RESEARCH ARTICLE

Background radiation impacts human longevity and cancer mortality: reconsidering the linear no-threshold paradigm

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Abstract The current linear no-threshold paradigm assumes that any exposure to ionizing radiation carries some risk, thus every effort should be made to maintain the exposures as low as possible. We examined whether background radiation impacts human longevity and cancer mortality. Our data covered the entire US population of the 3139 US counties, encompassing over 320 million people. This is the first large-scale study which takes into account the two major sources of background radiation (terrestrial radiation and cosmic radiation), covering the entire US population. Here, we show that life expectancy, the most integrative index of population health, was approximately 2.5 years longer in people living in areas with a relatively high vs. low background radiation. ($\geq$ 180 mrem/year and $\leq$ 100 mrem/year, respectively; $p < 0.005$; 95% confidence interval [CI]). This radiation-induced lifespan extension could to a great extent be associated with the decrease in cancer mortality rate observed for several common cancers (lung, pancreas and colon cancers for both genders, and brain and bladder cancers for males only; $p < 0.05$; 95% CI). Exposure to a high background radiation displays clear beneficial health effects in humans. These hormetic effects provide clear indications for re-considering the linear no-threshold paradigm, at least within the natural range of low-dose radiation.

Abbreviations

LNT	Linear no-threshold
NCRP	National Council on Radiation Protection and Measurements
EPA	United States Environmental Protection Agency
USGS	United States Geological Survey
USCS	United States Cancer Statistics
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
NCI	National Cancer Institute
IHME	Institute for Health Metrics and Evaluation
LLR	Low-level radiation
HLR	High-level radiation

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ICRP   International Commission on Radiological
         Protection

Introduction

In the early decades of the 20th century, and mainly
during World War II, extensive radiobiological studies
were preformed, in order to establish a basic radiation
protection policy and philosophy (Kathren 2002). The
concept of tolerance dose was developed and widely
accepted, based on two major postulates: (1) a
threshold dose exists, which when exceeded may
cause harmful effects; (2) even in case of certain
exceeding the threshold, a complete recovery from
radiation effects is still possible (Kathren 2002).
Moreover, an extensive experimental study suggested
a beneficial effect of moderate radiation levels on the
survival and tumor incidence in mice (Lorenz et al.
1955). Nonetheless, in 1946, Hermann J. Muller, who
received the Nobel Prize in Physiology or Medicine
for his work on the mutagenic effect of radiation,
stated in his inauguration lecture that "there is no
escape from the conclusion that there is no threshold
dose, and that the individual mutations result from
individual "hits", producing genetic effects in their
immediate neighborhood" (Muller 1946). This
strongly led to the embracing of the linear no-
threshold (LNT) hypothesis which postulated that
there is no "safe" level of radiation, and that even an
extremely small dose increases the risk for damage, in
direct proportion to the dose (Calabrese 2012). By the
middle of the 1960s, the LNT model for cancer risk
assessment was generally considered by the scientific
community (and subsequently by the policy makers)
as the safest approach to the establishment of radiation
protection policy and standards (Calabrese 2018).

Yet, the LNT model remains highly controversial.
Among the arguments against the LNT model are that
it was not based on concrete scientific data, but rather
ideologically motivated and politically influenced
(Calabrese 2019; Marcus 2016; Sacks and Siegel
2017). Some even claimed a deliberate counterfeit, up
to fabrication of the research record (Calabrese
2016, 2019). Most recently, the National Council on
Radiation Protection and Measurements (NCRP)
published a commentary provided by an interdisci-
plinary group of radiation experts who critically

assessed epidemiologic studies on populations
exposed to low dose ionizing radiation, and concluded
that the existing data does not challenge the LNT
model for radiation protection. As the Scientific
Committee proclaims: "It is acknowledged that the
possible risks from very low doses of low linear-
energy-transfer radiation are small and uncertain and
that it may never be possible to prove or disprove the
validity of the linear no-threshold assumption by
epidemiologic means… Currently, no alternative
dose-response relationship appears more pragmatic
or prudent for radiation protection purposes than the
linear no-threshold model" (Shore et al. 2019).

In this study, we undertook a comprehensive
analysis of the dose-response to background radiation
in the entire US population, with regard to life
expectancy and site-specific cancer mortality.

