the NCRP, including several studies the NCRP characterized as providing strong support for the LNT model, had ERR Gy^{-1} values less than 1.5 – well below the minimum level prominent epidemiologists have cautioned may indicate reliable evidence of causation.

In a 1995 article in *Science* that interviewed several well-respected epidemiologists, Taubes concluded,

> "So what does it take to make a study worth taking seriously? Over the years, epidemiologists have offered up a variety of criteria, the most important of which are a very strong association between disease and risk factor and a highly plausible biological mechanism. The epidemiologists interviewed by *Science* say they prefer to see both before believing the latest study, or even the latest group of studies".

These epidemiologists' preference for considering both the epidemiological data and biological data before concluding causation is especially noteworthy, as NCRP Commentary 27 was limited to epidemiological data only, and did not consider biological data (see further discussion in Section 4 below).

Furthermore, observational epidemiology studies are critically dependent on assumptions about dose-response models (Land, 1980). Because of imprecision and low statistical power, there is almost never strong enough evidence to reject an improperly defined LNT null hypothesis in favor of one of the limited set of alternative hypotheses, so the LNT persists. And why is the LNT improperly set as the null? Because it is currently the basis of the existing system of radiation protection, and benefits from the inexorable pull of institutional inertia initiated by the BEAR I Committee in 1956, and promulgated by advisory committees ever since. However, in a hopeful sign, as of the time of this writing, the EPA has issued a proposed rule (USEPA, 2018) that recognizes,

> "…there is growing empirical evidence of non-linearity in the concentration-response function for specific pollutants and health effects. The use of default models, without consideration of alternatives or model uncertainty, can obscure the scientific justification for EPA actions. To be even more transparent about these complex relationships, EPA should give appropriate consideration to high quality studies that explore: A broad class of parametric concentration-response models with a robust set of potential confounding variables; nonparametric models that incorporate fewer assumptions; various threshold models across the exposure range; and spatial heterogeneity. EPA should also incorporate the concept of model uncertainty when needed as a default to optimize low dose risk estimation based on major competing models, including linear, threshold, and U-shaped, J-shaped, and bell-shaped models."

Should this proposed rule ultimately be implemented, it would represent a profound break with EPA's historical pro-LNT bias, and would be a very positive step toward returning EPA's rules on low dose radiation to solid scientific foundations.

The policies of the EPA and other regulatory agencies is heavily influenced by advice from the NCRP. The many examples of shifting the burden of proof throughout (NCRP, 2018) range from overt and explicit, to subtle and implicit. Similar examples are grouped together below, followed by an analysis:

> *Page 1: "…in developing its basic recommendations, as currently given in NCRP Report No. 116 …, the Council reiterated its acceptance of the LNT model for the purposes of radiation protection. The purpose of this Commentary is to provide a review of recent data from studies with low dose rates and from the Life Span Study of atomic-bomb survivors to determine whether these epidemiologic studies broadly support the LNT model of carcinogenic risk or, on the contrary, whether there is sufficient evidence that the LNT model is inappropriate for the purposes of radiation protection" (emphasis added).*
>
> *Page 6: "The Committee also rated each study or group of studies on their strength of support for the LNT model…".*
>
> *Page 8: "…all studies have limitations, ranging from minor to serious, in their contribution to the quantitative evaluation of the LNT model".*
>
> *Page 10: "Indeed, in developing its basic radiation protection recommendations, as currently given in NCRP Report No. 116 …, the Council reiterated its acceptance of the LNT for the dose-risk relationship. Specifically, "based on the hypothesis that genetic effects and some cancers may result from damage to a single cell, the Council assumes that, for radiation-protection purposes, the risk of stochastic effects is proportional to dose without threshold, throughout the range of dose and dose rates of importance in routine radiation protection. Furthermore, the probability of response (risk) is assumed, for radiation protection purposes, to increase linearly with dose."*
>
> *Page 10: "As in previous reviews by the NCRP … the Council concluded that there was no conclusive evidence on which to reject the assumption of a LNT dose-response relationship for many of the risks attributable to low-level ionizing radiation…".*
>
> *Page 12: "It is important to note that the use of an LNT extrapolation model is really a default approach because of a lack of definitive evidence to the contrary (Preston, 2003)".*
>
> *Page 12: "The purpose is to determine whether these epidemiologic studies broadly support the LNT model of carcinogenic risk as used in radiation protection or, on the contrary, whether there is sufficient evidence that the LNT model is inappropriate"?*
>
> *Page 22: "The primary question to be addressed is whether the new epidemiologic evidence sufficiently supports a LNT model as a reasonable basis for radiation protection".*
>
> *Page 22: "The critique includes an assessment of the comprehensiveness, quality and uncertainties in the dosimetry used in each study, whether the analytic methods were appropriate and whether each study considered statistical alternatives to a linear dose-response trend".*
>
> *Page 128: "The Committee further rated each study or group of studies on their strength of support for the LNT model (Table 7.1)".*
>
> *Page 139: "This report has examined the evidence for or against the appropriateness of using LNT as a practical approach for managing radiation exposures to individuals".*

Rather than providing a neutral and objective evaluation of which dose-response model is optimal for radiation protection, and following the scientific method, where the null hypothesis is no effect, and various alternatives (*e.g.* the LNT, linear with threshold, hormetic, *etc.*) are tested against the null, the stated purpose of the Commentary sets up the LNT model as the default, or null hypothesis, and assumes it is acceptable unless contrary evidence is sufficient to disprove it. This approach is inconsistent with basic scientific principles by shifting the burden of proof onto the null hypothesis [*i.e.*, no effect at low doses (Green et al., 2011; Rothman and Greenland, 1998; Seiler and Alvarez, 1994). This inappropriately shift the burden of proof to proving that LNT is not valid, which is not possible (Hansen, 2015). The argument can always be made that a small, undetectable risk consistent with the LNT model may actually exist, and such an argument inoculates the LNT hypothesis from falsification. Basic scientific hypothesis testing dictates that compelling evidence must be provided that the true null (*i.e.* no effect at low doses) should be rejected in favor of an alternative hypothesis (*e.g.*, increases in cancer risk at low doses, as predicted by the LNT model). If the evidence supporting the tested alternative hypothesis is insufficient, the null stands.

The argument that some cancers may result from damage in a single

cell, and this somehow implies a LNT relationship for carcinogenesis, is a *non sequitur*. It ignores all the biology that occurs between initial damage and development of cancer years later. The NCRP's own prior evaluation of the LNT theory (Report No. 136), stated of this microdosimetric argument:

> "Application of this argument to complex endpoints such as radiation-induced carcinogenesis is, however, more uncertain. Based on these biophysical considerations about the shape of the dose-response relation for low-dose radiation-induced carcinogenesis, conclusions can be drawn if: (1) radiogenic cancer induction is causally related to radiation induced damage in a single cell and (2) the ways in which other cells or cell systems subsequently modify the probability that any given initially radiation-damaged cell becomes the clonal origin of a cancer do not vary with dose in a nonlinear fashion."

The current Commentary has omitted these prior caveats without explanation.

Speaking of the latest update to the Lifespan Study (LSS) of the Atomic Bomb Survivors cancer incidence data, the Commentary stated,

> *Page 47: "The lowest dose range that showed a statistically significant dose response using the sex- averaged linear ERR model was 0–100 mGy…".*

I interpret this statement as the authors asserting that when their analysis was restricted to the low-dose data (a dose range with a lower bound 0, and upper bound variable), they didn't observe a significantly elevated ERR until the upper bound of the restricted dose range reached 100 mGy. If the upper bound of the restricted dose range was less than 100 mGy (*e.g.* a range of 0–50 mGy, or 0–75 mGy, *etc.*), the ERR was not significantly elevated. This is a clear example of a practice that conceals possible thresholds by employing wide dose intervals in the low-dose region (Scott, 2018). As discussed above, if the LDDR data are insufficient to reject the no-effect null while the high dose, high dose-rate (HDDR) data are sufficient to reject the null, then this supports a threshold model. It is evident that statistical power limitations preclude the selection of one alternative hypothesis over the other (*e.g.*, LNT *vs.* linear quadratic). A threshold model is consistent with both the latest solid cancer incidence and mortality data (Doss, 2012; Furukawa et al., 2015; Sasaki et al., 2014; Siegel and Welsh, 2015; Socol and Dobrzynski, 2015), yet the Commentary's language here shows a confirmation bias favoring the LNT, and inappropriately shifts the burden of proof onto the null hypothesis of no effect (Siegel et al., 2017a), which at low doses corresponds to a threshold.

Continuing with its examination of the LSS data, the NCRP states,

> *Page 6: "To stimulate radiation epidemiology efforts to address the LNT model and low-dose risks…".*
>
> *Page 6: "An examination is needed of whether the dose-response LNT model applies to tumors of various organs or organ systems, insofar as statistical limitations permit, which will provide evidence regarding the generality of the LNT model across tumor sites".*
>
> *Page 43: "The LSS cohort of atomic-bomb survivors…has provided important data because it is a large cohort (~86,000 survivors of all ages) with… over 1000 excess cancer cases associated with radiation exposure".*
>
> *Page 132: "Evaluation of LNT for various organs or organ systems. Evaluate whether dose-response LNT is similar for tumors of various organs or organ systems, insofar as statistical limitations permit. This will provide evidence regarding the generality of the LNT model and the need for a low-dose effectiveness factor (LDEF) across tumor sites".*
>
> *Page 135: "Future dose response analyses should include dose uncertainties in the analysis of ERR Gy^{-1}".*
>
> *Page 138: "Analyzing epidemiologic data in conjunction with relevant radiobiological concepts and data also has the potential to provide insights into LNT that go beyond those gained from merely analyzing the empirical epidemiologic data in isolation…".*

Rather than testing whether the evidence supporting the LNT alternative hypothesis is sufficient to reject the no-effect null, the Commentary presents an estimate of excess cancer cases in the LSS cohort, which was calculated using the LNT, as an established fact. The suggestion that future analyses evaluate uncertainties in ERR Gy^{-1}, implicitly assumes a LNT dose-response, rather than appropriately treating the LNT as an alternative to be tested against the no-effect null. Limiting future radiation epidemiology to focus exclusively on the LNT model inappropriately elevates LNT above other competing alternative dose-response models.

The NCRP did not completely ignore the possibility of thresholds, but rather shifted the burden of proof from the LNT model to the threshold model (which corresponds to the no effect null at low doses):

> *Page 2: "Formal dose threshold analyses for both solid cancer incidence and mortality are compatible with no dose threshold…". [referring to the latest updates to the Lifespan Studies of the Atomic Bomb Survivors]*
>
> *Page 9: "Nevertheless, most large and high quality low- dose studies show positive risk coefficients (Shore et al., 2017), suggesting there may be cancer effects at low doses, which is consistent with, though not necessarily proving, the applicability of the LNT model for radiation protection".*
>
> *Page 46: "The 95% confidence band is broad and compatible with no excess risk below about 150 mGy but is more compatible with the LNT model throughout the lower dose range".*
>
> *Page 139: "…most large and high quality low- dose studies show positive risk coefficients (Shore et al., 2017), suggesting there may be cancer effects at low doses, which is consistent with, though not necessarily proving, the applicability of the LNT model for radiation protection".*
>
> *Page 139: "Several studies also performed explicit dose-threshold analyses and found the estimates of dose thresholds to be compatible with zero dose (i.e., no threshold)".*
>
> *Page 140: "While the LNT model is an assumption that likely cannot be scientifically validated by radiobiologic or epidemiologic evidence in the low-dose range, the preponderance of epidemiologic data is consistent with the LNT assumption…".*

These statements reverse the burden of proof by suggesting the data are "consistent" or "compatible" with the LNT. Due to imprecision at low doses, multiple alternative dose-response models could be consistent with the data at low doses. The appropriate question is, are the data for any alternative dose-response model sufficient to reject the no-effect null, or not? If the LDDR data are insufficient to reject the no-effect null while the HDDR data are sufficient to reject the null, then this supports a threshold model. In fact, the most recent LSS update on cancer mortality states, "the estimated lowest dose range with a significant ERR [excess relative risk] for all solid cancer was 0–0.20 Gy" (Ozasa et al., 2012b). Similar to the conclusions of the LSS incidence data, I interpret this statement as the authors asserting that when their analysis was restricted to the low-dose data (*i.e.* a dose range with a lower bound 0, and upper bound variable), they didn't observe a significantly elevated ERR until the upper bound of the restricted dose range reached 200 mGy. If the upper bound of the restricted dose range was less than 200 mGy, the ERR was not significantly elevated. This interpretation is consistent with the authors' later conclusion,

> "The lowest dose range with a significant ERR for all solid cancer was 0–0.20 Gy with an estimated ERR/Gy of 0.56 (95% CI: 0.15, 1.04, P = 0.01) and included 74,444 persons with 9063 solid cancer deaths. *For the range of 0–0.18, the ERR/Gy was 0.43 (95% CI: −0.0047, 0.91, P = 0.052)* and included 8920 deaths" (emphasis added).

The authors also concluded that, "…statistically significant upward curvature was observed when the dose range was limited to 0–2 Gy.. The curvature over the 0–2 Gy range has become stronger over time".

Page 9: "…no alternative dose-response relationship appears more pragmatic or prudent for radiation protection purposes than the LNT model".

Page 46: "Their semiparametric analysis indicated clear excess risk above 100 mGy, but below 100 mGy the confidence bounds did not exclude either no risk or a linear dose response, though the slope was generally positive below 200 mGy".

Page 139: "NCRP concludes that, based on current epidemiologic data, the LNT model (perhaps modified by a DDREF) should continue to be utilized for radiation protection purposes. This is in accord with judgment by other national and international scientific committees, based on somewhat older data than in the present report (ICRP, 2007; NA/NRC, 2006; UNSCEAR, 2008), that no alternative dose-response relationship appears more pragmatic or prudent for radiation protection purposes than the LNT model."

Page 140: "The current data are not precise enough to exclude other models…".

Page 140: "The current judgment by national and international scientific committees is that no alternative dose-response relationship appears more pragmatic or prudent for radiation protection purposes than the LNT model…".

Alternative dose-response models (*e.g.* linear with threshold, hormetic, *etc.*) don't have to be "more pragmatic or prudent" than the LNT. Rather, they have to be tested against the appropriate no effect null hypothesis. If the evidence in favor of any tested alternatives is insufficient to reject the no-effect null, then the null stands. Furthermore, when testing the other, non-LNT alternative hypotheses, the correct null of no-effect has to be excluded in favor of one (or more) alternative hypotheses.

4. Cherry-picking: arbitrarily excluding alternative dose-response models suggested by biological data

The fallacy of suppressed evidence (Dowden, 2018), more commonly known as cherry-picking the evidence, is also committed by regulatory agencies and advisory bodies in defense of LNT. An obvious example is arbitrarily excluding any consideration of the substantial body of evidence for hormesis – the biphasic dose response model which predicts a beneficial effect (or reduction in harmful effects below background levels) from low radiation doses or dose-rates, and harmful effects at higher doses or dose-rates (Upton, 2001; Vaiserman, 2010; van Wyngaarden and Pauwels, 1995) (Fig. 1). Hormesis is an alternative dose-response model which is mutually exclusive with the LNT model.

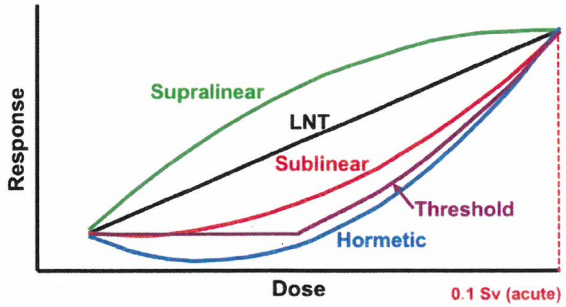

Fig. 1. Alternative dose-response models.

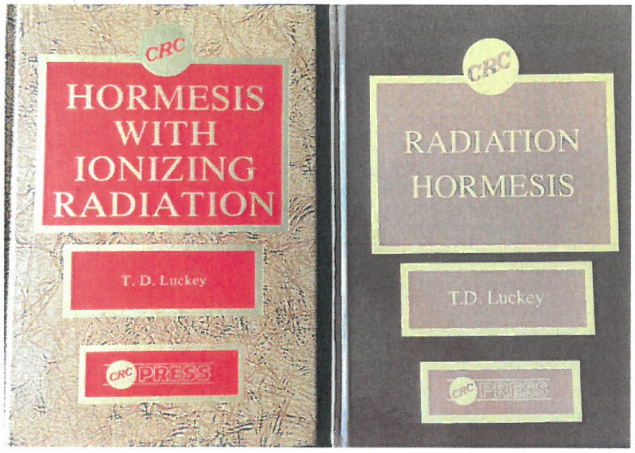

Fig. 2. Comprehensive hormesis references (Luckey, 1980, 1991).

There are numerous modern references that have observed a high frequency of hormetic dose-responses in toxicology [*e.g.* (Calabrese, 2005, 2006)], and the most comprehensive and authoritative radiation hormesis references are (Luckey, 1980), which cites 1269 supporting documents, and (Luckey, 1991), which cites 1018 supporting documents (Fig. 2). These references were neither cited nor acknowledged in either of the two most recent NCRP reports on LDDR radiation dose-responses (NCRP, 2001, 2018), or in the BEIR VII report by the NAS (National Research Council, 2005). The latest NCRP commentary (NCRP, 2018) did not even use the words "hormesis" or "adaptive response" a single time. To the best of this author's knowledge, none of the NCRP or NAS reports has systematically and objectively evaluated this significant body of evidence supporting hormesis. There is also evidence of genomic instability, and supralinear dose-responses in some cellular and molecular endpoints. The interpretation of these endpoints in terms of effects at the organismal level are unclear, but should be part of a comprehensive and objective analysis of the totality of the evidence on the biological effects of LDDR radiation exposure.

Regulatory agencies have also disregarded evidence of nonlinear dose-responses, especially hormesis. For example, the EPA has explicitly excluded any consideration of beneficial effects in risk assessment, stating, "…as the purpose of a risk assessment is to identify risk (harm, adverse effect, *etc.*), effects that appear to be adaptive, non-adverse, or beneficial *may not be mentioned*" (emphasis added) (USEPA, 2004), an arbitrary policy for which they have been heavily criticized (Calabrese, 2012; Cardarelli and Ulsh, 2018). The NRC's disregard of evidence for nonlinear dose-responses has also been criticized (Doss et al., 2015b; Marcus, 2015).

Unfortunately, epidemiological model selection is rarely informed by modern biological data. Just three years ago, (NCRP, 2015) called for "…understanding of low-dose specific mechanisms based on radiation biology data should be incorporated where possible into the process of extrapolating from epidemiologic data at higher doses to predict responses at low doses and low dose rates", but (NCRP, 2018) gave only passing mention to biological data. There is much work to do to integrate radiation biology and epidemiology, but there is already an overabundance of biological data to suggest the prudence of routinely considering dose-responses beyond the typical LNT model (*e.g.* threshold and hormetic models) in epidemiological studies. In particular, most epidemiological studies start with a predetermined set of parametric dose-response models that are tested over the entire range of doses. These invariably include LNT models, and sometimes linear-quadratic and/or linear with threshold, but almost never hormetic models. In the cases where multiple models (typically LNT *vs.* linear quadratic) are tested, procedures like Aikake Information Criteria or a likelihood ratio test is applied to determine whether or not any

improvement in model fit compared to a LNT model is justified by the additional complexity of more highly parameterized models.

The assumption that one parametric model is sufficient to cover the entire dose range from zero to lethal, is a critical, implicit assumption (personal communication with Bill Sacks). The consequences of improper model selection can be significant, particularly at low doses. It is common in epidemiological studies that the slope of an LNT model is most substantially determined by high dose data, while low dose data have relatively little impact, and this results in low dose risk estimates with unreliable uncertainty estimates (Furukawa et al., 2015). Arbitrarily limiting possible model selection to, for example, LNT and linear-quadratic (LQ) ignores evidence demonstrating that the biological responses to LDDR are distinct from those in response to HDDR. This contradicts the underlying assumption of the LNT model that there is no qualitative difference in responses across doses, only a quantitative difference (Paunesku et al., 2017; Ulsh, 2010). In an attempt to rescue the LNT model from its failure to accurately describe LDDR effects, proponents introduce a post-hoc data manipulation in the form of a DDREF, which in effect converts the overall dose-response from LNT to sublinear at low doses (Fig. 1) without the admission of having done so.

