More recent understandings of mutations disclose a substantial number of spontaneous, endogenous double-strand breaks (DSBs) (EDSBs), and further studies of the close fidelity of DSB repairs between EDSBs and radiation-induced DSBs (RIDSBs) for low doses/dose rates (as with CT scans) demonstrate that there can be no identifiable, increased CT-induced cancer risk compared with the background risk from spontaneous EDSBs in the whole body. This results from the body's adaptive responses to LDR.

Many CT scans produce doses less than 10 mSv, most are less than 20 mSv, and all are low in the LDR range. For a typical, low-dose CT scan covering 10% of the body, current literature shows that such low doses affect only DNA in a small fraction of cells in the target mass/volume. The RIDSBs from those are only about 3 in 1 million of the spontaneous EDSBs occurring in the body over the same time. Un- or misrepaired RIDSBs from higher doses are about 0.001% of the un- or misrepaired EDSBs in the body over the same time. For an essentially equal repair fidelity of RIDSBs and EDSBs, as discussed previously (*6*), un- or misrepaired RIDSBs are only about 0.0003% of un- or misrepaired EDSBs in the body over the same time. Further, all un- or misrepaired DSBs still require other low-probability events (which are also addressed by adaptive response) to arrive at some cancerous prelude.

Finally, the U.S. government has recently reported that cancer incidence declined by about 1%/y, and cancer mortality declined by about 1.6%/y over recent years, whereas CT usage has expanded, in support of increasing early detection and decreasing cancer mortality. Duncan et al. (*1*) repeat the words that "a threshold requires processes that leave no cells harboring DNA mutations" (*3*). Contradictorily, Duncan et al. (*1*) then cite how DNA errors of EDSB repair can lead to inactivating tumor suppression genes through premalignant lesions. These are obviously background, spontaneous DNA events, and with large contributions of EDSBs harboring DNA mutations, the fallacy of the quotation (*3*) is apparent: large, spontaneous, EDSB backgrounds exist in the body due to its metabolism, environments, and other factors; thresholds exist because LDR stimulates adaptive responses to remove IRDSBs and EDSB backgrounds, an enhanced dose response that reduces the body's inventory of potential cancer precursors.

REFERENCES

1. Duncan JR, Lieber MR, Adachi N, Wahl RL. Radiation dose does matter: mechanistic insights into DNA damage and repair support the linear no-threshold model of low-dose radiation health risks. *J Nucl Med.* 2018;59: 1014–1016.
2. Siegel JA, Greenspan BS, Maurer AH, et al. The BEIR VII estimates of low-dose radiation health risks are based on faulty assumptions and data analyses: a call for reassessment. *J Nucl Med.* 2018;59:1017–1019.
3. National Research Council (U.S.). Committee to Assess Health Risks from Exposure to Low Level of Ionizing Radiation. *Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII Phase 2.* Washington, DC: National Academies Press; 2006.
4. Lloyd DC, Edwards AA, Leonard A, et al. Chromosomal aberrations in human lymphocytes induced in vitro by very low doses of x-rays. *Int J Radiat Biol.* 1992; 61:335–343.
5. Pohl-Rüling J, Fischer O, Haas G, et al. Effect of low-dose acute x-irradiation on the frequencies of chromosomal aberrations in human peripheral lymphocytes in vitro. *Mutat Res.* 1983;110:71–82.
6. Vilenchik MM, Knudson AG. Endogenous DNA double-strand breaks: production, fidelity of repair, and induction of cancer. *Proc Natl Acad Sci USA.* 2003;100: 12871–12876.

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Radiation Dose Does Indeed Matter: Proof That Invalidates The Linear No-Threshold Model

TO THE EDITOR: In their Invited Perspective (*1*), Duncan et al. "respectfully disagree" with our commentary challenging the Biologic Effects of Ionizing Radiation (BEIR) VII report conclusions (*2*). In it, we demonstrate point by point *and without speculation* that the BEIR committee's conclusions are contradicted even by their own selected evidence. Choosing to ignore the evidence presented, Duncan et al., emphasizing facts that we show to be irrelevant, proclaim their unwavering *belief* in the correctness of BEIR VII's conclusion that the linear no-threshold (LNT) model is valid. Since BEIR VII is a frequently cited source on the legitimacy of the LNT model, a solution to this controversy is crucial.