Methods

Data sources

Our data included the entire US population of the 3139
US counties (N), encompassing a total number of over
320 million people. The variables in the analysis
included the background radiation levels, age-adjusted
cancer mortality rates, and life expectancy data for
each county. Data on radiation levels was calculated
using the United States Environmental Protection
Agency's (EPA) radiation dose calculator (https://
www.epa.gov/radiation/calculate-your-radiation-
dose), taking into account the two major sources of
background radiation: terrestrial radiation and cosmic
radiation. Information about specific average height of
every county was taken from The National Map
(TNM) tool of the United States Geological Survey
(USGS)   (https://viewer.nationalmap.gov/theme/
elevation/#). Data on cancer statistics was collected
from the United States Cancer Statistics (USCS), the
official federal statistics on cancer incidence and
deaths, produced by the Centers for Disease Control
and Prevention (CDC) and the National Cancer Insti-
tute (NCI) (https://www.statecancerprofiles.cancer.
gov/deathrates/index.php). The collected data inclu-
ded the average of 5-year (2011–2015) age-adjusted
cancer mortality rates (total and site-specific) for the
entire US counties, separately for males and females.
Data on life expectancy was collected from the

Institute for Health Metrics and Evaluation (IHME), an independent population health research center at the University of Washington Medical Center (http://ghdx.healthdata.org/us-data).

Data analysis

Data was analyzed using JMP®^{TM} software for statistical analysis. The data was screened for outliers, entry errors, missing values and other inconsistencies that could compromise the analysis. Jackknife resampling technique was used to estimate the bias and the variance of the data. Since cancer and life expectancy data exhibited normal distribution (data not shown), the statistical significance of the differences between the categories was determined by t-test or by ANOVA test, when two categories or more were involved, respectively. Data on esophagus, melanoma of the skin, oral cavity & pharynx, thyroid, and uterus cancers was not sufficient enough for a reliable statistical evaluation, and thus was not included in the analysis. Parametric (Pearson) coefficient of correlation was estimated, and in all cases p-values of less than 0.05 were considered statistically significant. The p-values of less than 0.1 were considered as a tendency (Hackshaw and Kirkwood 2011). We used both p-value and CI because they provide complementary types of information (du Prel et al. 2009). In life expectancy and total cancer mortality rates analysis, the average dose of each exposure level was calculated and plotted against the variable. Only exposure levels of N > 5 were taken into account.

Results

Distribution of background radiation levels in the US

The background radiation levels have a 2.5-fold difference between the lowest and the highest levels, ranging from 92 to 227 mrem/year, with a median value of 115 mrem/year. The lower levels are mainly found at the Gulf and Atlantic coasts states, and the higher levels are mainly found at the Colorado Plateau states (Online Resource 1).

Life Expectancy

As seen in Fig. 1, a highly significant positive correlation of life expectancy with background radiation levels was found for both males and females (r = 0.647 and r = 0.651, respectively; p < 0.001; 95% confidence interval [CI]). According to the regression line, every 10 mrem/year extend the life expectancy by 2.4 months in males, and by 1.8 months in females, so that within the natural range of background radiation this provides a maximum increase in life expectancy of 2.7 and 2.4 years for males and females, respectively.

Total cancer mortality rate

The analysis revealed a strong negative correlation between age-adjusted cancer mortality rates and background radiation levels, for both males and females (r = − 0.90 and r = − 0.77, respectively; p < 0.001; 95% CI). The range of exposure levels within the background radiation lies within 92 and 227 mrem/year, i.e. 135 mrem/year interval. According to the regression equation, an increase in background radiation by approximately 2 mrem/year in males and 4 mrem/year in females is accompanied by a decrease in the total cancer mortality rate by 1 death per 100,000 people. Thus, the maximum radiation-dependent effect would be around 69 deaths per 100,000 people in males (p < 0.001; 95% CI), but almost two-fold lower in females (35 deaths per 100,000 people; p < 0.001; 95% CI) (Fig. 2).