These qualitatively different biological response regions sever the link between LDDR and HDDR, undermine the basis for extrapolating effects from HDDR to LDDR (Mothersill and Seymour, 2004), and imply that the dose-responses in these regions should be evaluated independently. Critically, it cannot be concluded that the existence of sufficient data to reject the no-effect null in favor of a positive risk from HDDR exposures (which is widely accepted), says anything at all about the effects of LDDR exposures. If an independent evaluation of LDDR effects fails to reject the no-effect null while the null is rejected in the HDDR region, then this is consistent with a threshold dose-response. If the LDDR evaluation is sufficient to reject the no-effect null in favor of an increased risk, then this would be consistent with a LNT or LQ without threshold model. If the LDDR evaluation rejects the no-effect null in favor of decreased risks, then this would be consistent with a hormetic dose-response.

Examples of cherry-picking by ignoring or dismissing evidence for nonlinear dose-responses in (NCRP, 2018) include:

Page 2: "This Report represents an update of the guidance provided in NCRP Report No.136, Evaluation of the Linear-Nonthreshold Dose-Response Model for Ionizing Radiation (NCRP, 2001)".

The NCRP's previous assessment (NCRP, 2001) acknowledged several dose-response models, including but not limited to supralinear, LNT, threshold, and hormetic (Fig. 3), and Section 9.3.8.1 of that report gave at least cursory consideration of the hormetic model. Since Commentary 27 is presented as an update of NCRP Report No. 136, it is notable that it arbitrarily excludes the hormetic (and supralinear) model, even from the figure on the cover illustrating various dose-response models (Fig. 3). Note that the left panel in Fig. 3, from (NCRP, 2001), includes a hormetic dose-response model. The right panel is on the cover of (NCRP, 2018), and the hormetic dose-response has been omitted. Most of the studies evaluated considered only LNT and sometimes linear quadratic models, and some considered a possible threshold (but inappropriately shift the burden of proof onto the no-effect null). None of the studies reviewed considered the possibility of a hormetic model, and similarly, Commentary 27 completely ignores this possibility, and there is no explanation for this apparently arbitrary exclusion. The omission of the hormetic dose-response model as an alternative to the LNT is not consistent with an objective and neutral evaluation of the various alternative dose-response hypotheses, instead inappropriately establishing a confirmation bias favoring the LNT.

The NCRP's minimization of the possibility of nonlinear dose-responses is evident in their evaluation of the Mayak studies:

Page 3: "After adjusting for plutonium exposure, the ERR Gy^{-1} was 0.12 (95% CI: 0.03, 0.21) for solid cancer based on the external dose to the colon, and there was no indication of nonlinearity ($p > 0.5$) (Sokolnikov et al., 2015)".

Page 38: The Commentary asserts that Mayak studies, "Showed good correspondence with a linear model".

Page 49: "For external dose to the colon and mortality from all solid cancers excluding lung, liver and bone (i.e., excluding cancers at the major sites of plutonium deposition), ERR Gy^{-1} = 0.12 (95% CI: 0.03, 0.21) adjusted for plutonium exposures with no indication of nonlinearity ($p > 0.5$)".

Examination of the Mayak solid cancer incidence data (Fig. 4) shows that seven of the eight data points (and all of them < 1 Gy) had relative risk confidence intervals that included 1.0, and the 95% confidence interval on the linear fit included negative slopes.

Table 4.3 in (NCRP, 2018) lists a threshold of 0.2 Gy for the Mayak solid cancer mortality data. Examination of the data for solid cancers excluding lung, liver and bone (Fig. 5) reveals that for the solid cancer mortality ERR three of the four lowest data points have central estimates less than zero, and for the lowest dose category is significantly less than zero. Yet the possibility of a threshold has been excluded, and hormetic model was not considered or even mentioned. The assertion that there was no indication of nonlinearity is misleading.

Evidence for nonlinearity was also ignored for the Techa River studies:

Page 4: "The recent studies of the Techa River cohort have found

associations between radiation dose and incidence and mortality rates for solid cancers and leukemia (other than CLL) that they report are linear in dose response (Davis et al., 2015; Krestinina et al., 2013; ...) (Section 4.3.1). For the 2300 deaths from solid cancers the linear ERR Gy^{-1} was 0.61 (95% CI: 0.04, 1.27), but there was uncertainty as to the shape of the dose response, especially at low doses (Schonfeld et al., 2013)".

Page 4: "For non-CLL leukemia incidence the ERR Gy^{-1} was 2.2 (95% CI: 0.8, 5.4) and the linear model provided the best fit (Krestinina et al., 2013)".

There is also possible evidence of hormesis in the solid cancers data from the Techa River Cohort (Davis et al., 2015), as discussed in (Cardarelli and Ulsh, 2018). Once again, the authors claimed,

"There is a statistically significant (P = 0.02) linear trend in the smoking-adjusted all-solid cancer incidence risks".

The data in Fig. 6 shows that the two lowest dose categories have ERR estimates lower than the zero dose controls, consistent with a hormetic dose-response. It cannot be determined whether the data is sufficient to reject the no-effect null in the low dose region, as the authors did not include any analysis of this possibility, and no error bars were included in their graphical presentation of the data (Fig. 6). This is not discussed in (NCRP, 2018). This study cannot be presented as providing support for the LNT model when a hormetic model wasn't even considered.

As discussed in (Cardarelli and Ulsh, 2018), the low dose leukemia data from the Techa River cohort also shows evidence of a hormetic dose response, but this was not acknowledged or discussed by the authors. The total leukemia rates reported for the five lowest dose groups were lower than the control group (those who received < 0.01 Gy). Only the two highest dose groups (those receiving 0.5–1 Gy and 1 + Gy) exceeded controls [Table 4 of (Krestinina et al., 2013), reproduced here as Fig. 7]. For leukemia excluding CLL, the rates for two of the three lowest dose groups were below that for the control group (Fig. 7), suggesting a threshold or hormetic effect, which was not discussed in (NCRP, 2018). Instead, the authors claimed that their data, "...are consistent with a linear dose response...". Given the appearance of a

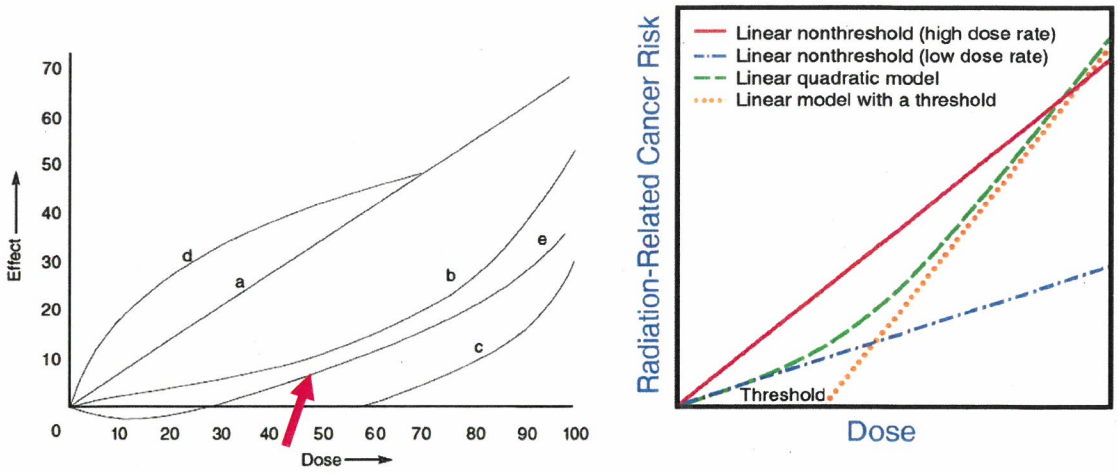

Fig. 3. Dose-response models. The left panel is Figure 2.1 from (NCRP, 2001). Red arrow added for emphasis showing a hormetic model. This graph was described as, "Schematic representation of contrasting types of dose-response relationships. (a) linear-nonthreshold dose-response relationship over the entire dose range, down to zero dose; (b) linear-nonthreshold relationship only at low-to-intermediate levels of dose, above which the curve bends upward (as is characteristic of the linear-quadratic type of relationship); (c) threshold dose-response relationship, in which no effect is produced at doses below the threshold indicated on the intercept; (d) supralinear response in which the effects per unit dose at low doses exceeds that of higher doses; (e) hormetic response in which the frequency of effect is reduced at low doses and increased only at higher doses". (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.). The right panel is the cover image from NCRP Commentary 27.

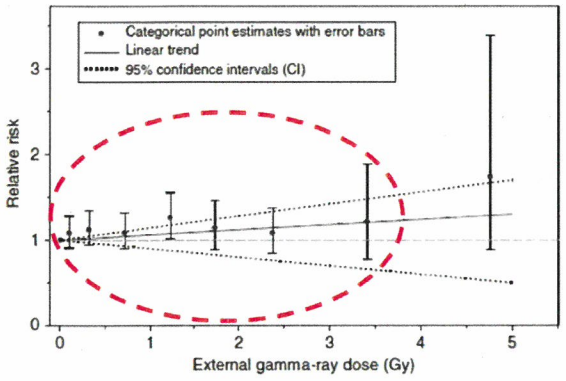

Fig. 4. Data from [(Hunter et al., 2013), Fig. 2, which was reproduced as Figure 4.3 in (NCRP, 2018)]. Dashed oval added for emphasis. The authors described this data as, "Relative risks of other solid cancer incidence in relation to external exposure categories and the linear trend (and 95% CI), having adjusted for internal exposure (based on 0-year lag)".

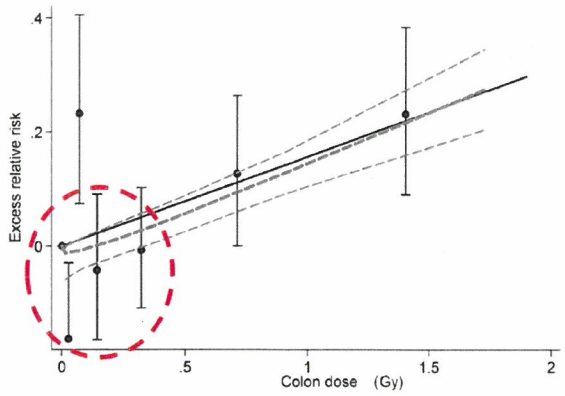

Fig. 5. Mayak mortality data for solid cancers other than lung, liver, and bone from Fig. 2 of (Sokolnikov et al., 2015), reproduced as Figure 4.4 in (NCRP, 2018). Dashed oval added for emphasis. The authors described this data as, External exposure dose response for solid cancers other than lung liver and bone....for doses below 1.5 Gy. The solid line is the fitted linear dose response, the points are ERR estimates in dose categories. The thick dashed line is a non-parametric smooth fit to the categorical estimates while the thin dashed lines indicate plus or minus one standard error from the smoothed curve. The models used in this analysis included no adjustment for plutonium exposure".

hormetic dose-response, but the lack of any related analyses, the Commentary should not cite these results as supporting the LNT model and excluding the threshold or hormetic models.

The NCRP continued to ignore evidence of nonlinearity in their recommendations for future research:

> *Page 6: "The large bank of blood and tissue samples should be studied more robustly by the biomedical community to identify bioindicators of drivers of adverse outcome pathways that mediate between radiation and disease development".*

> *Page 8: "For radiation-induced adverse health outcomes, a clear need is to identify bioindicators that define the pathway from normal to malignant cells that can be used for developing biologically based dose-response models. Analyzing epidemiologic data in conjunction with relevant radiobiological concepts and data has the potential to provide insights about low-dose risk that augment knowledge gained from the empirical epidemiologic data in isolation (NCRP, 2015)."*

The study of bioindicators should not be arbitrarily limited to possible *adverse* outcomes. No rationale for excluding possible protective outcomes consistent with adaptive or hormetic responses is presented.

The NCRP's consideration of confounding also ignores the potential for thresholds:

> *Page 14: "Because a risk factor correlates with a disease (e.g., smoking and lung cancer) does not necessarily mean it confounds the radiation association with that disease. It can confound the radiation-disease association only insofar as the risk factor is also correlated with the amount of radiation exposure".*

While this is strictly true, the Commentary seems to implicitly discount potential biases unless they are correlated with recorded radiation dose. However, the "NT" part of the LNT model can be incorrectly indicated if important sources of radiation dose are neglected, whether they are correlated with radiation dose or not, by shifting the linear part of the dose-response toward the origin. It appears that this possibility

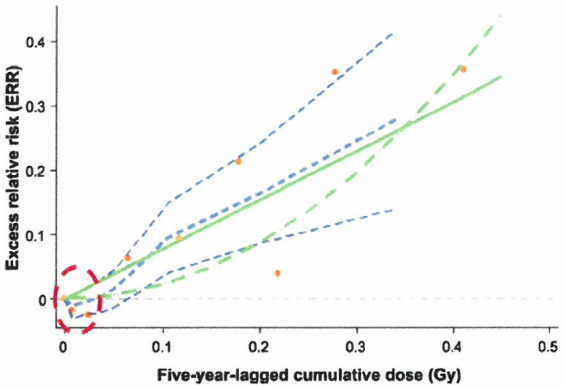

Fig. 6. Techa River solid cancer incidence data from [(Davis et al., 2015) Fig. 1, reproduced as Figure 4.7 in (NCRP, 2018)]. Dashed oval added for emphasis. The authors described this data as, "Solid cancer dose response. All results shown are based on models with adjustment for smoking in the baseline rates. The green lines are the fitted linear (solid) and quadratic (dash-dot-dot) dose-response curves. The orange points are ERR estimates in dose categories while the thick-blue-dashed curve is a nonparametric smooth fit to these points. The outer blue-dashed curves represent approximate (pointwise) 6 standard error limits on the nonparametric smooth". (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

	Leukaemia			
	Total		Without CLL	
Category	Cases	Rate	Cases	Rate
Bone marrow dose (Gy)				
<0.01	12	12	6	6
0.01–0.5	6	5.9	2	2
0.5–0.1	5	9.1	4	7.3
0.1–0.15	4	6.8	3	5.1
0.15–0.3	16	10.7	10	6.7
0.3–0.5	13	10.6	10	8.2
0.5–1	22	14.4	20	13.1
1+	21	19.7	17	16
Total	99	11.7	72	8.5

Fig. 7. Techa River leukemia incidence data from Table 4 of (Krestinina et al., 2013). Dashed ovals added for emphasis.

was not considered.

> *Page 16: "...unshared classical error (i.e., random individual dosimetry error), if present, can bias the dose-response slope toward the null [i.e., zero (Stram et al., 2015); ...]. However, adjustment for shared, Berkson and random measurement uncertainties is unlikely to change a significant dose response to a nonsignificant response (i.e., if the confidence bound for a risk estimate does not include the null value, the uncertainty-adjusted bound usually will not include the null value either)(Stram et al., 2015). There does not seem to be a reasonable case that the positive dose-response associations that are consistent with a LNT model are due to dosimetry inaccuracies, especially for studies with measured doses in individuals".*

The assertion that the effects of dosimetry errors is to bias dose-responses toward the null is based on the implicit assumption that the true underlying dose-response has a LNT form. This assumption is explicitly stated in the reference NCRP cited, (Stram et al., 2015), "In this paper we derive expected scores and the information matrix for a model used widely in radiation epidemiology, *namely the linear excess relative risk (ERR) model that allows for a linear dose response (risk in relation to radiation)* and distinguishes between modifiers of background rates and of the excess risk due to exposure" (emphasis added), however this LNT assumption is not disclosed in (NCRP, 2018). It is not clear that this assertion is accurate when the true underlying dose-response has a different form (*e.g.* linear with threshold, or hormetic), and is inappropriately modeled with a LNT dose-response. This section of text ignores the possibility that evidence of a threshold can be erased by omitting important sources of exposure.

> *Page 18: "The statistical precision of a study is a key determinant of the study's contribution toward evaluating the shape and slope of the dose response risk for detrimental health outcome".*

Statistical precision of a study would also be a key determinant of the study's contribution to an unbiased evaluation of all alternative hypotheses – including a hormetic dose-response – not just for determining the slope of a LNT model. This possibility doesn't seem to have been considered by the NCRP.

> *Page 18: "To assess the main dose-response model, functional forms such as linear, quadratic, linear-quadratic, nonparametric, categorical (the risk in each category of a set of predefined dose categories), and dose threshold ideally should be examined".*

The NCRP arbitrarily excluded the possibility of a hormetic dose-response, without explanation.

Cherry-picking by ignoring the possibility of nonlinear dose-responses was evident in the NCRP's evaluation of other studies too:

> *Page 39: The Commentary asserts that the Rocketdyne study, "Couldn't evaluate shape of dose response because risk estimate was negative for solid cancer".*

A negative risk estimate does not prevent an evaluation of the shape of the dose-response. It suggests a hormetic model. This possibility was omitted and apparently not considered.

As previously mentioned, the NCRP's evaluation of the LSS data inappropriately set the LNT up as the null hypothesis. The evidence for thresholds in the LSS data was also dismissed and even ignored:

> *Page 45: "The estimated lowest dose range with a significant ERR for all solid cancer was 0–0.20 Gy, and a formal dose-threshold analysis indicated no threshold; i.e., zero dose was the best estimate of the threshold".*

> *Page 48: "The LSS cohort of atomic-bomb survivors has provided important data because it is a large cohort with accurate dosimetry, a wide dose range, all ages at exposure and over 60 y of high quality mortality follow-up, a relatively large number of excess solid-cancer cases (992) and cancer deaths (527), and features that enable relatively high statistical power and precision of risk estimates, including a statistically significant dose response, not adjusted for smoking, for all incident solid cancer over the dose range 0–100 mGy (or significant for the range 0–200 mGy in the mortality data)"*

> *Page 49: "A pure quadratic model provided a significantly poorer fit to the dose-response data than a linear model for both solid cancer incidence and mortality, and there was no evidence of a significant dose-response threshold for either endpoint".*

> *Page 49: "An analysis of the most recent mortality data indicated excess risk over the range of 0–200 mGy that was congruent with the LNT slope, and the new tumor incidence data showed a statistically significant dose response slope over the range of 0–100 mGy".*

Page 49: "...the [LSS] study provides strong indirect support for the use of a LNT model, with consideration of a DDREF factor, for use in radiologic protection".

The authors concluded, "...a formal dose-threshold analysis indicated no threshold; *i.e.*, zero dose was the best estimate of the threshold" (Ozasa et al., 2012a, 2012b). Reviewing the threshold analysis conducted by the authors of the LSS cohort (Ozasa et al., 2012a, 2012b), others found that the LSS authors excluded the possibility of negative risk values despite eight of the ten lowest data points having confidence intervals including negative values. Alternative analyses that did not exclude negative values were consistent with a nonzero threshold (Doss, 2012; Sasaki et al., 2014; Siegel and Welsh, 2015; Socol and Dobrzynski, 2015; Ulsh, 2015). The NCRP did not acknowledge or address these alternative analyses. A threshold model is also consistent with both the latest solid cancer incidence and mortality data, yet the Commentary's language here shows a confirmation bias favoring the LNT.

The NCRP also ignored criticisms of some of the other studies it cited. For example, considering a meta-analysis of thyroid cancer risks, the NCRP stated,

Page 5: "A recent pooled analysis of external thyroid irradiation in childhood and subsequent thyroid cancer in nine studies showed a significant dose response from 0 m to 100 mGy and no evidence of non-linearity (Lubin et al., 2017)".

Page 105: "The analyses reported in the Lubin et al. (2017) paper provide strong support for use of the LNT model. They indicate that, at least for the association of radiation with thyroid cancer, there is a statistically significant dose-response over the restricted range of 0 – 100 mGy that is compatible with linearity. This is strongly supportive of the use of the LNT model as prudent for radiation protection."

Page 105: "A dose-threshold analysis showed a maximum likelihood at 0 mGy and had a threshold upper bound of 40 mGy".

Page 126: "A pooled analysis of studies of childhood external irradiation and thyroid cancer also showed a significant dose-response association over the dose range of 0–100 mGy (Lubin et al., 2017)".

The study by Lubin discusses thyroid cancer incidence, which is very vulnerable to overdiagnosis and a screening effect (Takano, 2017). In the aftermath of a widespread radiation exposure, public health responses sometimes include mass thyroid screenings. The screening programs detect previously occult thyroid nodules that naturally existed in the population unrelated to the radiation exposure, that are mistakenly attributed to the radiation exposure upon detection. The incidental observation of thyroid nodules can trigger additional diagnostic imaging and lead to subsequent diagnosis of thyroid cancer, even though the relationship between thyroid nodules and lethal thyroid cancer has not been definitively established. This situation occurred in the aftermath of the Fukushima accident (Cuttler et al., 2017; Yamashita et al., 2018).

Since no cost-benefit analysis or optimization study of the LNT model was presented, it says nothing whatsoever about the prudence of using the LNT model for radiation protection (See Section 7).