Duncan et al. repeat arguments made in their previous letter that we have already refuted (*3*). They ignore our refutations that demonstrate the need for reassessment of BEIR VII. In this brief response, we focus on 2 misconceptions [emphasis ours]:

1. ". . .a threshold [for cancer causation] requires processes that leave *no* cells harboring DNA mutations."
2. LNT "remains the best, and certainly the most *conservative*, means of estimating the risk of exposing humans to varied levels of ionizing radiation."

The existence of a threshold for radiation exposure does *not* require that *all* cells with mutations be completely repaired or removed, leaving no cells with mutations. All that is required is that *fewer* such cells be left with mutations after radiation exposure than before, *once sufficient time is allowed for repair and removal processes to take place—usually less than 24 h.* This *decrease* in the baseline mutation rate is the essence of hormesis.

Duncan et al. grant that endogenous processes cause mutations whether radiation—beyond the omnipresent natural background radiation—is present or not. Mutations occur continually throughout our bodies, so the baseline from which radiation operates is not zero mutations, yet some 60% of us never develop clinical cancer. This must indicate there are processes that repair or *remove* cells in which DNA damage could theoretically lead to cancer, a fact that is demonstrated by hundreds of studies (*4,5*). Thus, unrepaired and misrepaired mutations, along with double-strand breaks that exist in the absence of or after low-dose exposure, are *not* sufficient for the development of clinical cancer.

The claim of colinearity across dose ranges characterized by different biologic responses dissociates mathematics from its putative referent in reality. The well-established linearity of the dose response to higher-dose acute exposures (>100 mSv), as noted by Duncan et al. and undisputed by us, is irrelevant to the claim of linearity at lower doses, let alone to the existence or absence of a threshold. Furthermore, there is no credible evidence *at lower doses* of either

linearity or absence of a threshold for carcinogenesis; both are simply assumed or based on faulty reasoning.

Although linearity may describe *initial* damage after low-dose exposure, the body's complex multilevel response to this damage is nonlinear, making the overall result nonlinear. Only at high doses are these responses inhibited or overwhelmed, thereby preserving this linearity: thus, nonlinearity in the low-dose range and linearity in the high-dose range.

The second bulleted misconception above contains 2 assertions by Duncan et al.: that LNT (a) "remains the best" and (b) provides "the most conservative" estimate of risk. First, from what we have shown, LNT is not the "best," because, while being a mathematic convenience, it is empirically false. And second, it would be the most conservative *only* if there were no negative side effects from overestimating risk or imputing risk where none exists and where there is actual benefit. However, as we have indicated elsewhere, the radiophobia reinforced by LNT and its corollary ALARA (as low as reasonably achievable) has several negative side effects (*6*). These include refusal of medically indicated radiologic imaging; misdiagnoses due to underdosing, which can lower test accuracy; and unwarranted and deadly forced relocations in the vicinity of nuclear power plant accidents.

Duncan et al. offer assumptions without evidence, irrelevant facts, and serious misconceptions, instead of evidence and rational argument. The search for the truth requires a critical reading of the literature, not uncritical acceptance of proclamations by recognized voices of authority devoid of evidence (*7*).

REFERENCES

1. Duncan JR, Lieber MR, Adachi N, Wahl RL. Radiation dose does matter: mechanistic insights into DNA damage and repair support the linear no-threshold model of low-dose radiation health risks. *J Nucl Med.* 2018;59:1014–1016.
2. Siegel JA, Greenspan BS, Maurer AH, et al. The BEIR VII estimates of low-dose radiation health risks are based on faulty assumptions and data analyses: a call for reassessment. *J Nucl Med.* 2018;59:1017–1019.
3. Siegel JA, Sacks B, Pennington CW, Welsh JS. DNA repair after exposure to ionizing radiation is not error-free. *J Nucl Med* [reply]. 2018;59:349.
4. Luckey TD. *Radiation Hormesis.* Boca Raton, FL: CRC Press; 1991.
5. Aurengo A, Averbeck D, Bonnin A, et al. Dose effect relationships and estimation of the carcinogenic effects of low doses of ionizing radiation. Paris, France: Académie des Sciences–Académie nationale de Médecine; March 2005.
6. Siegel JA, Pennington CW, Sacks B. Subjecting radiological imaging to the linear no-threshold hypothesis: a non sequitur of non-trivial proportion. *J Nucl Med.* 2017;58:1–6.
7. Sacks B, Siegel JA. Preserving the anti-scientific linear no-threshold myth: authority, agnosticism, transparency, and the standard of care. *Dose Response*. 2017;15: 1559325817717839.