Radiation effect on site-specific cancer mortality rates

Our next step was to evaluate whether the radiation-dependent effects on age-adjusted cancer mortality rates are site-specific. For this purpose, we compared the effects of low vs. high background radiation levels, as categorized above (see Online Resource 1). The results of this analysis are presented in Table 1. In both males and females, we discovered a significant decrease (p < 0.005; 95% CI) in mortality rates for lung & bronchus cancer, pancreas cancer, and colon & rectum cancer. In males, but not in females, a significant decrease for brain & ONS cancer, and bladder cancer (p < 0.05; 95% CI) was also observed, as well as a clear tendency toward significance for
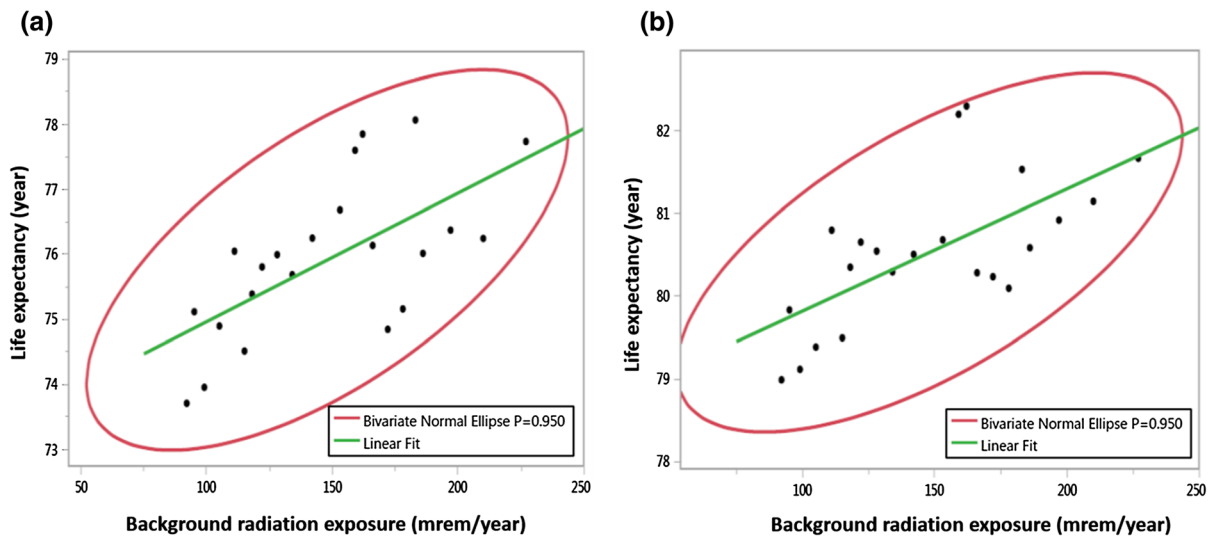
(a)

(b)

Fig. 1 The life expectancy was plotted against the average estimated radiation level of each exposure level. The regression equations for males (**a**) and females (**b**), respectively:

$LE = 0.02BRL + 73.0$ and $LE = 0.015BRL + 78.3$, where LE stands for life expectancy in years, and BRL stands for background radiation levels in mrem/year
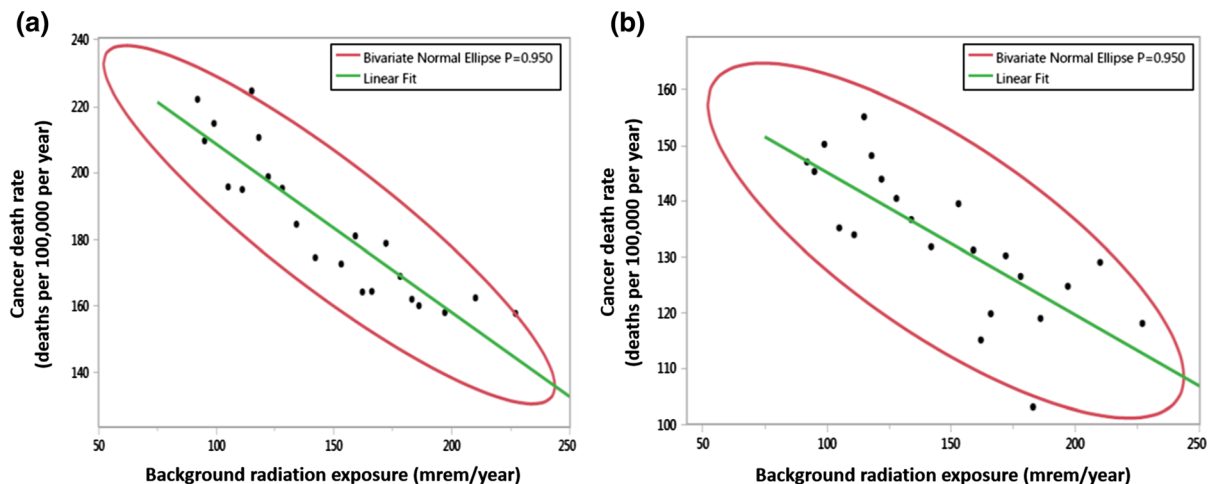
(a)