Seven of the nine data points less than 100 mGy presented in (Lubin et al., 2017) have confidence intervals that include a relative risk value of 1.0 (Fig. 8, upper panel), and visual inspection of the cubic spline fit appears to indicate a slightly negative slope at low doses (Fig. 8, lower panel). Therefore the data over the restricted range of 0–100 mGy is compatible with a threshold, which corresponds to the null of no effect. This is not strongly supportive of the use of the LNT model.

Furthermore, (Lubin et al., 2017) state, "Estimates of threshold dose ranged from 0.0 to 0.03 Gy, with an upper 95% confidence bound of 0.04 Gy". (Lubin et al., 2017) further states,

"We examined deviances to estimate threshold dose (h). For, 0.2 Gy, deviances (open circle) and a moving-average smoothing (solid line) increased (*i.e.*, poorer fit) with possible threshold values, with minimum deviance (star symbol) at 0.00 Gy (Fig. 2, main panel). Deviances changed little through 0.02 Gy. For, 0.1 Gy, the minimum deviance occurred at 0.025 Gy, with no change through 0.03 Gy (inset panel), indicating limited ability to identify a specific threshold. One-sided upper 95% CIs were 0.036 for, 0.2 Gy and 0.044 for, 0.01 Gy (dash line)."

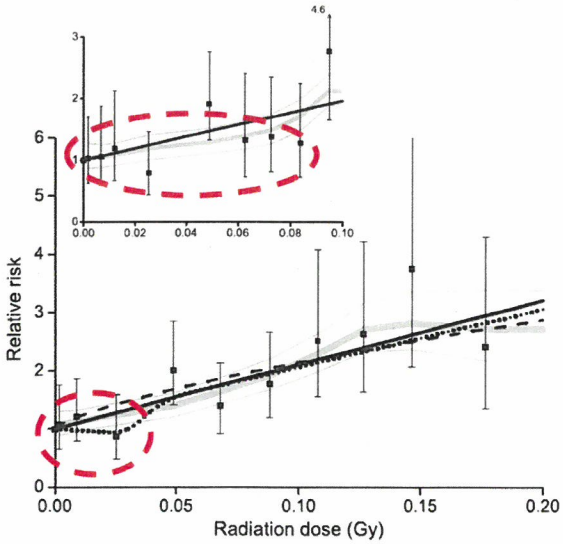

Fig. 8. Data from [(Lubin et al., 2017), Fig. 1, which was reproduced as Figure 4.9 in (NCRP, 2018)]. Dashed ovals added for emphasis. The authors described this data as, "Category-specific RR of thyroid cancer by thyroid radiation dose (solid symbol) with 95% CI, a moving-average smoothing (gray line) and standard deviation (thin gray line), the fitted linear ERR model (solid black line), and a restricted cubic spline (dash-dot-dot line). Data pooled from nine cohort studies and limited to, 0.2 Gy (main panel) or, 0.1 Gy (inset). Also, the linear-exponential-linear model...fitted to all data with the full range of doses (dash line)".

An examination of Fig. 9 reveals approximately equal deviances up to perhaps 0.03 Gy (estimated by visual inspection), which is consistent with a nonzero threshold.

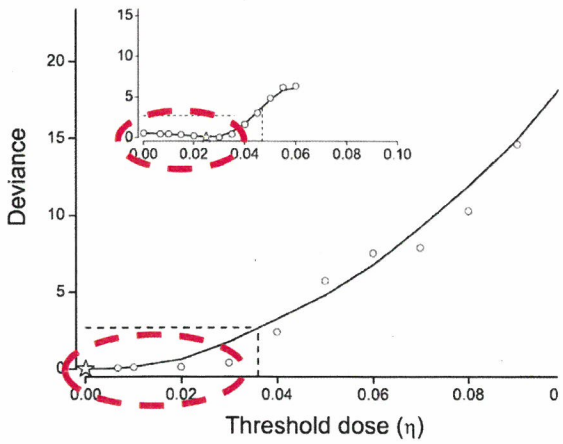

Fig. 9. Data from [(Lubin et al., 2017), Fig. 2]. Dashed oval added for emphasis. The authors described this data as, "Deviances for linear ERR models given a threshold dose (h) (open symbol) (see text for model), with deviances rescaled to zero at the minimum deviance (star symbol) and a moving average smoothing. Dash line identifies one-sided 95% confidence limit. Data pooled from nine cohort studies and limited to ,0.2 Gy (main panel) and ,0.1 Gy (inset)".

The NCRP also limits their consideration of future research needs to supporting the LNT:

Page 138: "Information on new and as yet undiscovered biomarkers of radiation risk (rather than of exposure) of cancer or cardiovascular endpoints need to be explored as potential mediators or modifiers of radiation effects…These could eventually be built into the statistical analysis of cancer risk at low doses. Analyzing epidemiologic data in conjunction with relevant radiobiological concepts and data also has the potential to provide insights into LNT that go beyond those gained from merely analyzing the empirical epidemiologic data in isolation …".

Current radiobiological data [*e.g.* (Feinendegen, 2016; Luckey, 1980, 1991)] suggest the possibility of thresholds and/or hormetic dose-response models, yet this Commentary has dismissed threshold models, and ignored hormetic models. Radiobiology has the potential to provide insights into low dose, low dose-rate biological effects (Paunesku et al., 2017) – not just into the LNT model – and those insights should inform future epidemiological studies to incorporate appropriate study designs which will allow for rigorously testing any plausible dose-response hypothesis (Sacks et al., 2016). Arbitrarily limiting this suggestion only to LNT is symptomatic of a pro-LNT bias.

Page 140: "…while some have argued in support of a practical threshold for management of the risk of radiation-induced cancer, epidemiology alone will not be able to resolve the issue of whether there are dose thresholds for radiation risks, thus also supporting the need for further integrated radiobiology and epidemiology research (NCRP, 2015)".

Agreed. Yet (NCRP, 2018) dismissed the radiobiological evidence suggesting thresholds, and completely ignored the radiobiological evidence suggesting hormetic dose-responses [*e.g.* (Feinendegen, 2016; Luckey, 1980; Luckey, 1991)].

5. Suppression of evidence: ignoring criticisms and limitations

Numerous criticisms of the studies cited by (NCRP, 2018) have been published, alleging serious methodological problems, and identifying numerous examples where conclusions supporting the LNT model are more enthusiastic than the underlying data warrant. By and large, these criticisms were not acknowledged or cited in (NCRP, 2018). Examples include:

Page 3: "INWORKS: Large studies that combine data from workers from numerous nuclear installations in a number of countries have been conducted …. An important study is the INWORKS, which included ~308,000 workers from nuclear facilities in France, the United Kingdom, and the United States and ~18,000 solid cancer deaths… INWORKS found an association between the cumulative external photon dose to the red bone marrow (RBM) and mortality from non-chronic lymphocytic leukemia (CLL) with an excess relative risk (ERR) Gy…$^{-1}$ of 3.0, 90% CI: of 1.2–5.2 (90% CI: 1.2, 5.2). External dose to the colon (used as the prototypic organ) was associated with mortality from all solid cancers combined (ERR Gy^{-1} of 0.47; 90% CI: 0.18, 0.79). For solid cancer there was no evidence of nonlinearity ($p = 0.44$). These risk estimates were similar to those in the LSS data. Even when the cumulative colon dose was restricted to 0–100 mGy, a marginally statistically significant dose response was seen for all cancers excluding leukemia. These results in the low dose range, however, might be interpreted with some caution because statistically significant risks were seen for cancers not convincingly linked to ionizing radiation (such as the testis, rectum and peritoneum), positive associations reported for asbestos-related cancers (pleura and mesothelioma), and puzzling results regarding neutron exposures (Richardson et al., 2018; UNSCEAR 2008)".

Page 9: "…few studies have analyzed radiation risks with control for possible confounding by lifestyle (e.g., smoking), other disease risk factors or other sources of radiation exposure; these factors may diminish the consistency of findings. Nevertheless, it should be emphasized that lifestyle or other disease risk factors will cause confounding only if their frequency (or intensity) varies appreciably according to dose".

Page 17: "On the other hand, if individual doses were imputed based on a dose reconstructions from limited information, there may be unknown biases in the shared-dose estimates, but dosimetrists involved in the major studies have devoted much effort to providing reasonably accurate estimates of shared doses".

Page 18: "Interpretation, however, becomes difficult if the organ dose from other exposures exceeds the gamma ray dose".

Page 49: "INWORKS found associations between the cumulative dose from external sources of photons to the red bone marrow (RBM) and leukemia (excluding CLL) mortality, ERR Gy–1 = 2.96 (90% CI: 1.17, 5.21), and the external dose to the colon and mortality from all solid cancers combined, ERR Gy–1 = 0.47 (90% CI: 0.18, 0.79). For solid cancer there was no evidence of nonlinearity ($p = 0.44$). These risk estimates are compatible with predictions based upon LSS data."

Page 55: "It is extremely important to pay particular attention to the doses and their uncertainties for the early periods of exposure (1940s and 1950s) when doses tended to be highest, since those with higher cumulative doses tend to drive the analytic results. But this is the period when the least information from the historical records is available, so uncertainties potentially would be the greatest. It is unclear how adequately the investigators surmounted this challenge."

Several methodological issues have been identified with the INWORKS studies (Doss, 2015a; Nagataki and Kasagi, 2015). In addition, no fewer than twelve methodological shortcomings have been identified by (Sacks et al., 2016). In addition to the many methodological shortcomings identified by others, the omission of *occupationally required* medical imaging exams [which are distinct from medical doses received by the public at large through mass tuberculosis screenings (Haygood, 1994)], can result in potentially significant underestimation of external radiation dose (Cardarelli and Ulsh, 2018). None of these issues were discussed or even mentioned in (NCRP, 2018).

Page 53: Of the dosimetry for the INWORKS studies, the Commentary states, "the original dosimetry is mostly inaccessible".

At least for the US sites included in the study, this is not true. In most cases, the original dosimetry for nuclear weapons workers has been collected by the National Institute for Occupational Safety and Health, which is the employer of some of the INWORKS authors.

Page 3: "Overall the nuclear worker studies lend considerable support to the inference that an excess risk of cancer exists following protracted exposure to low doses received at a low dose rate, and the excess risk is compatible with a LNT model", and "the studies provide substantial support for the LNT model".

Page 49: "Overall, the nuclear worker studies lend support to the inference that an excess risk of cancer exists following protracted exposure to low doses received at a low dose rate, and the excess risk is compatible with a LNT model".

Given the significant methodological issues identified in the INWORKS studies, and the results of the Mayak studies, this conclusion is not justified.

Page 60: "Notably, even over the range of 0–100 mGy the risk was marginally statistically significant [using their criterion of $p < 0.05$ on a one-tailed test (i.e., the dose response would not be statistically significant based on a two-tailed test)]".

The fact that the INWORKS studies used a one-tailed test, instead of a more appropriate two-tailed test, demonstrates a bias by arbitrarily excluding the possibility of negative risk estimates. This is not discussed in either the INWORKS study or the Commentary.

Page 139: "Some studies explicitly found risk in the dose range of 100 mGy or less, e.g., the atomic-bomb survivor studies, the INWORKS worker study, and the pooled radiation and thyroid cancer analysis".

The LSS incidence study itself (Grant et al., 2017) concludes, "At this time, uncertainties in the shape of the dose response preclude definitive conclusions to confidently guide radiation protection policies". The Commentary contradicts the authors of the incidence study by concluding that the LSS studies provides strong evidence for the LNT model, when no significant risks were detected below 0.2 Gy (mortality) or 0.1 Gy (incidence), and statistically significant curvature (nonlinearity) was observed. The Commentary ignored significant criticism of the INWORKS study, as detailed above.

Page 37: The Commentary lists the following limitations of the LSS study,

- *"Only one acute, high dose-rate exposure, not protracted exposures.*
- *Study started in October 1950, > 5 y after the bombings, so early data missing.*
- *Possible "healthy survivor effect," particularly at high doses.*
- *Low proportion of men of military age.*
- *Malnourished Japanese population at time of bombing and for several years thereafter.*
- *Retrospective dosimetry, no personal measurements, and some doses uncertain.*
- *Incidence data for solid cancer available only beginning 13 y after exposure.*
- *Out-migration: could not ascertain tumor incidence outside of Hiroshima and Nagasaki prefectures, but mortality data available for all of Japan.*
- *Curvature for incidence data is attributable to male data in the range of 0.2 – 0.75 Gy, not for 0 – 0.2 Gy; reasons for that unclear.*
- *Curvature for mortality data is seen over 0 – 2 Gy range."*

Page 45: "The Hiroshima and Nagasaki city/prefecture (regional) tumor registries provide high-quality tumor incidence data. Limitations are that such data are available only since 1958 and only for the two prefectures, but AHS participation data provide a way to estimate the prefecture out-migration rates by age, sex, and temporal period, so the incidence denominators are adjusted for population migration… Sociodemographic variations, such as urban/rural differences, have been examined to a limited extent… Background disease rates in Japan have historically differed from those in western populations [e.g., higher Japanese rates of stomach cancer, liver cancer, and stroke; lower rates of breast cancer, colon cancer, and ischemic heart disease (IHD)], which creates uncertainties about how to extrapolate atomic-bomb survivor risk estimates to western populations. This has usually been approached as an across-the-dose-range generalization issue [e.g., ERR versus excess absolute risk (EAR) extrapolation], and there is no information about how disparate background disease rates of variant lifestyles might affect low dose risk estimation."

Page 46: "Examination of the dose response for the full dose range or the 0–2 Gy range suggests that excess risk was relatively depressed compared to the linear model over the range of roughly 0.2–0.7 Gy for unknown reasons…"

The Commentary does not discuss that the LSS dosimetry included only acute gamma and neutron exposures, while the role of other bomb-caused factors, *e.g.* fallout (Sutou, 2017), induced radioactivity, thermal radiation (UVR), electromagnetic pulse (EMP), and blast, were excluded (Aleta, 2009). Thermal radiation, EMP, and blast had a distribution pattern similar to radiation dose (decreasing with distance from the hypocenter) (Evans, 1950; Pearse and Payne, 1949), and could therefore reasonably be suspected of introducing unaccounted biases.

An explanation for the observed depression in risk from 0.2 G to 0.7 Gy has been proposed by (Doss, 2013),

"In calculating the ERR values, the authors did not use a zero dose cohort as a baseline group since even the lowest dose cohort had some exposure to the atomic bomb radiation (See Table 1 of the report) (Ozasa et al., 2012). Instead, they fitted the cancer mortality data for all the different dose cohorts using ERR in the form of a linear (or linear plus quadratic) function of dose multiplied by an effects modification factor to account for other variables such as age, sex, *etc.*, and extracted the ERR values from the fit to the whole dataset (see page 231 of the report) (Ozasa et al., 2012). In this procedure, the cancer mortality rates of the lowest dose cohorts effectively determined the baseline cancer mortality rate through linear extrapolation to zero dose. If the low dose radiation cohorts had reduced cancer rates compared to the baseline cancer rate due to radiation hormesis, then this procedure would introduce a negative bias in the baseline cancer rate, since the lower cancer rates at low doses (extrapolated to zero dose) would effectively be used as the baseline cancer rate during the fitting process."

The Commentary ignored this possible explanation, and instead asserted that the explanation was unknown. This is misleading.

Page 48: "The upward curvature seen in males does not necessarily argue against LNT; it may rather suggest a LDEF > 1, i.e., a lower slope at low doses than at high doses".

The data exhibits significant curvature and this most certainly does argue against the LNT. It is consistent with the radiobiological data suggesting qualitatively different responses to high doses and low doses. The fact that the Commentary explains away these results to preserve the LNT, while ignoring a plausible explanation proposed in a peer-reviewed paper (Doss, 2013), suggests pro-LNT confirmation bias.

The NCRP also evaluated the 15-country study:

*Page 51: "…there are concerns about doses recorded during early time periods of the study, especially between 1944 and 1957 when annual recorded doses tended to be higher than in later years and major changes were occurring in dosimetry measurement technology and administrative practices. Furthermore, the impact of neutron dose and internal dose on the dose response is not clear, and there is a distinct possibility that better accounting of these doses could affect the estimates of risk. The methods of accounting for doses that were below the limits of detection were another source of uncertainty. In summary, although the 15-Country Study dosimetry effected a significant improvement in the overall dose estimates, questions of underestimation of dose due to missed dose, neutron dose, and internal dose remain, as acknowledged by the dosimetry investigators (*Thierry-Chef et al., 2015*)."*

One issue not mentioned by the NCRP is the failure to account for doses from medical screening required as a condition of employment, resulting in potentially significant underestimation of external radiation dose, as discussed for the INWORKS study above (Cardarelli and Ulsh, 2018). Neglecting this important source of exposure seriously compromises the conclusions of the 15-country study.

6. Circular reasoning: incorporating implicit assumptions that favor LNT, then claiming evidence supports LNT

All scientific studies necessarily include initial assumptions. But problems arise specifically with radiation epidemiology studies when practices, often implicitly accepted without discussion, favor or even dictate a LNT outcome, and the study is subsequently cited as supporting the LNT model. This is an example of circular reasoning (Dowden, 2018), and has the effect of concealing possible thresholds or hormetic outcomes, and/or inflating risk estimates.

A particularly pernicious example of circular reasoning is assuming (without evidence) that null results (*i.e.* risks not significantly different from zero) are the result of statistical imprecision (Sacks et al., 2016). While this is certainly possible, the most parsimonious explanation, indeed the scientifically correct but frequently ignored conclusion, is that the data are insufficient to reject the null of absence of risk,

therefore the null stands.

Examples of circular reasoning in (NCRP, 2018) are provided below:

Page 4: Discussing Chernobyl thyroid cancer data, the Commentary states,

"Both cohorts showed strong linear dose-response functions with no evidence of nonlinearity, though perhaps with a somewhat lower risk per unit dose than seen in studies of children exposed to external gamma radiation. The thyroid doses are believed to be sufficiently accurate to support a LNT interpretation."

The data presented in (Brenner et al., 2011) reveals that the authors used Poisson regression and assumed a linear excess risk model (they also mention linear-exponential and linear-quadratic models). They make no mention of testing for a threshold. Furthermore, they state, "The fitted linear dose response was adjusted to pass through the lowest I-131 category", which arbitrarily disallows a threshold, even if there was one. So there is no basis for concluding that this study provides evidence against a threshold. The study also lists 11 dose categories, but no tabular results of risk by dose category are provided. The graphical presentation of results [shown as Fig. 1 in (Brenner et al., 2011)] only shows six data points. The graph provides no error bars for thyroid dose, and the paper states that even though dose uncertainties were calculated in previous papers (with GSDs ranging from 1.6 to 5.0), the arithmetic mean of thyroid doses were used, presumably as a point estimate. Therefore the basis for the Commentary's conclusion that the thyroid doses are sufficiently accurate to support a LNT interpretation is not obvious.

Pages 9, 139: "Because individual studies with low doses (less than 100 mGy) almost inevitably have relatively low statistical power, the findings for radiation and solid cancer are often not statistically significant".

Lack of statistical power is one possible explanation for null findings. However, the most obvious and parsimonious explanation is to accept the null hypothesis that there is no effect at low doses unless the evidence is sufficient to reject the null in favor of a nonzero risk. The fact that this explanation is not even mentioned is an example of pro-LNT confirmation bias. The Commentary provided no evidence to definitely conclude that the failure to observe risks at low doses is due to statistical imprecision, rather than to a real absence of a risk.

Page 18: "In the baseline model it is usually appropriate to adjust for sex, age at exposure, attained age, and sometimes calendar period or birth cohort to avoid confounding, as well as to explore whether those variables may be effect modifiers of the radiation dose response. When information on smoking, alcohol-intake, or other lifestyle or socio-demographic factors is available, it is important to examine whether it may be a confounder or an effect modifier... Sometimes it may be appropriate to adjust for factors such as duration of employment in worker studies, and medical risk factors (e.g., obesity or diabetes) for some types of outcomes such as CVD."

This section of the Commentary omits the importance of uncertainty in study-derived estimates in baseline risk compared to actual population baseline risks. Failing to account for this can lead to spurious estimates of risk increases incorrectly attributed to radiation exposure (Scott, 2016).

Page 139: "It is important to point out that there may be a DDREF involved that is greater than one, so that the LNT does not imply a single straight-line proportionality of effects from high, acute doses to low doses and/or low dose rates".

By definition, the LNT hypothesis certainly does imply "a single straight-line proportionality of effects from high, acute doses to low doses and/or low dose rates". The DDREF is an external, post-hoc manipulation factor applied to the data because the LNT model doesn't fit the low-dose data. If the LNT model were accurate and sufficient, no DDREF would be necessary.

