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*).

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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

examples. Studies of cancer immune surveillance demonstrate that the immune system can protect the host against tumor development but that tumors often circumvent the immune system (*17,18*). The term *immunoediting* has been used to describe the process and its 3 phases, namely elimination, equilibrium, and escape. Although our critics focused exclusively on the immune system's ability to eliminate developing tumors, we believe a more balanced approach is needed. There is no escaping the fact that cancers commonly occur in humans with fully functional immune systems. Furthermore, Martincorena and Campbell considered the evolution of protective mechanisms against cancer and observe that "selection is virtually powerless to fight causes of death after reproductive age, so mechanisms will mainly evolve to reduce cancer in the young" (*14*).

The letter from Bevelacqua suggests a need to consider dose rates (*2*). However, as nicely summarized by Beyea, there is compelling evidence from several epidemiologic studies that future cancer risk increases with protracted, low-dose exposures (*19*). This supports our claim that radiation-induced mutations accrue over time. That review also rightfully acknowledged that a substantial number of patients in developed countries already have lifetime exposures from medical imaging that exceed 100 mSv. This again emphasizes the need to carefully balance the benefits of medical imaging against its relatively low risks.

In summary, we appreciate the interest in our recent commentary but stand by its conclusions.

DISCLOSURE

James R. Duncan reports personal fees from Bayer HealthCare LLC, Institute for Healthcare Improvement, and Ascension Health and other from Novation and Washington State Hospital Association, all of which are outside the submitted work. Richard L. Wahl reports consulting fees from Nihon Medi Physics and from Clarity Pharmaceuticals Inc; research grants from White Rabbit AI and Actinium Pharmaceuticals; and travel reimbursement from Siemens Medical and GE Medical, all of which are outside the submitted work. These relationships are managed by the Washington University Conflict of Interest Committee. No other potential conflict of interest relevant to this article was reported.

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