(b)

Fig. 2 Background radiation levels were plotted against age-adjusted cancer mortality rates of each exposure level. The regression equations for males (**a**) and females (**b**), respectively: $CDR = -0.51BRL + 259.2$ and $CDR = -0.26BRL + 170.7$,

where CDR stands for the number of cancer deaths per 100,000 per year, and BRL stands for background radiation levels in mrem/year

liver & bile duct cancer (p = 0.08; 95% CI). In contrast, neither for males nor for females, any significant effects were found for leukemia, kidney & renal pelvis cancer, and stomach cancer (p > 0.2; 95% CI), as well as for the gender-dependent cancers (cervix, breast, and prostate; with a clear tendency for ovarian, p = 0.08; 95% CI).

Discussion

The linear no-threshold (LNT) model of radiation damage is still widely accepted (Shore et al. 2019; Puskin 2009). Moreover, this concept determines the current radiation protection policy as reflected by the ALARA guiding principle of the International Commission on Radiological Protection (ICRP): "As Low As Reasonably Achievable" (ICRP 2007; Burtt et al.

Table 1 Site-specific cancer mortality rates (deaths per 100,000 people; the means ± SD) in response to low-level radiation (LLR) and high-level radiation (HLR), in both males and females

Cancer type	Males		Females	
	LLR	HLR	LLR	HLR
Lung & Bronchus	68.6 ± 18.8	42.5 ± 20.3*	41.1 ± 10.7	30.7 ± 11.7*
Pancreas	13.8 ± 3.2	12.2 ± 3.2*	10.2 ± 2.4	9.5 ± 1.8*
Colon & Rectum	20.4 ± 6.1	18.6 ± 6.0*	13.8 ± 3.7	12.1 ± 3.7*
Brain & ONS	5.8 ± 1.6	5.1 ± 0.7*	3.9 ± 1.1	3.7 ± 0.5
Bladder	8.4 ± 2.1	7.5 ± 1.7*	2.4 ± 0.6	2.3 ± 0.3
Liver & Bile duct	10.2 ± 3.0	9.1 ± 3.6**	4.0 ± 1.4	4.3 ± 1.3
Breast	–	–	22.6 ± 5.1	21.9 ± 6.1
Leukemia	9.5 ± 2.1	9.6 ± 2.8	5.3 ± 1.2	5.1 ± 1.1
Kidney & Renal pelvis	6.0 ± 1.6	6.1 ± 1.8	2.6 ± 0.8	2.5 ± 0.6
Cervix	–	–	2.5 ± 0.8	2.4 ± 0.7
Ovary	–	–	7.6 ± 1.8	8.1 ± 1.3**
Prostate	21.8 ± 6.6	22.2 ± 3.9	–	–
Stomach	4.8 ± 1.5	5.4 ± 2.7	2.5 ± 0.7	2.5 ± 0.8

*$p < 0.05$
*$p = 0.08$

2016). ALARA assumes that any exposure to ionizing radiation carries some risk, thus every effort should be made to maintain the exposures *as low as possible*. Consequently, each year hundreds of billions of dollars are spent worldwide to maintain extremely low radiation levels (Sanders 2017). Yet, our results provide clear indications for *re-considering* the LNT paradigm, at least within the natural range of background radiation. Indeed, we have shown that not only that the highest background radiation levels (from 180 and up to 227 mrem/year) do no harm compared to the lowest levels of less than 100 mrem/year, but also display clear beneficial health effects. Life expectancy, the most integrative index of population health, was found to be approximately 2.5 years longer in people living in areas with a relatively high vs. low background radiation. This radiation-induced lifespan extension could to a great extent be associated with the decrease in cancer mortality rate observed in HLR areas for several common cancers including lung, pancreas, colon, brain, and bladder cancers. Such trends of lower cancer mortality rates in higher background radiation areas were also found in India (Nambi and Soman 1987), Iran and China (Tang and Loganovsky 2018), and are in line with the studies on US population conducted by Cohen (1995, 1997) and Hart (2010, 2011).