7. Policy judgements without foundation

The suitability (or lack thereof) of the LNT model as an alternative scientific hypothesis is distinct from its use as a radiation protection instrument. In fact, it has been argued that even if the underlying dose-response relationship is nonlinear, the LNT model is still appropriate for use in radiation protection based on practicality (Breckow, 2006), a characterization the NCRP has embraced.

It is true that the LNT is easy to use, as it allows for the additivity of doses received in different exposure scenarios (*e.g.* an acute, external exposure *versus* a chronic, internal exposure) or at different times. However, the assertion that applying the LNT is more practical than applying other alternative dose-response models, especially a threshold, is simply stated *prima facie* in (NCRP, 2018). No supporting evidence was provided to support this claim. The NCRP goes further, and judges the use of the LNT model as prudent without providing the necessary cost-benefit analysis required to support such a claim. The prudence of applying the LNT model for radiation protection is certainly debatable, as the experiences at Chernobyl and Fukushima amply demonstrate (Gonzalez et al., 2013; Jaworowski, 2008; Siegel et al., 2017b; Thomas, 2017; Thomas and May, 2017; Waddington et al., 2017b; Yumashev et al., 2017). Such challenges to the prudence of the current reliance on the LNT model for radiation protection are worthy of discussion. However, such a discussion is completely absent from (NCRP, 2018). Examples of unfounded policy judgments in (NCRP, 2018) are provided below:

Page 9: "...no alternative dose-response relationship appears more pragmatic or prudent for radiation protection purposes than the LNT model".

Page 9: "While the ongoing development of science requires a constant reassessment of prior and emerging evidence to assure that the approach to radiation protection is optimal, though not necessarily perfect, NCRP concludes that, based on current epidemiologic data, the LNT model (perhaps modified by a DDREF) should continue to be utilized for radiation protection purposes".

Page 10: "For over 40 y the linear nonthreshold (LNT) dose-response model has been used to develop practical and prudent guidance on ways to protect workers and the general public from the potential harmful effects of radiation while, at the same time, balancing the beneficial, justified, and optimized uses of radiation in our society. The LNT model is practical because a linear relationship is easy to apply, and prudent because it is unlikely to underestimate risk at low doses".

The Commentary presented no cost-benefit analysis, or any other evidence, to support this assertion that LNT is pragmatic or prudent. Without such an analysis, this conclusion is not supported. It is no longer possible to simply accept pronouncements of the pragmatism, and especially the prudence of the LNT model as the basis of radiation protection when such assertions are contradicted by recent retrospective analyses of the responses to the Chernobyl and Fukushima accidents. According to the fundamental principle of justification, radiation protection measures should do more good than harm (ICRP, 2007). But in both of the real-world examples of large-scale radiological incidents, the accidents at Chernobyl and Fukushima, the LNT model has been applied to calculate hypothetical risks from low radiation exposures, and the resulting responses have been problematic (Gonzalez et al., 2013; Socol et al., 2013), and done more harm than good (Higson, 2014; Thomas, 2017; Thomas and May, 2017; Waddington et al., 2017a, 2017b; Yumashev et al., 2017). Ignoring the lessons from the Chernobyl and Fukushima accidents, and continuing to assume the prudence of the LNT model in spite of the demonstrated negative public health consequences is no longer defensible. Similarly,

the NCRP's assertion that the LNT model is prudent because it is unlikely to underestimate risk is incompatible with the latest guidance in (ICRP, 2018), which although it asserts the prudence of the LNT model (a position with which I disagree), notes that,

> "…there are remaining uncertainties at low levels of exposure that necessitate value judgements. Decision making requires prudence as a central value. However, *prudence should not be taken to be synonymous with conservatism* or never taking risks". (emphasis added)

> *Page 139: "The most recent epidemiologic studies show that the assumption of a dose-threshold model is not a prudent pragmatic choice for radiation protection purposes".*

This conclusion is unsupported. Table 4.3 of (NCRP, 2018) lists five of 19 (26%) studies that putatively considered possible thresholds, including the INWORKS studies. However, neither the INWORKS solid cancer study (Richardson et al., 2015) nor the INWORKS leukemia study (Leuraud et al., 2015) reports a threshold analysis. Therefore, only four of 19 studies (21%) analyzed for a possible threshold, and 15 of 19 (79%) did not. The NCRP's review cannot be considered informative about thresholds, given 79% of the studies evaluated didn't even consider the possibility of thresholds. Furthermore, the Commentary did not contain any cost/benefit analysis of a threshold model as a prudent and/or pragmatic choice for radiation protection purposes, nor did it conduct any optimization analysis demonstrating the superiority of the LNT model relative to any of the other alternative models (ICRP, 1992). In the absence of such an analysis, this conclusion lacks scientific foundation.

8. Conclusion

Reliance on preconceived biases and logical fallacies was evident even as early as the BEAR I Committee itself. The geneticists on the panel came into the study convinced of the correctness of the LNT model, and fiercely determined that the recommendations of the committee should not convey that there was any safe dose of radiation, an idea at odds with their opposition to nuclear weapons testing (Hamblin, 2007). The fateful 1956 decision by the BEAR I Committee to embrace the LNT model in controversial circumstances began six decades of intellectual investment by advisory bodies in this dose-response model. Unfortunately, advisory bodies have adopted the role of *advocates* of the LNT model, rather than serving as neutral skeptics (Mossman, 2009) objectively testing and evaluating multiple plausible alternative hypotheses. Just eight years after BEAR I accepted the LNT model, (Platt, 1964) cautioned against the practice of becoming too attached to any particular scientific model. Platt quoted T.C. Chamberlain,

> "Chamberlin says our trouble is that when we make a single hypothesis, we become attached to it. The moment one has offered an original explanation for a phenomenon which seems satisfactory, that moment affection for his intellectual child springs into existence, and as the explanation grows into a definite theory his parental affections cluster about his offspring and it grows more and more dear to him…There springs up also unwittingly a pressing of the theory to make it fit the facts and a pressing of the facts to make them fit the theory…To avoid this grave danger, the method of multiple working hypotheses is urged. It differs from the simple working hypothesis in that it distributes the effort and divides the affections…Each hypothesis suggests its own criteria, its own means of proof, its own method of developing the truth, and if a group of hypotheses encompass the subject on all sides, the total outcome of means and of methods is full and rich."

The advisory bodies following BEAR I have fallen into the trap of defending LNT model against its critics, rather than performing rigorous hypothesis testing designed to challenge various alternative hypotheses (*e.g.* LNT, linear with threshold, hormetic, supralinear, *etc.*).

The stated intention of the NCRP's latest commentary "…is to determine whether these epidemiologic studies broadly support the LNT model of carcinogenic risk as used in radiation protection or, on the contrary, whether there is sufficient evidence that the LNT model is inappropriate". Because of the inherent shift of the burden of proof in this stated purpose, the actual effect of (NCRP, 2018) will be to provide political cover for regulators' ongoing reliance on the LNT model to predict LDDR effects (Sacks and Siegel, 2017). This is a missed opportunity for an objective analysis of the effects of low dose, low dose-rate radiation effects, and it is unlikely to advance our understanding of this important topic or convince skeptics of the validity of using the LNT model as a tool for radiation protection. To make progress in this long-running debate, I recommend that the next expert review on the topic of LDDR effects:

1. Appropriately frame the null hypothesis (no effect of radiation on cancer risk), and various alternative dose-response models (*e.g.* LNT, linear quadratic, linear with threshold, hormetic, *etc.*);
2. Acknowledge and objectively evaluate criticisms of the LNT model as a tool for radiation protection;
3. Acknowledge and objectively evaluate the significant body of evidence suggesting nonlinear dose-response relationships, between particularly LDDR radiation exposures and cancer risk;
4. Consider the entire body of evidence on the topic of health effects of LDDR radiation exposure, explicitly including both biology and epidemiology;
5. Critically evaluate real-world experiences applying the current LNT based system of radiation protection, including appropriate cost-benefit analyses to inform judgments about prudence. To the extent possible, such an evaluation should consider whether or not regulatory strategies based on alternative dose-response models (*e.g.* a linear threshold model) provide superior public health outcomes.

An objective review which incorporated these recommendations by an expert body with the prestige of the NCRP would represent the most significant progress in decades toward bridging a seemingly intractable gap fracturing the radiation protection community. Due to the NCRP's Congressional charter to serve as the nation's pre-eminent source of expert advice on radiation protection matters, no organization is better positioned to conduct such a review. It is my hope that the issues raised in this paper will encourage this critical undertaking.

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Original Article

The Linear No-Threshold Model of Low-Dose Radiogenic Cancer: A Failed Fiction

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Abstract

The linear no-threshold (LNT) model for low-dose, radiogenic cancer has been a fixture of radiation protection and regulatory requirements for decades, but its validity has long been contested. This article finds, yet again, more questionable data and analyses purporting to support the model, this within the "gold-standard" data set for estimating radiation effects in humans. Herein is addressed a number of significant uncertainties in the Radiation Effects Research Foundation's Life Span Study (LSS) cohort of atomic bomb survivors, especially in its latest update of 2017, showing that the study's support of the LNT model is not evidence based. We find that its latest 2 analyses of solid cancer incidence ignore biology and do not support the LNT model. Additionally, we identify data inconsistencies and missing causalities in the LSS data and analyses that place reliance on uncertain, imputed data and apparently flawed modeling, further invalidating the LNT model. These observations lead to a most credible conclusion, one supporting a threshold model for the dose–response relationship between low-dose radiation exposure and radiogenic cancer in humans. Based upon these findings and those cited from others, it becomes apparent that the LNT model cannot be scientifically valid.

Keywords

low-dose radiation (LDR), linear no-threshold (LNT), threshold, Life Span Study (LSS), Hiroshima and Nagasaki atomic bomb survivors, radiogenic cancer, Radiation Effects Research Foundation (RERF), radiation protection, radiation regulatory requirements

Introduction

The linear no-threshold (LNT) model has been a fixture in radiation protection and regulatory requirements for decades, but its validity has long been contested, even repudiated, as a variety of studies clearly demonstrate.[1-5] Support for the LNT model relies on epidemiological studies suggesting its truth, on its acceptance by the BEIR VII Committee, or the Radiation Effects Research Foundation's (RERF) Life Span Study (LSS) of Hiroshima and Nagasaki atomic bomb survivors, considered the "gold-standard" data set for estimating radiation effects in humans.

Many epidemiological studies attempt to justify the LNT model, but a recent article has shown some studies compromise the scientific method, using incomplete data and invalid statistical methods for hypothesis testing, resulting in circular reasoning and rendering their conclusions indefensible.[6] Likewise, a recent study exposes the errors in the BEIR VII Committee Report, invalidating its conclusions in support of the LNT model.[7]

Objectives

This article reviews the LSS data's and analyses' shortcomings and inconsistencies, demonstrating their failure in applying the LNT model for low-dose radiation (LDR). The LSS data analyses generally concentrate on atomic bomb radiation exposure as a cause of cancer incidence or mortality, and RERF analyses seem to miss relevant, published data reflecting known biology regarding various other significant causalities likely far more responsible for carcinogenesis than LDR exposure. As we illustrate, the assumed low-dose cancer risk is not probable; the dose–effect relationship is nonlinear and the risk estimates exhibit large uncertainties, which include negative values.

The other causalities include extensive and long-term incidence of tobacco smoking, severe physical and psychological stress and distress, and widespread infectious diseases and

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dietary/physical conditions that have plagued Japan for decades. We appropriately account for these causalities and attempt to demonstrate that hypothetical solid tumor cancer risk attributed to LDR is not probable, potentially supporting, not the LNT model, but rather a hormetic one.

We first discuss the latest 2 analyses of solid cancer incidence among the LSS cohort, which do not support the LNT model, then consider the error of biologic omission, and briefly note that longevity may be a better measure of LDR health effects than cancer mortality. Finally, we consider some inconsistencies, errors, and missing causalities in LSS data and analyses that show RERF places reliance on uncertain, imputed data and apparently flawed modeling requiring correction, which further invalidates the LNT model.

Methods to Evaluate LSS Solid Tumor Cancer Data and the LNT Model

What the LSS Data Have Been Telling Us

Three analyses exist for solid cancer incidence among the LSS cohort of atomic bomb survivors in Hiroshima and Nagasaki. Comprehensive analyses of solid and hematopoietic cancer incidence data among the LSS cohort with follow-up through 1987 were first reported in 1994, then updated through 1998 in 2007, and again updated recently through 2009 in 2017. Below, we focus on the last 2 analyses, illustrating nonlinearity at low doses, thereby invalidating the LNT model.

(1) LSS data for solid cancer from 1958 to 1998 as presented in the RERF website (www.rerf.or.jp/en), see Figure 1, and as reported by Preston et al[8] and later reanalyzed by Furukawa et al.[9]

Furukawa et al[9] analyzed the LSS data employing a semiparametric, dose–response model that assumes no specific, parametric function form. Compared to the conventional LNT model, the semiparametric model estimated smaller risks with wider confidence interval estimates at low doses, indicating no clear evidence of an increased risk up to 100 mGy of exposure. Furukawa created an expanded graph (doses from 0 to 0.4 Gy) to better illustrate the low-dose data points, since they are obscured when examining the dose response over the entire dose range. This graph, modified by us to show only the reported low-dose solid cancer data points without the superimposition of the Furukawa models, is shown in Figure 2.

When focusing on the low-dose data, the dose response is neither as positively sloped as the high-dose data nor linear, even suggesting a hormetic response. The LSS data that have been touted as supporting the LNT model for years, in fact, do not—4 of the 5 excess relative risk (ERR) values (for solid cancer) below 100 mGy are less than 0, with a fit having negative slope, supporting a hormetic model. This is worth repeating—the ERR values, for the most part, are negative below 100 mGy, and this has generally been ignored or dismissed. Our independent analysis of these same LSS data confirmed these findings; as illustrated in Figure 2, positive-sloped linearity at low doses does not exist; rather, it is forced by the high-dose extrapolation of the LNT model.[4]

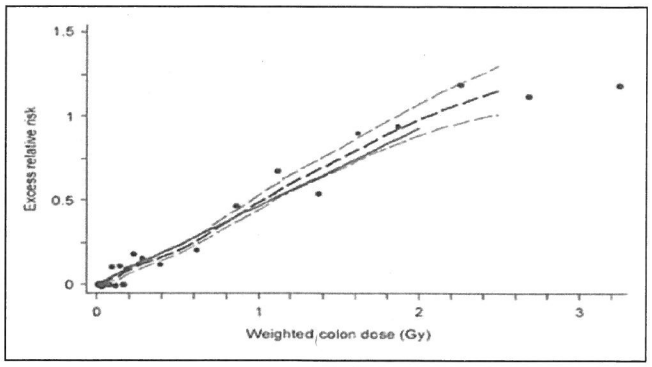

Figure 1. LSS solid cancer incidence, excess relative risk (ERR) by radiation dose, 1958 to 1998, using DS86 dosimetry system.[8] Note that doses <0.1 Gy appear to have ERRs <0. LSS indicates Life Span Study.

(2) LSS data from 1958 to 2009, latest update, and analysis of LSS data as reported by Grant et al.[10]

This study provides the most recent analyses of solid cancer incidence among the LSS cohort through 2009 using a revised dosimetry system (DS02R1). The dose response for males confined to the low-dose range (0-<200 mGy) is shown in Figure 3.

It is apparent again that when focusing only on low-dose data (<200 mGy), the dose response is not linear with a positive slope, invalidating the LNT model. Therefore, based on these studies, the dose–effect relationship is nonlinear and the risk estimates exhibit large uncertainties that include negative values. This clearly indicates the conventional wisdom is wrong—the associated cancer risk estimates are overly conservative and incorrect, invalidating the LNT model for predicting solid cancer risk in the 0 to 100 mGy dose range.

For completeness, a 2012 study by Ozasa et al reported and analyzed solid cancer mortality, as opposed to incidence, among the LSS cohort using the DS02 dosimetry system,[11] again exhibiting nonlinearity at low doses; in fact, statistically significant curvature at low doses was observed. It is apparent from Ozasa's Figure 4 that not only are the uncertainties extremely large for the ERR values, but these values are lower at high doses and higher at low doses when compared to the incidence dose–response data exhibited in Figure 1; the reason for both these latter findings is not well understood and has never been adequately described.

Mortality follow-up data have been reported 14 times since 1961, but, according to Grant et al,[10] these data, although highly valuable, do not provide adequate information on less fatal cancers. The LSS cancer incidence data enable risk estimates for both fatal and nonfatal cancers with better diagnostic accuracy and disease onset date.

Biology Matters: Modeling Must Follow the "Rules of Boxing"

The phrase "rules of boxing" was first presented in another publication[12] and simply expresses the "rules" for the proper

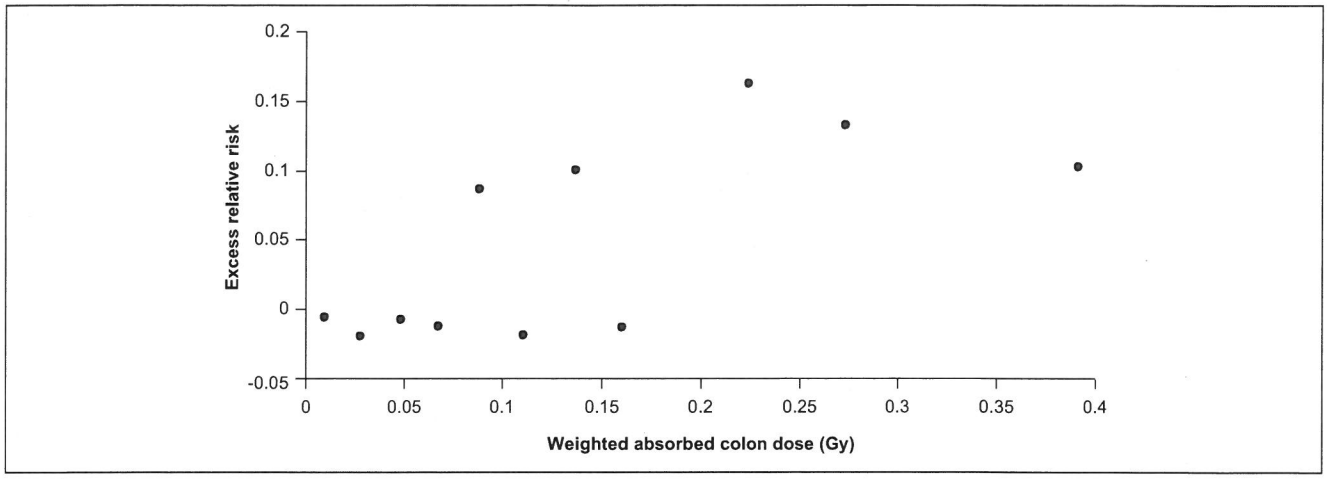

Figure 2. LSS solid cancer incidence in the 0 to 0.4 Gy dose range derived from that reported by Furukawa.[9] LSS indicates Life Span Study.

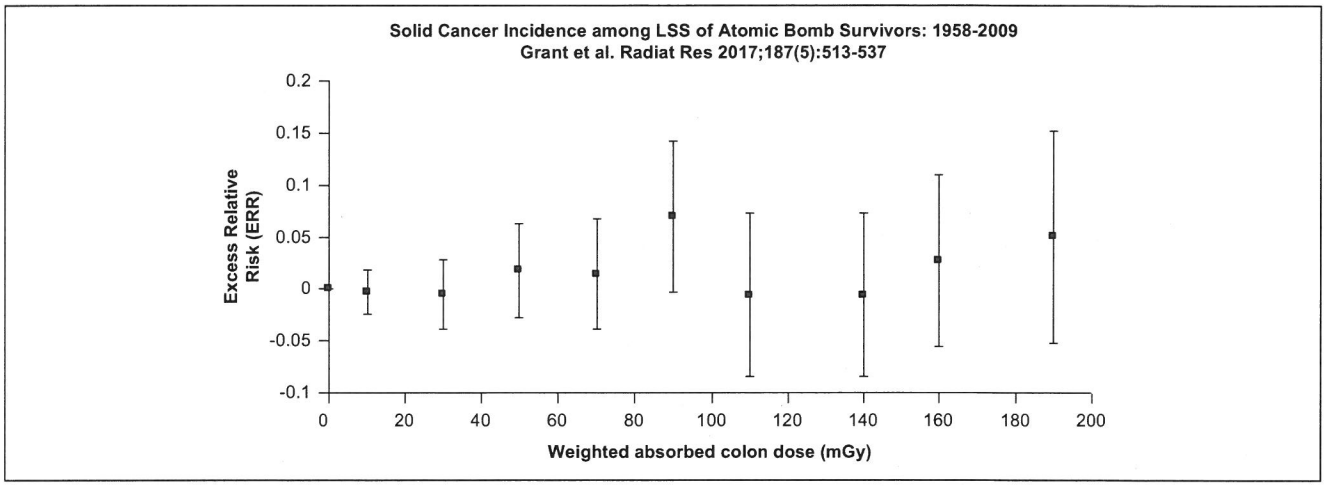

Figure 3. LSS data derived from Grant's reported data in Appendix Table E1.[10] ERR values are shown with 95% confidence intervals, indicating large uncertainties. LSS indicates Life Span Study; ERR, excess relative risk.

grouping (or binning) of dose–response data. Models explain the dose–response relationship of LDR with cancer incidence to reflect physical processes (rules) occurring in the range of data under consideration, which may be termed "the box." If the rules change, so will the resulting pattern of the data, such that some data (eg, low-dose data on the order of less than 200 mGy) belong in one box, while the higher dose data fall into a different box where different rules apply. Researchers often analyze data using statistical methods that inappropriately force the entire dose range's data into one box. The problem is that if one believes all the data fall under one set of rules when they do not (the LNT model problem), one will wrongly sort the data into a single box, yielding a faulty analysis.