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REPLY: We read with interest the letters from Siegel et al., Bevelacqua, Doss, and Pennington (*1–4*). We respectfully disagree with the logic they use to refute the linear no-threshold model. However, we are encouraged that Siegel et al. agree that "linearity *may* describe initial (DNA) damage after low-dose exposure" (emphasis added). We remain convinced that they and the other authors underestimate the long-term ramifications of that damage. Although selective removal of cells harboring DNA damage can occur, the available evidence indicates that most cells survive exposure to ionizing radiation at the levels used for medical imaging (*5,6*). The vast majority of the DNA double-strand breaks (DSBs) caused by ionizing radiation are repaired by nonhomologous end joining, an error-prone process (*7*). As a result, the surviving cells are left with mutations as permanent "information scars." Finally, there is little, if any, evidence that cells containing these DNA mutations are later removed with sufficient reliability to eliminate the low but finite risk of future cancers.

In a series of elegant in vitro experiments, Asiaithamby and Chen exposed human cells to between 5 and 1,000 mGy of γ-irradiation (*8*). They then studied the distribution of YFP-53BP1, a fluorescent marker of DNA DSBs. Irradiation resulted in a linear increase of nuclear foci that then recruited YFP-53BP1 within the next 30 min. They observed approximately 19 DNA DSBs per Gy, which is similar to the 20–40 DNA DSBs per Gy of γ-irradiation reported by other groups (*9–11*). After sustaining this damage, the same cells did not succumb to apoptosis but rather showed resolution of the fluorescent nuclear foci over the next 8 h related to their repair at those sites.

With this data in mind, we suggest that Siegel et al. and the other authors reconsider the fate of cells with DNA DSBs. During coronary angioplasty procedures, skin cells at the beam entry point frequently receive greater than 1 Gy (*12*). Even though this dose likely leads to more than 20 DNA DSBs per cell, the skin remains viable. Observable tissue reactions occur once the acute dose exceeds 2 Gy (*13*). This agrees with other studies that demonstrate how repair is the typical response to low-level damage even though repair of DNA DSBs is error-prone (*5–7*). In contrast, the DNA damage response pathways favor apoptosis when faced with more severe damage (*5,6*). These findings argue against Siegel et al.'s contention that "all that is required is that fewer cells be left with mutations after radiation exposure than before" (*1*). After a 50-mGy exposure where on average there will be 1 DNA DSB per cell, removing even half the damaged cells would have a profound effect on tissue integrity and still leave an increased number of cells with DNA mutations.

The assertion by Siegel et al. that "mutations . . . are not sufficient for the development of clinical cancer" runs counter to our current understanding of carcinogenesis (*1*). A recent review by Martincorena and Campbell summarizes how clinically relevant neoplasms are caused by the accumulation of multiple mutations over time (*14*). The mutations caused by each medical imaging study will be superimposed on preexisting mutations arising from inheritance, normal metabolism, environmental radiation, or exposure to other carcinogens. We agree that at some low level of ionizing radiation, the additional risk becomes small relative to DNA damage associated with reactive oxygen species intrinsic to physiologic oxidative respiration. Although there is little we can do about the mutations acquired from natural causes, the additional risk caused by medical imaging is under our control. We therefore reaffirm the need to optimize radiation use in medical imaging, especially in children (*15*). We strongly disagree that such efforts are detrimental (*16*).

The letters' authors suggest that DNA damage from low doses of ionizing radiation is a nonissue because humans possess systems that can reliably protect us from radiation-induced cancers (*1–4*). They suggest the immune system and other adaptive responses as