As mentioned above (see Introduction), the NCRP experts recently re-evaluated the LNT model for radiation protection policy and came to the conclusion that there is no reason to modify the current concept (Shore et al. 2019; NCRP Commentary No. 27, 2018). This conclusion may appear controversial to our findings on the longevity-promoting and cancer mortality-reducing effects of high-level background radiation. However, a more careful examination of the data reveals otherwise. First, the range of radiation levels analyzed in the NCRP's study was at least several folds higher (and in many cases even several orders higher) than in our study. Second, even in those relatively high levels, no significant association was found between radiation and several site-specific cancers, among which are gender-dependent cancers (cervix, breast, and prostate) and leukemia (Shore et al. 2019)⁻ the results that are in fact consistent with ours. Furthermore, the NCRP's study did not relate to cancers in which we did find a significant negative correlation of mortality rates with background radiation levels (i.e., pancreas, colon, brain, and bladder). All in all, it is reasonable to suggest that a radiation threshold does exist, yet it is higher than the upper limit of the natural background radiation levels in the US (227 mrem/year). Below the threshold level, the opposed relationships between the background radiation and its health effects are observed, so that the higher radiation exposure, the longer life expectancy and the lower cancer-associated mortality. Of note, even the NCRP Committee recognizes that "the risks from LD/LDR are small and uncertain" (Shore et al. 2018). It is important to mention in this regard that

Hermann J. Muller (1946), who stated that there is no threshold dose, the notion which lies in the basis of the LNT model, based his assumption on his work on mice. However, Neel et al. (1989) proved that there are major differences between mice and humans with regard to sensitivity to the genetic effects of radiation, so that humans are much less sensitive to radiation as projected from the mouse paradigm.

While the biological effects of high radiation (generally artificial) were extensively investigated (Burtt et al. 2016; Candéias and Testard 2015; Christensen et al. 2014), the studies on the effects of low levels (comparable with natural background) on human health and longevity are limited, and often inconclusive because of the relatively small population size analyzed. Overall, these studies, which are reviewed elsewhere (Cameron 2005; Dobrzyński et al. 2015; Hendry et al. 2009), are in line with our major findings on the association of higher background radiation with less cancer mortality and lifespan extension. Experimental studies on mammals (mice, rats, beagle dogs, chipmunks, etc.) also suggest the existence of a radiation range with lifespan-extending effect, a phenomenon known as "longevity hormesis" (Lorenz et al. 1955; Thompson et al. 1990; Vaiserman et al. 2010, 2018). Hormetic effects of low-dose radiation could be the result of several potential mechanisms, such as the activation of DNA repair, activation of endogenous antioxidant systems, induction of the heat shock protein response, stimulation of immune responses, etc. (Guéguen et al. 2019; Sanders 2010; Tharmalingam et al. 2019; Vaiserman et al. 2019). Yet, our conclusions are based on indirect measurements of background radiation, and further investigation with direct measurements is warranted. In human studies, confounding factors influencing life expectancy and health status (like income level, smoking, etc.) should be considered when evaluating biological effects of background radiation. In an attempt to distinguish between the radiation effects and selected confounding factors, we undertook a pilot stepwise (forward) multivariate regression analysis which showed that background radiation exposures, income level, and smoking all significantly influence life expectancy, but to a great degree it occurs independently (data not shown; paper in preparation). Whatever the case, it seems that Kondo was indeed correct when stated that "*The collected data strongly suggest that low-level radiation is not harmful, and is,*

in fact, frequently 'apparently beneficial' for human health." (Kondo 1993).