At high doses, proven, adaptive, biological responses that reduce both LDR and metabolic damage are suppressed, while at low doses they are stimulated, repairing or eliminating much of all damage.[4,13] The LNT model demands that one box contain all doses, violating these rules of boxing and ensuring modeling linearity. But this is scientifically invalid for predicting LDR responses and precludes discovery of a threshold or hormetic dose–response.

The LSS dose–response data have been updated by the RERF over time, all the while reporting the dose response is essentially consistent with the LNT model down to 0 dose. To be fair, Grant et al[10] did report that for males, significant upward curvature over the full dose range was observed indicating a linear quadratic model is favored over the LNT model, raising unresolved questions. So much so that the authors concluded, "At this time, uncertainties in the shape of the dose response preclude definitive conclusions to confidently guide radiation protection policies."

Still, as shown in Figures 2 and 3, if only the low-dose data points ranging from 0 up to ~400 mGy are examined, these data points do not display the high-dose, positive-sloped

linearity. Positive-sloped linearity at low doses is a fiction forced by extrapolating high-dose data based on the LNT model. If the low-dose data alone are analyzed, it is inescapable that the LNT model is incorrect. By forcing positive-sloped linearity from high-dose data, a no-harm or benefit-inducing threshold is rendered invisible by the preconception that none exists—a self-fulfilling prophecy. Therefore, the LNT model cannot and does not apply to LDR data. This conclusion is a direct consequence of the demonstration that the body responds to LDR exposure by repairing/eliminating any damage,[4] that is, since there is repair, it is unlikely that the LNT model is true. Further, spontaneous biological damage exists, and LDR-induced biological defenses operate on both radiogenic and spontaneous damage. Intact organisms possess a steady state of DNA-damaged cells that permit adaptive processes, stimulated further by LDR, to repair and/or remove, not only most of the added DNA-damaged cells due to the radiation, but also some of the preexisting, steady-state, DNA-damaged cells. The net effect is a decrease in the number of damaged cells relative to the preexposure steady-state number, indicating not only that a threshold exists but that the LDR is also supportive of hormesis. That such repair and/or removal may not be 100% efficient is correct, but it is incomplete when mention of the steady-state preexposure damage level is omitted from the argument.[14]

Results: LSS Solid Tumor Cancer Data Do Not Support the LNT Model

Enough Is Enough

The low-dose, LSS dose–response data set is generally obscured by graphing the full dose range. Any apparent nonlinearity at low doses can then simply be ignored in favor of the unequivocally erroneous observation that the data support the LNT model. The RERF's stated objectives from its Articles of Incorporation include "... to conduct research and studies for peaceful purposes on medical effects of radiation and associated diseases in humans, ..." (https://www.rerf.or.jp/uploads/2017/09/aie.pdf). To this end, the RERF has performed numerous studies calculating what they believe is a certain number of excess cancers, but, as discussed herein, these study results are questionable, as the cancers claimed to be due to radiation exposure are based on use of the LNT hypothesis and various flawed methodologies, including lack of consideration of various other significant causalities likely far more responsible for carcinogenesis than LDR exposure.

To further complicate RERF results, albeit in a more subtle way, its extensive use of ERR versus dose graphs likely shifts (moves) the x-axis right and left and the y-axis, up and down:

1. Doses are associated with large uncertainties—right and left shift. They are not measured but model based, which have changed over the years based on various dosimetry systems (DS)—DS86 to DS02 to DS02R1 (a revised DS02), amounting to an ill-defined (imprecise) shift along the x-axis.
2. ERR values are based on methods used to determine baseline rates that are variable (derived from 0 dose cohorts either not-in-city or in-city for the bombings or based on Poisson regression), causing y-axis shifts.

Incidence and mortality data have both been reported and the DS have been different. If one examines Figure 1 (incidence data by Preston using DS86), one will note that ERR values are <0 for doses <100 mGy. This is more easily appreciated in Figure 2. If one examines Ozasa's Figure 4 mortality data using DS02,[11] the ERR values are greater than 0 in this low-dose range, likely due to using the Poisson regression intercept that has been reported to underestimate the baseline mortality rate; that is, the ERR values are artificially inflated.[3]

Further, the LSS cohort doses may have been underestimated because fallout radioactivity was not accounted for. Sutou has reported that 10% of each bomb blast's energy was residual radiation,[15] the majority of which was fallout. Bomb survivor doses were estimated solely on the basis of initial blast radiation. This could mean LSS doses were underestimated, leading to overestimated cancer risk in the LSS cohort. Sakata et al[16] concede that fallout radiation data and its effects are quite difficult to determine, even over long years of research. They report the findings remain inconclusive, such that the "deleterious health effects from rain exposure immediately after the atomic bombing cannot be completely ruled out."

The final defense of the LNT model is that its "conservatism-derived" policies will be protective. But that has been proven to be untrue, as use of the LNT model has led to ignoring beneficial/no health effects from LDR, and the model's actual risks that are far greater than the hypothetical carcinogenic risk purportedly avoided (eg, radiation fear/fearmongering, degraded radiological imaging, nuclear event evacuation policies, etc, which have produced harmful effects in millions of people).[2,4]

We also note that some have suggested longevity is a better measure of the health effects of radiation than is cancer mortality.[17] As reported in a study by Cologne and Preston,[18]

> The average decrease in life expectancy for those in the Life Span Study cohort with non-zero dose estimates below 1 Gy (mean 0.14 Gy) is about 2 months. For the 40 403 (43%) of exposed survivors in the cohort with non-zero dose estimates less than 0.25 Gy (mean 0.055 Gy), the decrease in life expectancy is estimated as 21 days.

This decrease in 21 days is associated with a reported 95% confidence interval of approximately ± 5 years. The LSS data have indicated that the health effects at low doses are, therefore, not only highly uncertain but also, up to now, provide no documented evidence of either an increase in cancer or a decrease in longevity. Further, as reported by many, LDR effects could hardly have a role in any decreased life

Table 1. Abbreviated Form of Grant et al Table 8.[10] Radiation Dose Response for Both Males and Females: LSS Solid Cancer Incidence Cohort With Known Doses, 1958 to 2009.

Dose (Gy)	Person-Years	Cases	Background	Radiation-Only	AF Radiation (%)	Radiation–Smoking Interaction	AF Radiation–Smoking (%)	Smoking-Only	AF Smoking (%)
<0.005	1 794 130	12 592	10 646	3.3	0	0	0	1857	15
0.1	807 885	5674	4785	82	1	6	0	867	15
0.2	164 111	1217	996	80	7	6	1	179	15
0.5	169 177	1414	1023	188	13	16	1	191	13
1.0	88 992	889	526	228	26	22	2	99	11
2.0	42 236	560	239	211	38	29	5	54	10
2.0+	12 953	192	67	104	54	17	9	16	8
Total	3 079 484	22 538	18 284	895	10	97	1	3263	15 for cases >0.005 Gy

Abbreviations: AF, attributable fraction; LSS, Life Span Study.

expectancy in survivors, due to the physical injuries, burns, biological injuries, poor nutrition, bad hygienic conditions, and special psychological distress that led to early mortality.

Methods to Determine Inconsistencies and Omissions in LSS Data and Analyses

Who Are the Atomic Bomb Survivors?

The survivors of the Hiroshima and Nagasaki bombings are a cohort of special people known as the "hibakusha." They were treated as outcasts, exposed to extreme physical and psychological distress for decades by their countrymen and the occupation forces[19,20] who feared that these sick and injured people might be contagious or carriers of disease. The hibakusha suffered ongoing physical, economic, and emotional abuse arising from social and government discrimination due to society's fears.[21] A mental health assessment of 3756 atomic bombing survivors in 1997 indicated that they suffered from serious psychological distress (SPD).[21] Research in the United States has shown that SPD is a major factor in reduced life expectancy and is therefore likely the foremost contributor to reduced life expectancy within the hibakusha.[22] Adults with SPD have significantly higher age-adjusted death rates compared to those without SPD for each of the 3 leading causes of death: heart disease, cancer/malignant tumors, and assaults/accidents/unintentional poisonings. Low-dose radiation (LDR) cannot account on any biological basis for such reduced life expectancy.

Although the RERF acknowledges the issue,[23] essentially all of the LSS reports have neglected the study of SPD and its effects. Kamiya et al reported in 2016 the potential for increased mortality, but that, although the study of radiation effects has mostly focused on natural science and essentially ignored the psychosocial problems of radiation exposure, most accept the results of the LSS as is "... studies of psychosocial aspects of the bombings were very limited. Although ... bomb-related injuries not caused by radiation might increase mortality risks, the results of the LSS are accepted by epidemiologists worldwide."[24]

However, the Chernobyl and Fukushima Daiichi nuclear power plant accidents provide convincing evidence of adverse psychological effects among people who experienced the trauma of the accidents. Even with estimates of low public doses and health effects, psychosocial problems around these plants have had devastating effects on millions of peoples' lives. Later, we will address this matter further. First, we present our analysis of the effects of smoking on the LSS cohort.

Observations on the Inconsistencies of Data and Analyses Associated With Smoking

For the first time in an LSS update report, the RERF offers tobacco smoking as a cause of cancer incidence among the LSS cohort.[10] Table 8 in that report (see abbreviated form in our Table 1) presents a breakdown of the LSS cohort's solid tumor cases.

All LSS cases are now divided into 4 subsets: those associated with radiation, those that arise only from smoking, those that have radiation–smoking interaction, and those that are background cases and not associated with radiation or smoking. No other causalities are identified, Importantly, radiation-only cases are the sole Table 1 entry that remains a variable in the LSS cohort's solid tumor cancer cases. Corrections increasing the smoking-related cases in the LSS cohort require an in-kind decrease in radiation-only cases. We show corrections resulting from both unreliable smoking data and the smoking model are necessary, thereby eliminating radiation-only cases at low doses. Other corrections imposed by new causalities not likely considered in the background cases, such as stress, also require a diminution in the radiation-only cases, as we show later.

Since the focus here is on LDR effects that the RERF has always insisted arise from the bomb blast radiation, the following applies in the 0 to 0.5 Gy dose range. The total number of solid tumor cases is 20 897: Of these, 17 450 are background cases, which are difficult to corroborate (apparently derived from modeling and attributed to nonradiation and nonsmoking causalities, their previous reporting remains unknown to us); 3094 are attributed to smoking-only; and 381.3 are attributed to radiation-only and radiation–smoking

interaction. Note also that the radiation-only, solid tumor case rate in this dose range is 1.82%.

With respect to smoking-only cases, significant issues arise, these being recognized and reported by the authors, including the smoking data are questionable and incomplete—the data were collected through questionnaires having only a 61% response rate; smoking status was unknown for about 60% of the total follow-up time and smoking status at the time of diagnosis was unknown for about 40% of the cases; almost half of the cases having smoking data and 40% of those without smoking data were imputed to be associated with smoking; among those responding to surveys, 86% of the men and 18% of the women indicated that they were ever-smokers, but Table 4 of the study by Grant et al[10] shows only 50% of men and 11% of women are ever-smokers; patients' smoking habits were assumed to be the same after the subjects' final response on smoking, which was no later than 1992; in 2009, the LSS cohort's average age was 78 years and it was simply assumed unlikely that many had begun smoking and likely that many had quit smoking by that age, but the impact on radiation effects was unclear; despite the large cohort and case numbers, the data permitting inference regarding radiation–smoking interaction were still limited by a highly skewed dose distribution and the unavailability of histology information for about 30% of the cases.[10,25-27]

It is clear the authors knew of substantial gaps in the smoking data, but these are not the only source of uncertainty regarding the results reported in Table 1. Issues within the smoking model make the smoking data results also questionable.

The smoking model has been earlier described as applicable to lung cancer, not all cancers, and how the model has been changed to accommodate smoking's many other organ targets is not addressed.[10,25-27] Additionally, the model ignores a major confounder regarding high levels of radionuclides in tobacco resulting from deposition of radon and its high linear-energy-transfer (LET), α-emitting decay products on, and adhering to, tobacco leaves; these decay products are released into cigarette smoke and transferred to smokers' lungs and other organs, being increasingly retained over years of smoking.[28] Omitting these high-LET doses means the modeling of low-dose, low-LET, bomb blast radiation, essentially dwarfed by smoking's high-LET doses, may inflate the bomb blast's radiation-only, solid tumor causality, overstating LDR's case rate.

The LSS data also differ from Japanese national smoking and cancer incidence data. For example, the smoking attributable fractions (AFs) shown in Table 1 are well below Japanese national cancer surveys and research,[29-31] when they should be higher due to the prevalence of smoking in the 1950s to 1980s; and the smoking AFs tend to decline remarkably in the LSS data with increased smoking prevalence, the opposite of what has been reported.[29,30] These inconsistencies force a misperception that radiation above 0.5 Gy is a greater cause of solid tumor incidence than heavy smoking, which is in disagreement with what is known by medical science.[29]

Two noteworthy statistical aberrations arise when comparing the data in Table 1 with the research from national Japanese studies of smoking and cancer.[29-31] First, smoking's AF of the cases is quite low; indeed, for the highest dose categories, the AF dips as low as 8%, though it is 14.5% of smoking-only cases for dose categories greater than 0.005 Gy. A significant national study by the National Cancer Center (NCC) shows that smoking's age-adjusted, population-attributable fraction (PAF) of solid tumor cancer cases is 0.201.[29] Adjusting for the LSS smoking prevalence and the male and female population percentage differences in the LSS cohort, this PAF becomes 0.215, almost 50% higher than the Table 1 AFs. The understated AFs in Table 1 yield a solid tumor incidence rate for smoking of only 11 in 10 000 persons per year, even when including the radiation–smoking interaction cases with smoking-only cases.

The second statistical aberration arises when the Table 1 solid tumor incidence rate is compared to Japan's annual mortality rate for smoking-associated, solid tumor cancers, as reported by Funatogawa et al,[30] which provides data through 2010 for lung cancer mortality (not including other cancers associated with smoking) in its Figure 2 for the same average age as the LSS cohort. Using those data, adjusted for the male and female population percentages for the LSS cohort, the Japanese annual lung cancer mortality rate is estimated to be 26 in 10 000 persons. Kaneko et al[31] also provides similar data through 2001 in its Figures 1 and 2. Appropriately adjusting these data, the Japanese annual, lung cancer mortality rate for the same average age as the LSS cohort is estimated to be 28 in 10 000 persons. It is clear that such smoking-associated, lung cancer-only mortality rates are not consistent with the cancer incidence rates of Table 1 for all smoking-related, solid tumor cancers. Mortality rates for lung cancer 130% to 150% higher than the incidence rate for all smoking, solid tumor cancers are physiologically inexplicable. Toyoda et al's Figure 1 offers compelling data close to what the LSS's lung cancer incidence rate should be, using the city of Osaka's lung cancer-only, annual incidence rate (a population of similar smoking habits and average age as the LSS cohort).[32] This rate is estimated to be 34 in 10 000 persons, more than 200% above the Table 1-derived rate for incidence of all smoking-related cancers. That annual incidence rate is about 20% to 30% more than the national, annual, mortality rate, a rational, physiological relationship for lung cancer. Clearly, the smoking-only, Table 1 cancer incidence rate is likely well underestimated and thus flawed. This calls into question the putative radiation-associated cases, which should, therefore, be much lower than reported.

Considering these observations, it is interesting that one error may cause both of these statistical aberrations, namely, that there are too few smoking-only cases included in the LSS smoking data. A simple correction to this problem would be to use the NCC's Japanese national data set of tobacco smoking's adjusted PAF of 0.215 for solid tumor cancer incidence, rather than the likely flawed LSS smoking data and its calculational model.[29] The total cases in the LSS cohort from smoking-only would then be 4846 cases due to smoking-only, compared to

Table 2. Table 8.[10] Derived Low-Dose Solid Tumor Cases From LSS Data on Smoking and Cases Determined Herein: Comparative LSS Low-Dose Cancer Incidence.

Dose Range: Weighted Colon Dose in Gy	LSS Cases	Background Cases	Cases Less Background	Radiation-Associated Cases	Smoking-Only Cases	Smoking Cases Derived[29]	(Cases Less Background) Less Smoking Cases Derived[29] = Radiation-Associated Cases
NIEC + 0-0.005	12 592	10 646	1946	4	1857	2372	(426)
0.005-0.1	5674	4785	889	88	867	1354	(465)
0.1-0.2	1217	996	221	86	179	312	(91)
0.2-0.5	1414	1023	391	204	191	362	29
Total				382	3094	4404	

Abbreviations: LSS, Life Span Study; NIEC, Not in Either City.

the Table 1 LSS-derived 3360 cases, including the radiation–smoking interaction cases.

Table 2 shows the impact of NCC's smoking and cancer data to determine a more credible set of smoking-only cases and LDR-associated cases.

Clearly, with unreliable smoking data and an unsupportable smoking model, the LSS's LDR cases are nonexistent and should, instead, be considered as smoking-only or other background cases, up to a weighted colon dose of at least 0.2 Gy and likely approaching 0.5 Gy. That is, there are no bomb blast radiation, solid tumor cases below this threshold (the number of these cases is actually negative and shown in parentheses in Table 2), thus invalidating the LNT model based on the LSS cohort.

Because other studies have even higher age-adjusted PAFs,[33] this approach likely represents the most conservative threshold estimate for the LSS radiation-associated cases. Using higher PAFs produces even fewer radiation cases and a higher dose threshold, below which no radiation-associated cases are likely.

The LSS's Missing or Incomplete Data and Evaluations

Missing Evaluation of High Stress and Cancer Incidence

The RERF has peripherally recognized that physical and psychological stress resulting from the bomb blasts has some role in the LSS data.[11,23] However, this issue is no less important than getting the LSS smoking data corrected, and the RERF interest has never seemed to recognize the incredibly unusual and protracted SPD of the hibakusha, as discussed herein. Based upon its absence in Grant et al,[10] the role of stressors in the LSS data as an important causality of cancer incidence may have been ignored. Therefore, we offer this preliminary accounting for such data within the background cases.

In a recent 2017 report, Song et al[34] present the results of a prospective cohort study by the Japan Public Health Center on perceived stress levels from everyday life (work, family, health, etc) and the risk of solid tumor cancer incidence in a Japanese population. The study included 111 257 eligible patients having complete information on perceived stress level at a baseline and, using baseline and 5-year follow-up data, measured dynamic stress levels. A subcohort of 79 301 participants with repeated stress data in 6 groupings was also used to measure long-term perceived stress. The association between perceived stress and solid tumor cancer incidence was measured by a Cox proportional hazards regression model (representing the ratio of outcomes in the test group to outcomes occurring in the control group), adjusted for all known confounders.

Using these data, the study examined several areas of interest, including (1) the association between dynamic perceived stress level and solid tumor cancer incidence and (2) the association between long-term perceived stress level and solid tumor cancer incidence. For the first area, after controlling for all available confounders, a small but significant increase in the risk of cancer incidence was observed for patients under either a medium- or high-level of stress, compared to the reference group (low stress level), with multivariable, adjusted hazard ratios (HRs) of 1.04 for the medium stress-level group and 1.06 for the high stress-level group, showing a clear trend to increase.

For the second area, analyses were conducted on the subcohort patients who had repeated data on stresses. The relative risk of cancer incidence increased with higher long-term stress levels. Individuals with constantly high perceived stress level had an 11% excess risk for cancer incidence compared to those with persistently low stress levels.

Therefore, if the SPD stressors experienced among the hibakusha from protracted social ostracism and government discrimination, arising from society's fears, are taken into consideration, the excess solid tumor cancer incidence is likely to be significantly affected.

A recent observational, epidemiological study of Holocaust survivors who had emigrated to Israel determined that the population had experienced an increased risk for solid tumor cancer incidence due to a variety of stressors, including extended physical harm, psychological abuse, and thorough physical and mental deprivation, earlier discussed as SPD.[35,36] A Cox proportional hazards model was used for the analyses. The study included 152 622 people and the conditions identified are strikingly similar to, but of shorter duration than, those experienced by the hibakusha: physical harm, intake restriction, exposure to

biologic agents/infectious diseases, intense physical stress, physical and emotional abuse from society and government, and psychological responses to such stressors.[19,20]

The reported results show that, as has been surmised in other studies,[21] the stressors did increase the incidence of certain cancers. Further, other studies show that more typical stress levels of life produce fewer cancers in populations.[22] Using the Holocaust survivor main study's results, cancer incidence in the hibakusha could be estimated by applying the HRs for the test cohort to the same cancer sites in the LSS data to determine the number of cancer cases in the LSS cohort attributable to SPD. Further, since the Not in Either City control group was not hibakusha, the Song et al[34] study offers Japanese background stressor cancer data for use with that group. Although there is some complexity introduced by the ethnic differences between Holocaust survivors and a Japanese population that must be addressed by further study before direct application of the Holocaust survivor data to the LSS cohort can be fully credible, higher solid tumor cancer incidence from higher stresses is certainly a rational expectation.

Results: Data and Analyses Omissions/Errors Show LSS Doesn't Support the LNT Model

After adjusting the HRs from the Song et al[34] Tables 2 and 3 for the associations in (1) and (2) for the male and female population percentages of the LSS cohort population and applying those adjusted HRs to the LSS cohort data from Table 1 to estimate the excess solid tumor cancer incidence risk to the LSS population from typical stresses of living, we found the LSS cohort solid tumor excess cancer incidence from perceived stress fell in the range of 800 to 1200 cases, which then should be extracted from the cases associated with bomb blast radiation (if they were not previously accounted for in the background cases).

Yet, applying the data from the epidemiological study of Holocaust survivors to the impact of stressors on the LSS cohort, it was estimated that as many as 2150 solid tumor cancers might arise from the protracted SPD of the LSS cohort. Such a result would further diminish the number of LSS radiation-associated cases at low doses, showing the application of the LNT model to LDR and radiogenic cancer within the LSS cohort is fatally flawed.

In summary, these adjustments to the LSS solid tumor cancer incidence rates for smoking and stressors perhaps miss some overlap and therefore require a more formalized and rigorous analysis. However, although preliminary and requiring validation, the adjusted LSS cohort, smoking-only cases using the NCC data,[29] presented herein, likely exhibit a solid tumor cancer incidence, threshold radiation effect. Further, until now, unaddressed, solid tumor cancer incidence arising from SPD stressors provides further compelling evidence that the current LSS database does not support the LNT model for LDR.

Infectious Disease and Cancer Incidence in the LSS Data

Some LSS solid tumor cancer incidence data from infectious disease are likely included in Table 1 background cases, but the 2005 data from the NCC of Japan regarding Japanese cancer incidence from infectious diseases and other causalities may not have been.[29] Infectious diseases were widespread and a serious public health problem among many Japanese, including the hibakusha, before, during, and after World War II.[29] In 2005, 55% of cancer among men was attributable to preventable risk factors in Japan,[29] including smoking. The corresponding figure for women was lower, but still accounted for nearly 30% of cancer.[29]

The NCC information regarding the linkage between several infectious bacteria/viruses and solid cancers, along with some examples of the bacterial or viral infections and their influence on increased cancer risk, are summarized by Inoue et al,[29] as follows:

> Another important finding from our study is its confirmation of the notion that infectious agents are a major cause of cancer in the East Asian region [16]. Its advanced socioeconomic status and high degree of hygiene and sanitation notwithstanding, Japan is not an exception: H. pylori [Helicobacter pylori] and HCV [hepatitis C virus] are major infectious causes that account for a relatively large share of preventable cancers... The prevalence of these infectious agents shows a strong cohort effect, namely a huge variation by birth cohort, and has been declining rapidly among younger birth cohorts.
>
> The majority of gastric cancer in Japan is derived from the noncardia stomach (91% in men and 94% in women in 2000) [32], and the prevalence of H. pylori is >80% in the birth cohort born before 1950 and 40%–50% in those born after 1950 [33, 34].... Hepatocellular carcinoma, which accounts for 90% of all liver cancer cases, is primarily caused by chronic HCV infection in Japan. The peak incidence between the 1970s and the 1990s in Japanese men was affected by the birth cohort effect among those born during 1931–1935, which was attributed to HCV outbreaks in Japan [35].

Further, Inoue et al[29] provide more detailed data that show the range of the solid tumor cancer incidence associated with many of the infectious diseases that have plagued Japan for decades. For example, hepatitis C and B have been shown to be associated with liver cancer; the human papillomavirus with cancers of the oral cavity, oropharynx, anus, genitalia, and cerix uteri; and the Epstein-Barr virus with nasopharyngeal cancer, Burkitt lymphoma, and Hodgkin lymphoma.

For 2005, these NCC infectious disease data for Japan[29] resulted in a PAF of 0.206 for all solid cancer incidence arising from this generations-old abundance of these bacteria and viruses. This PAF is higher than that for smoking, showing the immense impact that infectious disease has on solid tumor cancer incidence in the Japanese population.[29]

The NCC data also show other causalities of solid tumor cancers in Japan, including alcohol intake, salt intake, fruit and vegetable intake deficiencies, body mass index, physical

inactivity, and exogenous hormone use, with a 2005 PAF greater than 0.1.[29] The impact of these other factors on hibakusha compared with controls remains unknown and requires further study.

Combining the NCC's solid cancer incidence causalities in Japan from preventable risk, more than 50% of such cancers arise from smoking, infectious diseases, and the other causalities identified above. The SPD stresses should also be included as a preventable risk factor, which would likely push solid cancer incidence in Japan arising from preventable risk even higher.

The LNT Model Is a Failed Fiction and Not Scientific Knowledge

Conventional wisdom says there are 2 LDR applications for the LNT model: one for risk assessment as a scientifically defensible hypothesis and one for radiation protection/management. Regulatory and advisory agencies such as the National Council on Radiation Protection and Measurements (NCRP) and the International Commission on Radiological Proection (ICRP) and other advisory agencies/organizations support the LNT model's use for LDR protection, but not risk assessment. As Lauriston Taylor, a past president of the NCRP, noted in 1980,[37] LNT model risk-based calculations are "deeply immoral uses of our scientific knowledge." Unfortunately, they defend the use for LDR protection on the fallacious grounds that it protects by "erring on the side of caution."

This claim of "prudence" is a dangerously ill-informed illusion, failing to consider a range of possible outcomes, as discussed earlier. Either the LNT model accurately describes responses to LDR, or it doesn't, and if it doesn't, as shown herein and elsewhere, then its use in risk management will regularly produce harmful effects.

We have herein shown the robust, counter-epistemological evidence against the LNT model for LDR, and scientific empiricism requires robust, epistemological evidence in order for the LNT model to be science. The LNT model is simply without empirical basis, and it is no longer science, if ever it was.

Conclusion

With the disclosures of the errors and false conclusions in BEIR VII, the flawed analyses and statistics in epidemiological and mechanistic LDR studies, the demonstration herein that the LDR dose response is nonlinear with negative ERR values, and the possible threshold we show when significant causalities, heretofore ignored in the LSS data's low-dose range, are considered, there exists irrefutable evidence that invalidates the LNT model. As we have reported,[7] BEIR VII asserts that "at relatively low doses, there is still uncertainty as to whether there is an association between radiation and disease, and if there is an association, there is uncertainty about whether it is causal or not." Our work demonstrates there is likely neither association nor causality. Therefore, the LNT model is now on a level beneath that of empirical knowledge, where logic is constrained by verification. Using the LNT model as the basis for regulation and practice within medicine and nuclear energy remains a continuing *non sequitur*, applying nonscience to regulate the highest levels of science within medicine and energy.

In science, what is true is unrestrainable and what is error is unsustainable. Herein lies the hope science offers all humanity: That truth must always be science's standard of practice.

Declaration of Conflicting Interests

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COMMENTARY Open Access

Low-dose radiation from A-bombs elongated lifespan and reduced cancer mortality relative to un-irradiated individuals

Shizuyo Sutou

Abstract

The US National Academy of Sciences (NAS) presented the linear no-threshold hypothesis (LNT) in 1956, which indicates that the lowest doses of ionizing radiation are hazardous in proportion to the dose. This spurious hypothesis was not based on solid data. NAS put forward the BEIR VII report in 2006 as evidence supporting LNT. The study described in the report used data of the Life Span Study (LSS) of A-bomb survivors. Estimation of exposure doses was based on initial radiation (5%) and neglected residual radiation (10%), leading to underestimation of the doses. Residual radiation mainly consisted of fallout that poured down onto the ground along with black rain. The black-rain-affected areas were wide. Not only A-bomb survivors but also not-in-the-city control subjects (NIC) must have been exposed to residual radiation to a greater or lesser degree. Use of NIC as negative controls constitutes a major failure in analyses of LSS. Another failure of LSS is its neglect of radiation adaptive responses which include low-dose stimulation of DNA damage repair, removal of aberrant cells via stimulated apoptosis, and elimination of cancer cells via stimulated anticancer immunity. LSS never incorporates consideration of this possibility. When LSS data of longevity are examined, a clear J-shaped dose-response, a hallmark of radiation hormesis, is apparent. Both A-bomb survivors and NIC showed longer than average lifespans. Average solid cancer death ratios of both A-bomb survivors and NIC were lower than the average for Japanese people, which is consistent with the occurrence of radiation adaptive responses (the bases for radiation hormesis), essentially invalidating the LNT model. Nevertheless, LNT has served as the basis of radiation regulation policy. If it were not for LNT, tremendous human, social, and economic losses would not have occurred in the aftermath of the Fukushima Daiichi nuclear plant accident. For many reasons, LNT must be revised or abolished, with changes based not on policy but on science.

Keywords: A-bomb survivors, Lifespan, Life Span Study, Linear no-threshold, LNT, Longevity, Residual radiation, Threshold

Background

Japan is the only country that has sustained a nuclear attack. The weapons dropped in 1945 killed approximately 200,000 people instantaneously. People around the world have been taught for decades since that ionizing radiation is limitlessly hazardous, This supposition is based on a linear no-threshold model (LNT): even the lowest doses of ionizing radiation are hazardous in proportion to their doses, Therefore, it is quite natural that most people think that ionizing radiation from the A-bombs killed people, shortened lifespan, and increased cancer mortality. The Fukushima Daiichi nuclear power plant accident presented an opportunity to study the effects of ionizing radiation on health, after which the author published associated books [1, 2] and papers [3, 4]. Through their composition, it became increasingly clear that LNT has a seriously flawed history [5]. The energy of A-bombs comprised 35% thermal radiation (heat and light), 50% blast energy (pressure shock waves), and 15%

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nuclear radiation [6]. In fact, instantaneous deaths were mostly ascribable to thermal and blast energy (85%), especially in the central area of the blast. People tend to forget that victims of heat and blast were affected in a moment or short period, whereas cancer induction has remained a menace even to the present day. For survivors of today, fear of A-bombs mostly overlaps with fear of cancer. It is less well known that ionizing radiation is not always hazardous. Low-dose radiation sometimes stimulates our defense mechanisms and beneficial (radiation hormesis) [7–10].

Taking these facts into consideration, the effects on lifespan and cancer incidence of A-bomb survivors were reexamined for the present analyses. Letting the data speak, one would hear that low-dose radiation from A-bombs has extended survivor lifespan and reduced cancer mortality on average for A-bomb survivors and not-in-the-city control subjects (NIC). The key to resolving the apparent discrepancy between the received notions and actual data is radiation hormesis and the radiation doses of a hormesis range to which a large fraction of A-bomb survivors and NIC were exposed. Of course, A-bomb survivors who received high doses exhibited shortened lifespan and increased cancer mortality, but they accounted for a minor fraction of all local residents. Therefore, results show that the "average lifespan" was longer and that "average cancer mortality" was reduced overall.

Radiation units such as rem, Sv, and Gy are used here as reference articles use, unless otherwise specified.

Longer lifespan of some people who were heavily irradiated by ionizing radiation

Reportedly the unhappiest man in the world, Mr. Tsutomu Yamaguchi, was A-bombed at Hiroshima. Later he relocated to Nagasaki, where he survived the second A-bomb attack [11]. He survived the two A-bomb attacks; he might be the happiest man in a sense that more than 70 people were evacuated from Hiroshima to Nagasaki: all except him were killed. More surprising is that the two A-bombs did not shorten his life: he died of stomach cancer at 93.

The Nikkei Shimbun reported on April 5, 2018 that Chairman Sunao Tsuboi of the Japan Confederation of A-Bomb and H-Bomb Sufferers Organizations was selected as an honorary citizen of Hiroshima City. When he was 20, the A-bomb attacks occurred when he was 1.2 km from the epicenter. He is 93 in 2018. He talked to then US President Obama to encourage efforts to abolish nuclear weapons. The occasion on May 27, 2017 was the first visit ever to Hiroshima by a serving president.

When he was 8, Shigeaki Mori was blown into a riverbed from a bridge and injured 2.5 km from the epicenter. He became a historian and discovered that American victims of the A-bomb were present in Hiroshima. His finding was reflected in President Obama's speech, "Why do we come to this place, to Hiroshima? We come to ponder a terrible force unleashed in the not so distant past. We come to mourn the dead, including over 100,000 Japanese men, women and children, thousands of Koreans and a dozen Americans held prisoner." After the speech, a tearful Mori was embraced by Obama. Born in 1937, he has lived longer than the average for Japanese men.

Dr. Don Wiles, Emeritus Professor of Chemistry at Carlton University, Canada, once engaged in extraction of radium from uranium ore for 16 months from 1947. Before the use of cobalt, radium ($20,000/g) encapsulated in a glass tube was used to treat cancer by embedding it into the malignant tissues. The crystallization process used by Marie Curie 50 years before included procedures that were apparently very lax and coarse compared to the present standard: encapsulation was performed with bare hands. Workers ignored the rule to wear rubber gloves because they were slippery. Radiation badges even under the lead shield became black at the daily check. Because radium is similar to calcium in terms of its chemical characteristics, radium was apparently accumulated in Dr. Wiles' bones. Born in 1925, he exhaled about 25 times the legal maximum of radon, a product of radium, at the age of 88. One might assume that he was seriously injured. He stated "About 65 years later, I am still healthy." [12]. These are some examples of increased longevity despite radiation exposure. Are they exceptional?

A-bomb survivors lifespans are unusually long

Figure 1 presents changes of the number of certificate holders who have been covered by the Law Concerning Relief to Atomic Bomb Survivors. The holders are regarded as A-bomb survivors. Until 1982, holders were more than expected because additional people had been admitted as holders; the holders' superiority in number does not necessarily mean that holders had a long lifespan. After 1982, the expected number became greater than the actual holders because few people were admitted as new and holders were getting steadily older year by year. The mortality ratio of the Japanese that was used to calculate the expected numbers was the average of infants, young people, adults, and elderly people, producing a result that is much less than that of the aged holders. Therefore, the holders' exposure and experience do not necessarily mean that their lifespan is short.

The average lifespan of certificate holders was 80.13 for 2014. The ratio of men to women is not available. The lifespan of Japanese men was 80.21 for 2013 and that for women was 86.61; the average was 83.49.

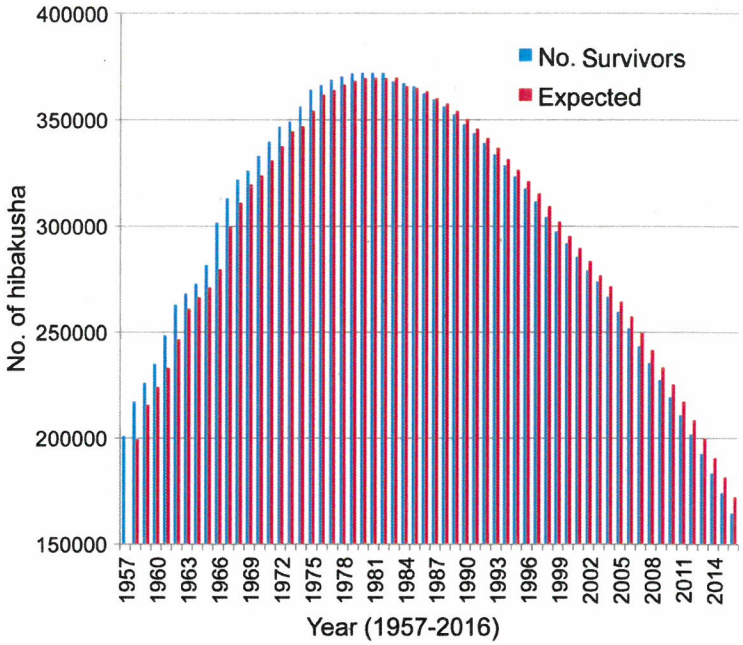

Fig. 1 Changes of people who have an A-Bomb Survivor's Certificates (Ministry of Health, Labour and Welfare [58] (blue). For example, a total of 183,519 certificate holders in 2014 comprised four classes: 1st class survivors, or direct victims (113,685); 2nd class survivors, or in-city victims who were within areas inside 2 km from the epicenter (42,529); 3rd class survivors, or rescue victims who engaged in rescue activities or physical treatments outside the 2 km areas and who were exposed to residual radiation (20,013); and 4th class survivors, or fetuses of people in one of the above three categories (7292). Their peak number was 372,264 in 1980. Expected numbers (red) were calculated as follows: holders in 1957 were 200,984; the death ratio of the Japanese in 1957 [59] was 0.008275 and 1663 (200,984 × 0.008275) were expected to die and 199,321 (200,984–1663) was the expected number in 1958 (the same hereinafter). Certificate holders are supported financially with six allowances and funeral fees. Some other benefits accrue: they can undergo free health examinations twice a year; and almost all sicknesses are treated at no charge. Patients with illness caused by a nuclear weapon were eligible to receive an allowance of 138,380 yen/m. The health control allowance is 34,030 yen/m. The funeral allowance is 206,000 yen. The total budget for fiscal year 2015 was 393,391,000,000 yen

The life expectancy (for remaining life) at age 80 is 8.61 for men and 8.19 for women. Therefore, the lifespan of A-bomb survivors is expected to be over 88, far exceeding the average. This elongated average lifespan of holders might be ascribable to good medical services offered by the Japanese government. This might have contributed to some degree, but apparently some other important factor has an influence: low-dose radiation stimulates human biological defense mechanisms.

A-bomb survivors lifespan was statistically shortened

Cologne and Preston investigated the longevity of 120,321 A-bomb survivors [13]. They concluded that "Median life expectancy decreased with increasing radiation dose at a rate of about 1·3 years per Gy, but declined more rapidly at high doses. Median loss of life among cohort members with estimated doses below 1 Gy was about 2 months, but among the small number of cohort members with estimated doses of 1 Gy or more it was 2·6 years. Median loss of life among all individuals with greater-than-zero dose estimates was about 4 months." Almost all readers of the summary sentences above must believe that ionizing radiation from A-bombs was hazardous and that it shortened A-bomb survivors' longevity to a greater or lesser degree. One must nevertheless be alert. The A-bomb survivors lifespan was not necessarily shortened, as described later. When a model cannot explain established facts, not the facts but the model must be wrong. What reasons are there in the discrepancy between actual life elongation and statistical shortening of lifespan? Apparently, three major factors engender wrong conclusions: 1) invalid LNT was promulgated – one never considers life elongation and cancer mortality reduction as effects of radiation; 2) a false assumption (zero exposure-zero risk) in NIC was used by neglecting residual radiation; and 3) radiation hormesis, the idea that low-dose radiation stimulates defense systems, was neglected. These three points are briefly examined before returning to discussion of Cologne and Preston's data [13] later.

LNT is not based on solid data

Muller's tenacity to maintain LNT

The origin of LNT dates back to 1927, when Muller found that X-rays induced sex-linked recessive lethality in *Drosophila melanogaster* [14]. This "data-poor/discussion-rich" paper was quite likely to have cleverly circumvented the normal peer review process [15]. Later, he presented related data. Apparent linearity at extremely high doses was extrapolated to lower doses without experimental data. He put forward the proportionality rule, an analog of LNT [16]. Then in 1939, World War II (WWII) broke out. The United States of America (USA) began production of the A-bomb under its Manhattan Project. Radiation effects on living organisms were investigated intensively. He learned of a threshold for positive excess risk in recessive lethality tests of *D. melanogaster* [17]. The US dropped A-bombs on Hiroshima and Nagasaki in 1945. Muller became a Nobel laureate in 1946 for his radiation research. Although he knew of thresholds to damage from radiation, he declared in his Nobel Prize lecture that there was "no escape from the conclusion that there is no threshold dose" [18].