Compliance with ethical standards

References

Burtt JJ, Thompson PA, Lafrenie RM (2016) Non-targeted effects and radiation-induced carcinogenesis: a review. J Radiol Prot 36:R23–R35. doi:https://doi.org/10.1088/0952-4746/36/1/R23

Calabrese EJ (2012) Muller's Nobel Prize Lecture: when ideology prevailed over science. Toxicol Sci 126:1–4. doi:https://doi.org/10.1093/toxsci/kfr338

Calabrese EJ (2016) LNTgate: how scientific misconduct by the U.S. NAS led to governments adopting LNT for cancer risk assessment. Environ Res 148:535–546. doi:https://doi.org/10.1016/j.envres.2016.03.040

Calabrese EJ, Hanekamp JC, Shamoun DY (2018) The EPA cancer risk assessment default model proposal: moving away from the LNT. Dose Response 16:1–4. doi:https://doi.org/10.1177/1559325818789840

Calabrese EJ (2019) The linear no-threshold (LNT) dose response model: a comprehensive assessment of its historical and scientific foundations. Chem Biol Interact 301:6–25. doi:https://doi.org/10.1016/j.cbi.2018.11.020

Cameron JR (2005) Moderate dose rate ionizing radiation increases longevity. Br J Radiol 78:11–13. doi:https://doi.org/10.1259/bjr/62063624

Candéias SM, Testard I (2015) The many interactions between the innate immune system and the response to radiation. Cancer Lett 368:173–178. doi:https://doi.org/10.1016/j.canlet.2015.02.007

Christensen DM, Livingston GK, Sugarman SL, Parillo SJ, Glassman ES (2014) Management of ionizing radiation injuries and illnesses, Part 3: Radiobiology and health effects of ionizing radiation. J Am Osteopath Assoc 114:556–565. doi:https://doi.org/10.7556/jaoa.2014.109

Cohen BL (1995) Test of the linear-no threshold theory of radiation carcinogenesis for inhaled radon decay products. Health Phys 68:157–174. doi:https://doi.org/10.1097/00004032-199502000-00002

Cohen BL (1997) Lung cancer rate vs. mean radon level in U.S. counties of various characteristics. Health Phys 72:114–119. doi:https://doi.org/10.1097/00004032-199701000-00016

Dobrzyński L, Fornalski KW, Feinendegen LE (2015) Cancer mortality among people living in areas with various levels of natural background radiation. Dose Response 13:1–10. doi:https://doi.org/10.1177/1559325815592391

du Prel JB, Hommel G, Röhrig B, Blettner M (2009) Confidence interval or p-value? Part 4 of a series on evaluation of scientific publications. Dtsch Arztebl Int 106:335–339. doi:https://doi.org/10.3238/arztebl.2009.0335

Guéguen Y, Bontemps A, Ebrahimian TG (2019) Adaptive responses to low doses of radiation or chemicals: their cellular and molecular mechanisms. Cell Mol Life Sci 76:1255–1273. doi:https://doi.org/10.1007/s00018-018-2987-5

Hackshaw A, Kirkwood A (2011) Interpreting and reporting clinical trials with results of borderline significance. BMJ 343:d3340. doi:https://doi.org/10.1136/bmj.d3340

Hart J (2010) Cancer mortality in six lowest versus six highest elevation jurisdictions in the U.S. Dose Response 9:50–58. doi:https://doi.org/10.2203/dose-response.09-051.Hart

Hart J (2011) Cancer mortality for a single race in low versus high elevation counties in the U.S. Dose Response 9:348–355. doi:https://doi.org/10.2203/dose-response.10-014.Hart

Hendry JH, Simon SL, Wojcik A, Sohrabi M, Burkart W, Cardis E, Laurier D, Tirmarche M, Hayata I (2009) Human exposure to high natural background radiation: what can it teach us about radiation risks? J Radiol Prot 29:A29–A42. doi:https://doi.org/10.1088/0952-4746/29/2A/S03

ICRP (2007) The 2007 Recommendations of the International Commission on Radiological Protection. ICRP Publication 103. Ann ICRP 37:(2–4)

Kathren RL (2002) Historical development of the linear non-threshold dose-response model as applied to radiation. Pierce L Rev 5:5–30

Kondo S (1993) Health effects of low-level radiation. Kinki University Press, Osaka Medical Physics Publishing, Madison, WI, USA