Oil industries felt uneasy about nuclear energy and took over the National Academy of Sciences

Standard Oil Co. Inc. was founded by John Rockefeller in 1870, who later established the Rockefeller Foundation (RF) in 1913. The oil industry might well have felt threatened by the discovery of atomic energy. The Republican Party had forged a close relationship with the oil industry, but the Democratic Party, led by F.D. Roosevelt (1933–1945) and H. Truman (1945–1953), governed the USA during and after WWII. When Republicans were reelected, Nelson Rockefeller was appointed as an important aide to President Eisenhower. Muller, in turn, had close ties to the RF. In 1954, the RF chose to finance a large project to evaluate ionizing radiation. RF asked the U.S. National Academy of Sciences (NAS) to organize the program, which was conducted under the auspices of NAS President Bronk of Rockefeller University, also an RF trustee. The Genetics Panel (GP) of the NAS Biological Effects of Atomic Radiation (BEAR) committee was established in 1954 and was chaired by Weaver, a mathematician and director of RF.

With no significant discussion, GP recommended LNT on June 12, 1956 [19]. The limit dose for nuclear workers of 500 mGy/y, which had been in place since 1934, was discarded. The next day, the front page of the New York Times, owned by an RF trustee, reported that radiation is dangerous. Other media followed suit. Soon, several leading biologists asked GP to provide documentation that supported LNT. GP refused to do so because they never possessed relevant data. This decision was cast, and reasonably so, as an ideologically motivated choice based on deliberate falsification and fabrication of research records [20]. Fossil fuel companies are opposed to nuclear energy even today.

Expansion of LNT from insect sperm to the human body

Lewis (a 1995 Nobel laureate) argued in 1957 that radiation-induced leukemia conformed to the LNT hypothesis [21]. This was a new deployment of LNT from germ cells (heritable effects) to somatic cells (cancer induction). Several prominent researchers criticized the Lewis' paper (Table 2 in ref. [22]). With no convincing data to support LNT reported for half a century, the Biological Effects of Ionizing Radiation committee of NAS published BEIR VII report in 2006 to support LNT [23]. This report includes several shortcomings, as discussed later. Moreover, LNT has been applied also to chemical carcinogens; the smallest amount of a carcinogen is hazardous without threshold for positive excess risk.

Radiation doses are underestimated by neglecting residual radiation or black rain

Residual radiation and the formation of black rain

The radiation doses for A-bomb survivors were estimated using radiation transport calculations based on radiation transport findings from tests conducted on the ground in the Nevada desert. The nuclear weapons dropped on Hiroshima and Nagasaki were detonated respectively at 600 m and 503 m heights. To obtain more accurate data, the ICHIBAN project was planned, for which a 510 m high tower was constructed in the Nevada desert [24]. A nuclear reactor or other radiation source was placed at the top of the tower and data were collected. The dosimetry of the ICHIBAN project was named tentative dose 1965 (T65D). Around the 1980s, results demonstrated that T65D did not correctly reflect A-bomb radiation intensity. Exposure doses were reexamined, after which the Dose System 1986 (DS86) was established. In the period around the 1990s, DS86 was revised again; Dose System 2002 (DS02) was established. DS02 was revised further as DS02R1, producing the current system used to estimate the exposure doses of A-bomb survivors [25]. Although dose systems have been revised several times, T65D is the basic one. Others are modified versions that do not deviate greatly from T65D. T65D was an outcome of a large-scale simulation model of A-bombs, but it included an important oversight, i.e., omission of residual radiation with a dose twice as large as the initial radiation on which the dose estimation was made.

The energy of a typical A-bomb comprises three components: 35% thermal radiation (heat and light), 50%

blast energy (pressure shock wave), and 15% nuclear radiation [6]. Of that latter 15%, 5% is initial radiation (released within 30 s). The remaining 10% is residual radiation, which consists of major fallout and minor induced radioactivity. Induced radioactivity is produced by the action of neutrons in making non-radioactive substances into radioactive ones, but its lifespan is very short and is mostly negligible. A large fraction of the fallout, 40–70%, is believed to settle onto the ground within a day, but this depends strongly on weather and geographical features. When T65D was established, Black rain never fell in the Nevada desert. At Hiroshima and Nagasaki, thermal radiation incinerated or scalded plants, animals (including humans), houses, and various organic substances, producing heat, carbon dioxide, and vapor and consuming oxygen. Heat killed people. A lack of oxygen contributed deaths by suffocation. Victims were therefore affected in various ways by the A-bombs. From many waterways in Hiroshima and Nagasaki, large volumes of water were evaporated. The water itself was sucked up as if by a tornado. The vapor and water went up into the sky and cooled, thereafter forming raindrops containing soot and other debris. The resultant black rain started to pour down 20–30 min after the detonation. The rainfall lasted for a few hours (Fig. 2). The heavy black rain is well known to be highly radioactive. The possibility exists that the black rain included the most fallout, two-thirds of the nuclear radiation energy, i.e., twice as much radiation as the initial radiation used to estimate the radiation doses.

Evidence that residual radiation fell to the ground with the black rain

An old Japanese article written in 1957 by G. Obo [26] was later translated into English [27]. For the article, approximately 4000 people who lived in a 7 km radius from the epicenter were interviewed personally if they entered the central area 1 km radius from the epicenter and if they had radiation acute effects such as skin burn, external injury, fever, diarrhea, sore throat, skin bleeding, or loss of hair. Students of Hiroshima University took part in this study. Fundamentally important data are presented in Fig. 3.

The left panel of Fig. 3 shows 1) positive relations between people with symptoms and distance from the epicenter, 2) outdoor people as more severely affected than indoor people as a matter of course, 3) people in the areas ≥3 km from ground zero (beyond the reach of γ-rays and neutrons from initial radiation) were affected, implying that this area was contaminated severely by residual radiation most probably carried by black rain, and 4) indoor and outdoor people who were at a distance ≥4 km and who entered the central areas were affected almost equally independent of their distance from the epicenter, strongly suggesting effects of residual radiation. The right panel of Fig. 3 shows that a large

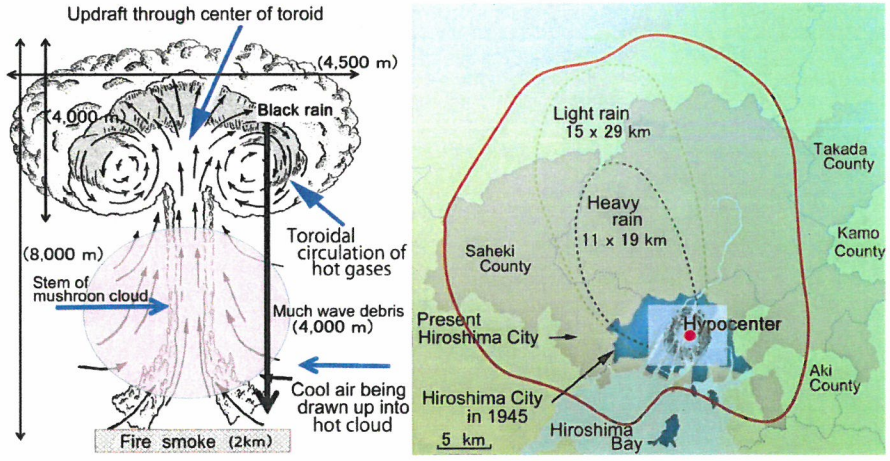

Fig. 2 Formation of black rain from the mushroom cloud (left), and black rain areas (right) [27]. Left: The A-bombs used to attack Hiroshima (16 kt TNT equivalent) and Nagasaki (21 kt TNT equivalent) were detonated respectively at 600 m and 503 m heights. A 500-m diameter fireball is formed by the detonation of a 20 kt bomb. The fireball rose like a skyrocket. During expansion of the ball, vaporized matter was condensed to a doughnut-shaped cloud with violent internal circulatory motion. Following the rising fireball, dirt and debris were sucked up from the Earth's surface. A Mach wave (the tip reaching 560 m 1.25 s after the blast) was reflected from the surface, whirling soil and debris up to form a Mach wave mass of 3800 t, producing black rain with raw materials together with the mushroom components. Trees, lumber, and other matter of 1.55×10^5 t were incinerated, forming a smoky fire 2 km in diameter, above the ground. Two references [65, 66] were used to draw this figure. Right: The probable heavy rain area reported in 1953 is shown as a thick broken line. That of light rain is shown as a thin broken line. The black rain area according to analyses of the "A-bomb Survivors' health awareness survey" in 2008 is shown as a solid red line (Hiroshima Peace Memorial Museum). A red circle off center denotes the epicenter. Black dots around the epicenter show locations of A-bomb survivors at the T65D survey [67]

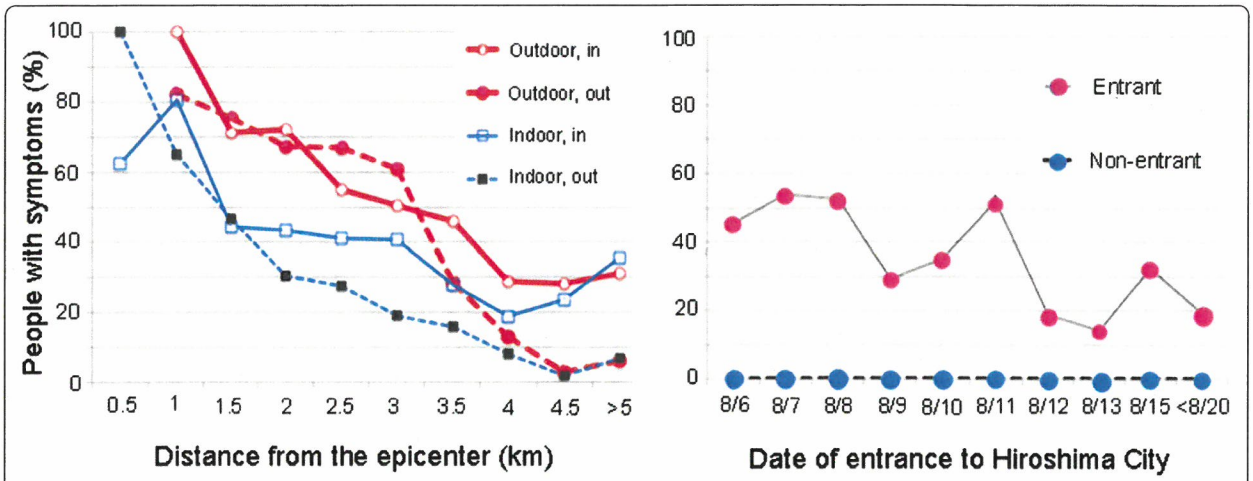

Fig. 3 Proportion of A-bomb survivors with symptoms (left) and that of non-A-bomb survivors with symptoms (right) [27]: Left, open circles (Outdoor, in), outdoor A-bomb survivors who entered the central area; filled circles (Outdoor, out), outdoor survivors who did not enter the central area; open squares (indoor, in), indoor survivors who entered the central area; and filled square (indoor, out): indoor survivors who did not enter the central area. Right, red circles (entrant), non-A-bomb survivors who entered the central area and blue circle (non-entrant), non-A-bomb survivors who did not enter the central area

fraction of non-A-bomb survivors entered the central area 2–3 weeks after detonation suffered from severe radiation sickness as if they were A-bomb survivors. This result indicates strongly that the area was heavily contaminated with residual radiation associated with black rain.

Report that black rain is negligible is refutable

The effects of black rain were studied using mortality data from 1950 to 2005 and cancer incidence data from 1958 to 2005 in Hiroshima and Nagasaki. The authors conclude that deleterious health effects from black rain exposure were not detected [28]. However, there is apparently a methodical fault. The authors asked people, "Was the person caught in Fallout Rain?" (Yes or No). According to the response, they were then divided into Yes or No groups. This grouping is almost meaningless because the important matter is not Yes or No, but if they had entered black rain affected areas within 2–3 weeks after detonation when residual materials remained active (Fig. 3). When solid cancer deaths and solid cancer incidence are extracted from the literature [29], excess relative risks (ERR) were smaller in the Yes group (caught in the rain) than in the No group (not caught in the rain) (Table 1). The data are suggestive of hormesis: slight radiation exposure is cancer-inhibitory.

The black rain affected areas were so wide that almost all A-bomb survivors and NIC must have been irradiated

Table 1 Excess relative risks for exposure to black rain for solid cancer death and solid cancer incidence (solid cancer incidence for 1950–2005 and solid cancer death for 1958–2005 were not available)

Data	Fallout rain status	No. of cases	Excess relative risk (ERR)
1962–2005			
Solid cancer death	No	3573	0.00
	Yes	1483	− 0.04
Solid cancer incidence No	5653	0.00	
	Yes	2283	−0.06
1950–2005			
Solid cancer death	No	3970	0.00
	Yes	1633	−0.02
1958–2005			
Solid cancer incidence	No	5982	0.00
	Yes	2430	−0.03

to a greater or lesser degree by residual radiation. The UNSCEAR 1958 report describes that almost all leukemia patients in zone C (1500–1999 m from ground zero) complained of severe radiation sickness in spite of an estimated dose of 50 rem (500 mSv in the International System of Units (SI)). Their doses must have been greater than 50 rem [30]. Exposure of around 2 Gy (close to 2 Sv in SI) is necessary to induce severe radiation sickness.

BEIR VII report fails to support LNT

BEIR VII report, the second problematic assertion by the National Academy of Sciences

Originally, LNT was based on Muller's experiments using repair-deficient *Drosophila* sperm [14]. He knew of the existence of thresholds for positive excess risk in *Drosophila* tests [17]. Indeed, later experiments by Japanese researchers indicate clearly that *Drosophila* irradiated with X-rays [31] or γ-rays [32] show not only thresholds but also hormesis. Hormesis has been observed in A-bomb survivors for solid cancers [29] and leukemia [33]. In spite of a large body of experimental data against LNT, NAS, the founder and advocator of LNT since 1956 [19], presented the BEIR VII report as basic LNT-supportive data (Fig. 4) [23]. The support, based on a Life Span Study (LSS) of A-bomb survivors, has been regarded as the gold standard to estimate radiation risk for human cancer. Nevertheless, this analysis presents serious flaws as explained below.

By the way, both Sv and Gy units are used according to original references in Fig. 4. Sv is a suitable unit for LNT and more generally acceptable Gy is used in this chapter.

Leukemia, a better indicator of radiation stochastic effects than solid cancer

Leukemia, a cancer of the blood cells, is a better indicator of radiation than problematic solid cancers because it is sensitive to radiation. It appears around 2 years after exposure and reaches a peak 6–8 years later, whereas solid cancers start to appear around 10 years after exposure and last for decades. Figure 4 (upper left insert, blue arrow) shows that ERR/Gy for leukemia is approximately 2, whereas that for solid cancer is approximately 0.55 (lower left, purple arrow). Therefore, leukemia is sensitive to radiation and a better indicator than solid cancers. The dose-response of leukemia is not linear but is instead linear-quadratic (upper left insert). That of solid cancer also fits better to linear-quadratic (red arrow) than linearity (orange arrow), but no statistical significance was found between the two; BEIR VII asserts linearity. This forcible logic is difficult to accept. Moreover, when taking into consideration neglected residual radiation, effects of blast/thermal wave injury on the immune system, and hormesis, dose responses might be deviated far from linearity.

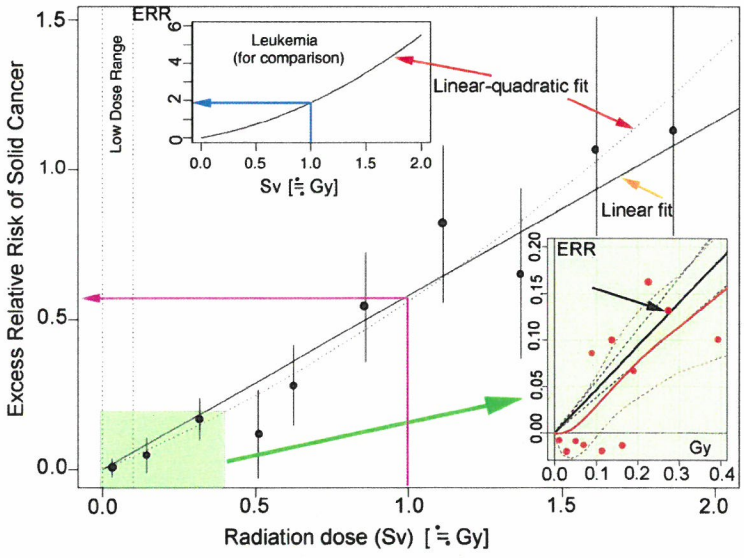

Fig. 4 Excess relative risk (ERR) of solid cancers for Japanese A-bomb survivors [23]. The plotted vertical lines represent approximate 95% confidence intervals. The thin blue, purple, red, and orange arrows respectively indicate ERR/Sv for leukemia, ERR/Sv for solid cancer, linear quadratic fit, and linear fit. The lower left area in pale green is enlarged as the lower right insert, which shows the results of two statistical analyses [35]. The black straight and dotted lines respectively show the linear fit of LNT and 95% confidence intervals. The red continuous and dotted lines respectively show the Bayesian fit and 95% credible interval. The black arrow indicates only one dot inside the 95% confidence intervals. Less than 100 mSv constitutes the low-dose range

Concealment of downturn

When radiation doses are much higher than 2 Gy, exposed people tend to die of adverse effects before reaching an age when cancer commonly occurs; ERR would show a downturn until finally reaching zero. The highest dose in Fig. 4 is 2 Gy, which conceals the downturn. Indeed, "The dose-response curve shows some downward bending in the high-dose range (2 + Gy in organ dose) for leukemia and even for all cancer except leukemia" [34]. When following the dots in Fig. 4 from low to high with downturn over 2 Gy in mind, one can easily imagine a sigmoid-like curve. This is shown by Bayesian analysis of LSS (Fig. 4, right below insert) [35]. A J-shaped curve is observed for solid cancers [36, 37] and leukemia mortality [33] in LSS. When hormesis and a downturn occur, the actual curve becomes instead an S-shaped curve [1].

Averaging of low-dose groups

Doses < 100 mGy are the most important for our risk analyses. No significant differences were found between the control subjects and A-bomb survivors at these doses. The BEIR VII report combined all data points < 100 mGy, to which more than 80% of all survivors belong, together into one point (Fig. 4). This has been explained as an old statistical trick. It was used by Lewis to insist on the validity of LNT [21]. This dishonest representation was successful in giving the impression that the dose response is linear and that no thresholds exist. The low-dose area < 400 mGy (Fig. 4, lower left in pale green) is presented in detail (lower right in pale green) [35]. The ERR dots are dispersed widely: only 1 dot (black arrow in lower right insert) out of 12 is inside the 95% confidence interval, indicating that dose responses are not linear in this area.

Inappropriate use of a false assumption (zero exposure-zero risk)

The line of LNT starts from zero according to the assumption that the exposure dose was zero and that ERR was zero in the control cohort (Fig. 4). This default model has been used to analyze LSS, but it is misleading because most A-bomb survivors and the control cohort people must have been exposed to residual radiation, as discussed later. The BEIR VII report based on that false assumption is therefore invalid. The dose-response line should not start from zero. Bayesian analysis does not assume this false assumption and allows more appropriate estimates. When the lower right insert of Fig. 4 is enlarged, crossing between the x-axis and the red line is roughly 25 mGy. An estimated zero dose might actually be 25 mGy. If these people were exposed to residual radiation, which was twice as great as the initial radiation, then A-bomb survivors and control subjects might have been exposed to additional 50 mGy: a total of 75 mGy.

LNT ignores hormesis and thresholds

Granted that A-bomb survivors and control NIC people were exposed to 25–75 mGy over the estimates, the false assumption (zero exposure-zero risk) must be abandoned. Bayesian analysis, which does not need this assumption, allows negative responses, i.e., cancer mortality is suppressed to below the background level. Figure 4 shows that six responses are indeed hormetic (red dots under the x-axis in lower right insert). Therefore, low-dose radiation can suppress cancer deaths. At the same time, hormesis indicates that thresholds for positive excess risk can be established between hormetic and carcinogenic doses.