Lorenz E, Weikel Hollcroft J, Miller E, Congdon CC, Schweisthal R (1955) Long-term effects of acute and chronic irradiation in mice, survival and tumor incidence following chronic irradiation of 0.11 r per day. Natl Cancer Inst 15:1049–1058

Marcus CS (2016) Destroying the linear no-threshold basis for radiation regulation: A commentary. Dose Response 14:1–3. doi:https://doi.org/10.1177/1559325816673491

Muller HJ. Nobel lecture (1946) Available at: https://www.nobelprize.org/prizes/medicine/1946/muller/lecture/

Nambi KS, Soman SD (1987) Environmental radiation and cancer in India. Health Phys 52:653–657. doi:https://doi.org/10.1097/00004032-198705000-00018

NCRP Commentary No. 27 (2018) overview: Implications of recent epidemiologic studies for the linear-non-threshold model and radiation protection. Available at: https://ncrponline.org/product-category/commentaries/

Neel JV, Schull WJ, Awa AA, Samh C, Otake M, Kam H, Yoshimoto Y (1989) Implications of the Hiroshima-Nagasaki genetic studies for the estimation of the human "doubling dose" of radiation. Genome 31:853–859

Puskin JS (2009) Perspective on the use of LNT for radiation protection and risk assessment by the U.S. Environmental Protection Agency. Dose Response 7:284–291. doi:https://doi.org/10.2203/dose-response.09-005.Puskin

Sacks B, Siegel JA (2017) Preserving the anti-scientific linear no-threshold myth: Authority, agnosticism, transparency, and the standard of care. Dose Response 15:1–4. doi:https://doi.org/10.1177/1559325817717839

Sanders CL (2010) Radiation hormesis and the linear-no-threshold assumption. Springer, Heidelberg

Sanders CL (2017) Radiobiology and radiation hormesis. Springer, Heidelberg

Shore RE, Beck HL, Boice JD, Caffrey EA, Davis S, Grogan HA, Mettler FA, Preston RJ, Till JE, Wakeford R, Walsh L, Dauer LT (2018) Implications of recent epidemiologic studies for the linear nonthreshold model and radiation protection. J Radiol Prot 38:1217–1233. doi:https://doi.org/10.1088/1361-6498/aad348

Shore RE, Beck HL, Boice JD Jr, Caffrey EA, Davis S, Grogan HA, Mettler FA Jr, Preston RJ, Till JE, Wakeford R, Walsh L, Dauer LT (2019) Recent epidemiologic studies and the linear no-threshold model for radiation protection-considerations regarding NCRP Commentary 27. Health Phys 116:235–246. doi:https://doi.org/10.1097/HP.0000000000001015

Tang FR, Loganovsky K (2018) Low dose or low dose rate ionizing radiation-induced health effect in the human. J Environ Radioact 192:32–47. doi:https://doi.org/10.1016/j.jenvrad.2018.05.018

Tharmalingam S, Sreetharan S, Brooks AL, Boreham DR (2019) Re-evaluation of the linear no-threshold (LNT) model using new paradigms and modern molecular studies. Chem Biol Interact 301:54–67. doi:https://doi.org/10.1016/j.cbi.2018.11.013

Thompson GA, Smithers J, Boxenbaum H (1990) Biphasic mortality response of chipmunks in the wild to single doses of ionizing radiation: toxicity and longevity hormesis. Drug Metab Rev 22:269–289. doi:https://doi.org/10.3109/03602539009041086

Vaiserman AM (2010) Hormesis, adaptive epigenetic reorganization, and implications for human health and longevity. Dose Response 8:16–21. doi:https://doi.org/10.2203/dose-response.09-014.Vaiserman

Vaiserman A, Koliada A, Zabuga O, Socol Y (2018) Health impacts of low-dose ionizing radiation: Current scientific debates and regulatory issues. Dose Response 16:1–27. doi:https://doi.org/10.1177/1559325818796331

Vaiserman A, Koliada A, Socol Y (2019) Hormesis through low-dose radiation. In: Rattan SIS, Kyriazis M (eds) The science of hormesis in health and longevity. Elsevier Science Publishing Co Inc, Academic Press, San Diego, pp 129–138