Cherry picking of reference data

Siegel et al. [38] criticized The BEIR VII report in detail. One point is especially worthy of mention. The BEIR VII report cited that chromosomal aberrations induced by low-dose radiation in non-proliferating human cells were not repaired, thereby supporting LNT. However, that finding was a misrepresentation by failing to present that the aberrations in proliferating cells were repaired in several hours to the background level or less. Consequently, the result was opposite to what the BEIR VII argues.

Low-dose radiation elongates A-bomb survivors' lifespan

Earlier studies of lifespan elongation

Stewart and Kneale [39] showed that deaths in 1950–1982 from all non-malignant diseases in LSS population were significantly lower in survivors exposed to low doses than in unexposed persons. This U-shaped dose response relationship was refuted in comments by an LSS report [40], in which the mortality of A-bomb survivors was found to fit to the linear-threshold model (the estimated threshold is 1.4 Gy (DS86)) on the basis of LNT. Mine et al. [41] and Kondo [42] analyzed total deaths among about 100,000 A-bomb survivors in Nagasaki in1970–1988 and found that 290 males exposed to 0.5–1.49 Gy (T65D) showed significantly lower mortality. Although this beneficial effect was not found in female subjects, earlier studies [39, 41, 42] hint that A-bomb survivors exposed to low to intermediate doses live longer.

Contradiction 1: Excess relative mortality of early entrants is lower than that of late entrants

A-bomb survivors' lifespans were apparently shortened as discussed earlier. Cologne and Preston's analyses [14] were based on LNT using an assumption of zero exposure and zero risk, with no consideration of the

possibility that lifespans could be elongated and that cancer deaths might be reduced. Their results are reproduced in Fig. 5.

As depicted in Fig. 3, early entrants were exposed to higher doses of residual radiation than late entrants. Excess relative mortality of early entrants, however, is lower than that of late entrants (Fig. 5A and B). The key to resolve this contradiction can be explained by radiation hormesis-related mechanisms (e.g., enhanced DNA damage repair, apoptotic removal of aberrant cells, and anticancer immunity stimulation): the B group people were exposed to higher residual radiation than the A group people. Exposure doses of the B group must be in a hormetic dose range.

Contradiction 2: Excess relative mortality is inversely proportional to distance from the epicenter

Radiation doses are expected to be higher in proximal areas than in distal ones. If LNT is correct, then excess relative mortality must be higher in proximal areas. Data show inverse proportionality (Figs. 5C–F). Because the number of people is not small and mortality (death or life) data are accurate, the neat inverse proportionality must be close to the truth. Here again, this contradiction must be explained by radiation hormesis. People nearer the epicenter received more radiation than people farther away. Hormesis-related natural defense mechanisms also likely played a positive role in elongating the lifespan of survivors.

Excess relative mortality shows a typical J-shaped curve, indicating hormesis and a threshold

The radiation dose group of 0.005–250 mGy (Fig. 4, G group) comprises 40,403 people. Its excess relative mortality is almost equal to that of all in-city individuals (n = 34,064, a total of C to F groups) whose radiation doses are estimated to be zero or < 0.005 mGy (Fig. 4, control level Y). Considering the large population size, a lack of health hazard observed in group G would not be ascribable to a simple fluctuation: it must reflect actual effects of 0–250 mGy. If they were exposed to residual radiation, which was twice as strong as the initial radiation, then they might have been exposed to additional 0–500 mGy, a total of 0–750 mGy.

The excess relative [43] mortality of H group (250–499 mGy is slightly higher than that of G group (0–250 mGy) and almost equal to D group (3–7 km from the epicenter). The mortality is below the control level X. These fluctuations are not random. At a glance from C to M in Fig. 5, one can see a beautiful J-shaped curve, an indicator of hormesis. When a J-shaped curve appears, we can establish a threshold at the crossing of the J and the x-axis. The threshold seems be between 250 and 499 mGy. Perhaps we could add 500–998 mGy of

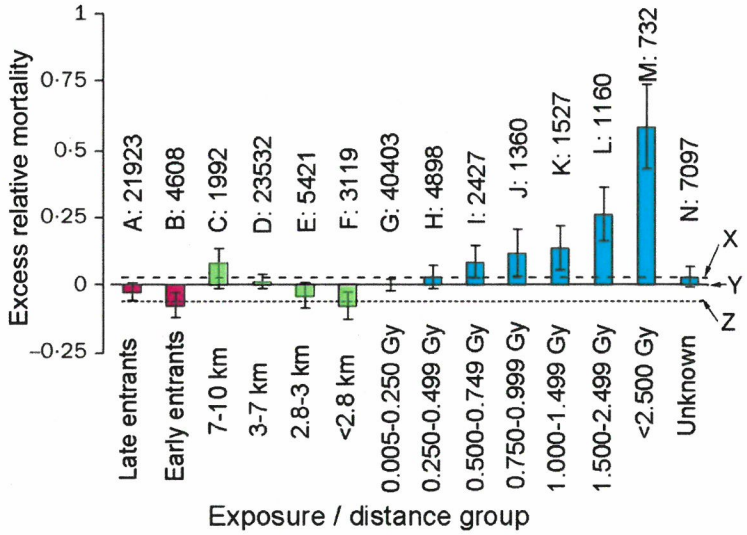

Fig. 5 Excess relative mortality by radiation dose or distance from the hypocenter. Figure 1 and Table 1 of an earlier report [13] are combined. The scale from left to right shows increasing proximity to the epicenter: A, late entrants (not in city, entered after 1 month); B, early entrants (not in city, entered within 1 month); C–F, in city at time of A-bomb, with different distance from the epicenter; G–M, seven dose groups with different doses; and N, distance from the hypocenter = 0.11–3 km with unknown doses. Numerals above A–N denote the number of people examined. The comparison group Y (baseline mortality, or excess relative mortality 0) is all in-city individuals (n = 34,064) with estimated doses of zero or < 0.005 Gy. Dashed line X is the in city zero dose distal groups C and D (n = 25,524). Dotted line Z is the in-city zero-dose proximal groups E and F (n = 8540). Y is the combined data of X and Z

residual radiation, twice as much radiation as estimated doses.

Cancer mortality of A-bomb survivors has been lower than the Japanese average

The US National Academy of Sciences proposed the spurious LNT in 1956 and put forward the problematic BEIR VII report in 2006 to support LNT (Fig. 4) [23]. The main reasons for the failure of the report are the use of LNT, use of the false assumption (zero exposure-zero risk), and neglect of hormesis effects. The Radiation Effects Research Foundation (RERF), a Japan–US scientific organization, has studied the health effects of A-bomb radiation. RERF has periodically reported research results and has insisted that the effects of radiation follow LNT in line with the BEIR VII report. The numbers of A-bomb survivors and solid cancer deaths are extracted from the latest three issues and are compared with Japanese averages (Table 2). The ratios of cancer deaths in both A-bomb survivors and NIC are smaller than those of Japanese averages. The numbers of people involved in Table 2 are not small. The differences are clear. Data must closely approximate reality. The finding that radiation of A-bombs reduces cancer mortality on average might be unexpected and incredible for LNT supporters. Nevertheless, such conclusions might be readily acceptable when one admits that low-dose radiation is hormetic under appropriate conditions and both A-bomb survivors and NIC who were exposed to low-dose radiation occupy a large fraction of the cohort. Consequently, low-dose radiation reduces cancer mortality on average and extends the lifespan (Fig. 5) as well.

Discussion

Earth has been exposed to ionizing radiation for billions of years

The current total heat flux from the Earth to space consists of half residual primordial heat and half radiogenic decay of uranium-238, and thorium-232, and potassium-40, the respective half lives of which are 4.46, 14.0, and 1.28 billion years [38]. Therefore, radioactivity was much higher 4 billion years ago when life started to appear on the earth. Radioactivity at our university campus in the air is less than 100 cpm, as measured with a Geiger–Muller counter, but that of nearby granite is around 500 cpm or so. Radioactive substances from the birth of the earth are still abundant on the earth now. Radon-222, a daughter of uranium-238, and radon-rich hot springs are frequently found around uranium ore.

The human body receive roughly 20,000 radiation hits each second

In addition, carbon-14 and tritium-3 are constantly produced by the action of cosmic rays in the atmosphere. They are incorporated into our bodies. Japanese foods contain polonium-210 and potassium-40 and commit an effective dose of 0.47 mSv [44]. Consequently, the total of our annual background exposure dose is 2.1 mSv: cosmic rays (0.3 mSv), ground radiation (0.33 mSv), foods (0.99 mSv from carbon-14, polonium-210, and potassium-40), and aerial radon (0.48 mSv) [45]. When these radiation levels are converted to Bq (disintegration/second) using an Sv-Bq conversion table, rough estimation is 20,000 Bq. Potassium, an indispensable nutrient, and its associated potassium-40 (0.0117% of all naturally occurring potassium) contribute 4000 Bq. Therefore, we are exposed to by and large 20,000 radiation hits a second from not only the environment but also from materials inside our body. We ourselves are radioactive entities. In actuality, sleeping next to someone exposes one to 0.00005 mSv, which is the equivalent of eating half of a banana (0.0001 mSv). Living within 80 km of a nuclear plant and a coal plant for a year are, respectively, 0.00009 mSv and 0.0003 mSv. The dose of a chest X-ray is 0.02 mSv (ca. 1,000,000,000,000 hits [46]). A jet-liner flight from New York to London is 0.04 mSv [47]. Of course, these estimates are quite rough with significant uncertainties.

Breathing is much more hazardous than low-dose radiation

The earth was anaerobic until 2.5 billion years ago when cyanobacteria started to add oxygen into the air. Oxygen

Table 2 Comparison of solid cancer mortality in the lifespan study of A-bomb survivors with Japanese cancer mortality. Japanese average cancer deaths were calculated by dividing cancer deaths by total deaths each year during 1958–2009 [68]. Averages corresponding to survey periods were determined

Reporters	Year	Survey period	No. *hibakusha* or [NIC[a]]	No. cancer deaths (%)	% Japanese average cancer deaths
Preston et al. [48]	2007	1958–1998 105,427	17,448 (16.6)	21.4 (1958–1998)	21.4 (1958–1998)
			[25,4273,994	(15.7)]	
Ozasa et al. [69]	2012	1958–200	86,611	10,929 (12.6)	22.3 (1958–2003)
			[26,529	NA[b]]	
Grant et al. [70]	2017	1958–2009	80,205	17,316 (21.5)	23.3 (1958–2009)
			[25,239	5222 (20.6)]	

[a], not in the city; [b], not available

is actually toxic, but it is useful to produce energy effectively through oxidative phosphorylation. Our ancestors started to use oxygen, but reactive oxygen species (ROS) are inescapable byproducts of the oxidative process. ROS themselves are toxic. Nine billion ROS are produced in a cell a day [48]. We developed systems to quench ROS instantaneously using radical scavengers such as glutathione and L-cysteine and using enzymes such as superoxide dismutase and catalase.

Hazards by both respiration and low-dose ionizing radiation are caused mainly by ROS, but ROS production by respiration overwhelms that by low-dose radiation by thousands to a million of times the magnitude. ROS-quenching systems developed under intensive ionizing radiation conditions for more than billion years before the appearance of oxygen in the air must be readily applied to quench ROS by respiration.

Low-dose radiation is not only beneficial but necessary

A benefit of oxygen beyond energy production is the shielding of ultraviolet (UV) light. We sometimes expose clothes and mats to the sunlight to dry them and simultaneously kill bacteria, fungi, and ticks. We are suntanned in the sun, by which dead epithelial cells are shed from the skin when UV is strong. When oxygen was not in the air, UV was so strong that organisms were unable to live on the ground. The ozone layer cuts most UV; organisms today can move across the ground. Although UV can kill some organisms, it is indispensable to produce vitamin D. We are using the toxic UV as a need. So are ROS. When leukocytes "eat" bacteria, they enzymatically produce large quantities of ROS to kill them. ROS are sufficient to kill bacteria, but cells are also killed later. We used to see pus, a pile of dead leukocytes, in or around the wound before antibiotics became popular. In fact, J.F. Miesher extracted DNA from pus for the first time in 1869.

Figure 5 and Table 2 respectively show radiation-hormesis-related benefits: 1) elongating of lifespan and 2) reduced cancer deaths. Other analyses of LSS show hormesis in solid cancers [29] and leukemia [33]. Hormesis has been reported for many organisms such as protozoa [38], Drosophila [31, 32], and mice [49]. Lung cancer incidence of humans exposed to radon-222 is also hormetic [50]. These are some examples, constituting only the tip of the iceberg. Radiation-hormesis-related health benefits are possibly universal among all living organisms. Low-dose radiation is apparently not only beneficial but also necessary. When human cells were cultured under unshielded (1.75 mGy/y) and 10 cm lead-shielded (0.3 mGy/y) conditions, heat shock proteins (products of adaptive responses) were produced more in shielded cells than in unshielded cells, indicating that reduced radiation was not relief, but was stressful to the cells [51]. When bacteria were cultured 650 m underground, where radiation levels were 1/80 those at ground level, bacterial growth was retarded [51, 52]. If LNT is correct, then growth should be enhanced by removal of hazardous ionizing radiation. The results were the opposite, indicating the failure of LNT. Low-dose radiation is sensed by bacteria and gene expression is changed greatly at the transcriptional level [48].

Systematically associated many-layered defense mechanisms that LNT ignores

The sanctuary zone of a 30 km radius in Chernobyl is a paradise for animals and birds. More than 315 species thrive there. Glutathione levels of rats are elevated, but no DNA lesions are found on the animals. Levels of this radical scavenger in birds of 16 species are also high [53]. The authors argue that hormesis is working there. Consequently, ROS are quenched before attacking DNA. If DNA is injured by a large amount of ROS, cells can repair most of them. If DNA injuries exceed the repair capacity, cells are killed by apoptosis and are removed. If cancerous cells are produced, then most of them are removed by vigilant survey of immune systems. These adaptive defense systems are only some examples acquired by living organisms through evolution as innate essential attributes. Humans have the ability to sense crisis and to prepare for defense. Even if ionizing radiation is neither seen nor sensed, its products, ROS, constitute signaling molecules for defense systems. Defense systems at various levels (cells, tissues, organs, etc.) by various mechanisms (ROS quenching, DNA repair, apoptosis, anticancer immunity, etc.) must be associated with hormetic dose-response relationship for radiation induced cancer. A fundamental failure of LNT is that it ignores these time-requiring biological systems. Indeed, LNT is aptly accused of "epidemiology without biology" [54].

Magic of epidemiology to change negative to positive

A large body of experimentally obtained results collectively indicates radiation hormesis, but LNT proponents ignore these data. Risk of death from leukemia and lymphoma in more than 300,000 radiation-monitored workers (INWORKS) was studied. Results indicate that the dose-response matched well with LNT [55]. This result was praised in an internationally prestigious journal: *Nature* [56]. Soon more than 20 researchers raised objections, some of which included 1) lack of negative control, 2) LNT-based analyses, 3) no consideration of natural background and smoking, 4) 90% confidence limits (usually 95%) to achieve easy statistical significance, 5) one-tailed tests ignoring possible hormetic response, and 6) primitive miscalculations a schoolboy would not make. Soon a correction appeared in *Nature*, "The original version of this article incorrectly calculated

an 'expected' death rate from leukaemia among the workers, and as a result, the risk posed by radiation increments was wrong. The story has been corrected to reflect this." At least two works have leveled detailed criticisms against INWORKS studies [57, 58]. Epidemiology is apparently the last foothold for LNT, but "flexibility in data collection and analysis allows presenting anything as significant" [59]. The present author required no sophisticated epidemiology to find the opposite of what the authors assert in elongation of lifespan in Fig. 5 and a decrease of cancer mortality in Table 2.

Tremendous human, social, and economic losses caused by obstinate application of the linear no-threshold model

The individual external doses of 421,394 Fukushima residents for the first 4 months after the 2011 earthquake and tsunami were the following: 62.0%, < 1 mSv; 94.0%, < 2 mSv; 99.4%, < 3 mSv. The arithmetic mean and maximum for individual external doses were 0.8 and 25 mSv, respectively [60]. When actual external exposure doses estimated by individual glass-badge measurements in Date City, Fukushima, were compared with official ambient doses presented by the Japanese government, the ratio was 0.15 [61]. If this figure is applied to the data above [51], then the effective doses can be calculated as follows: 62.0%, < 0.15 mSv; 94.0%, < 0.3 mSv; 99.4%, < 0.45 mSv. The respective mean and maximum doses were 0.12 and 3.75 mSv. Even the maximum external dose is below the Japanese average medical exposure dose: 4 mSv. At the time of the Fukxushima nuclear accident, the International Commission on Radiological Protection (ICRP) recommended reference levels of 20–100 mSv [62]. Less than 100 mSv, the so-called low-dose range (Fig. 4), is accepted as representing no difference between exposed and non-exposed people. These are acute doses. Hazardous effects can be reduced to 1/16.5 by prolonged radiation such as in Fukushima [63], meaning that 1.65 Sv (100 × 16.4 mSv) might be non-hazardous. If it were not for LNT, evacuation would not have been necessary in Chernobyl or Fukushima [37]. In Ramsar, Iran, people have lived continuously in environments of 260 mSv with no health problems [56]. Tremendous human, social, and economic losses caused by obstinate application of the failed LNT could have been avoided [3]. In truth, LNT is a deeply immoral. Prof. G. Walinder's words, "The LNT hypothesis is a primitive, unscientific idea that cannot be justified by current scientific understanding. As practiced by the modern radiation protection community, the LNT hypothesis is one of the greatest scientific scandals of our time." Madame M. Curie's words, "Nothing in life is to be feared, it is only to be understood. Now is the time to understand more, so that we might fear less." It is the time to reconsider the use of the LNT [64]. The author's sincere hope is that some unmasking of LNT can help Fukushima people and others to live their lives free of irrational fear.

Conclusion

The linear no-threshold hypothesis (LNT) was recommended without solid data by the National Academy of Sciences in 1956. The academy put forward the BEIR VII report in 2006 as supporting evidence of LNT. This report was based on the Life Span Study (LSS) of A-bomb survivors. LSS has three major defects: 1) Residual radiation to which both A-bomb survivors and control subjects were exposed was neglected. Specifically, the control subjects were not valid as representing the negative control. 2) LNT is the basis of risk analyses. The failed model cannot be used. 3) Radiation hormesis is beyond the scope of LSS, but it actually occurs. The average lifespan of A-bomb survivors is longer than the Japanese average. Solid cancer deaths of A-bomb survivors and control subjects were fewer than the Japanese average. Consequently, one can reasonably infer that radiation of A-bombs elongated their lifespan and reduced cancer deaths on average, indicating a failure of LNT. Unfortunately, LNT has served as the basis of radiation regulation. If it were not for LNT, then evacuation of Fukushima people would not have been mandated and tremendous human, social, and economic losses would have been avoided. To avoid unnecessary losses and fear, humanity must learn as soon as possible that low-dose radiation is not only harmless but beneficial.

Abbreviations

BEAR: Biological Effects of Atomic Radiation; BEIR: Biological Effects of Ionizing Radiation; ERR: Excess relative risk; GP: Genetics Panel; ICRP: International Commission on Radiological Protection; LET: Linear energy transfer; LNT: linear no-threshold model; LSS: Life Span Study; NAS: National Academy of Sciences of the United States of America; NIC: not-in-the-city; RERF: Radiation Effects Research Foundation; RF: Rockefeller Foundation; SI: International System of Units; USA: United States of America

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I am a member of Scientists for Accurate Radiation Information (SARI). Let me express my thanks to SARIans for their supply of valuable information. I am grateful to Prof. Edward J. Calabrese for providing me with excellent papers, only a few of which could be cited here. This paper is dedicated to the late Prof. Kimiyuki Tsuchiya who passed away on June 5, 2018. I met him at the National Institute of Genetics in 1972. He captured spiny county rats in Tokunoshima (*Tokudaia tokunoshimensis* Endo & Tsuchiya, for which karyotypes of both sexes are the same and the chromosome number is 45) and Amami Islands (*Tokudaia osimensis*, for which karyotype of both sexes are the same and the chromosome number is 25). Together, we showed that they have no mammalian sex determining gene *SRY*. Pancreatic cancer was found in Dr. Tsuchiya 1 year and 9 months ago. I recommended radiation hormesis therapy to him. He showed willingness to use it, but LNT has prevented development of this therapy in Japan.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Author's contribution
The author read and approved the final manuscript.

Author's information
The author was taught that ionizing radiation is limitlessly hazardous until March 2011. On the occasion of volunteer activity in Fukushima to measure contamination of evacuees, I examined the effects of ionizing radiation and found that LNT is invalid. As a scientist, I would like to relieve as many people as possible from unreasonable belief in LNT.

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable

Competing interests
The author declares that he has no competing interest related to this report.

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