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EDITORIAL COMMENT

Diagnostic Imaging, Radiation Exposure, and Carcinogenic Risk

Let's Be Realistic, Reasonable, and Rational*

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Cardiovascular imaging modalities such as computed tomography (CT) and nuclear cardiology procedures have a wealth of evidence on their effectiveness but also expose a patient to ionizing radiation. Clinical decision making must therefore balance the benefits of incremental diagnostic information with the projected risk after radiation exposure. Therein lies the nub of the problem: Despite numerous guidelines and research papers, we still do not have a good measure of the risks of radiation associated with current-day imaging for an individual patient.

High-dose radiation has clearly documented detrimental effects; however, the magnitude of risk in conventional medical imaging (i.e., low-dose radiation [LDR]) is still a controversial subject. Risk models span a spectrum from the *linear no-threshold* model, wherein any amount of radiation exposure is considered harmful on the basis of epidemiological data projected from survivors of high-dose radiation, to the hormesis model in which LDR might even be protective. Stochastic effects, such as lasting mutations in DNA and cancer risk, are the main concern, but they are not immediately obvious, might take a long time to express, and are likely affected by individual variation in susceptibility and robustness of compensatory repair mechanisms.

All our risk estimates for LDR are, at best, projections, which reflect our lack of robust causal evidence that radiation exposure from a cardiovascular imaging procedure might result in cancer. Procedural exposure from CT and nuclear imaging commonly has effective doses in the range of 5 to <20 mSv, doses equated to LDR, and there is an intense effort to reduce it further. There are really no clear and convincing data that radiation below 50 mSv is associated with cancer in adults (1), and carcinogenic risk data have been conflicting for the exposure of <100 mSv (2,3). The world of cardiovascular medicine is full of probability statements regarding surgical or other therapeutic risk estimates, so much so that we may often fail to recognize the importance of the term *projected*, because it means, in this case, that direct causal evidence is lacking. Because carcinogenic risk cannot be assessed by epidemiological methods alone, proving a direct link between radiation exposure and cancer will require tremendously large sample sizes (4) and detailed longitudinal databases to track thousands of patients over decades of complex care. And we do not have anything even close to go by.

A biomarker that is sensitive to a gradient of radiation damage could act as a dosimeter and would add important perspective to risk. Several approaches have been used to identify surrogates for radiation risk (2,5). Ionizing radiation often causes DNA damage through double-strand breaks (DSB) that are not repaired or are repaired badly, ending in oncogenic chromosomal mutations. Radiation damage also invokes a set of DNA damage responses that involve checkpoint modification and activation of repair mechanisms, and should they fail, they induce apoptotic machinery. Visualizing such changes can serve as a biomarker for radiation-induced DNA damage (e.g., phosphorylated histones, such as γH2AX). The lymphocyte is one of the most sensitive organs affected by radiation, and these cells are often used as a proxy. Chromosomal damage that

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could mediate tumorigenesis (6) has been linked with effective doses of ionizing radiation <50 mSv, doses common for cardiovascular imaging. However, there is wide variation in response to radiation-induced DNA damage or repair (7), which limits how much it can inform us about the clinical outcomes of such DNA damage, and these measurements do not tell us anything about the cumulative effects.

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In this issue of *iJACC*, Nguyen et al. (8) furthered this evidence by examining lymphocytic genetic biomarkers after radiation exposure from diagnostic coronary CT angiography in 67 patients. Median DNA damage was increased by 3.4%, registered as a change in phosphorylation of any DNA damage marker, and median apoptosis increased 3.1 times post-radiation; the absolute magnitude of affected cells was, however, small. Genetic pathways involved in DNA repair regulation (*DDB2*, linked to ultraviolet light exposure and skin cancer risk), DNA DSB regulation (*XRCC4*), and apoptosis regulation (*BAX*) were activated. These data are not unexpected but represent some of the most comprehensive data available about the near-term adverse consequences of exposure to ionizing radiation from medical imaging. The authors also found that most cells were successfully repaired by endogenous repair mechanisms, consistent with the fact that DSB repair is extremely efficient. It might thus not be absolutely correct to equate these cellular changes as cancer surrogates, because we do not know how much DNA damage is needed to sustain a stochastic effect. In fact, there is even evidence that LDR might stimulate reparative mechanisms that would make cells more resistant to further damage (9). Nguyen et al. (8) also found a dose dependency in radiation-induced DNA damage response, and a mixture of scanner technology allowed them to study a wide range of effective doses. The mean total effective dose was 36.9 mSv, far greater than anything we would use currently and many fold higher than what is possible in the future (10). Even within the National Institutes of Health–National Heart, Lung, and Blood Institute–sponsored PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial, cumulative 90-day effective doses were, on average, in the range of 10 to 14 mSv (11). This becomes important because the relationship with DSB may be linear within a range of radiation doses from 1 mGy to 1 Gy (12). In the present study, DNA damage was more often identified in patients with higher blood radiation doses (~40 mSv vs. 23 mSv for those without damage, $p < 0.0001$). Interestingly, no DNA damage was observed in patients undergoing CT angiography with a dual-source scanner at an effective dose of <7 mSv. Among radiation risk models, one less known model, the *linear-threshold model*, assumes a linear range but also a level of radiation below which there is minimal risk of cancer (4,13). This formulation does not exclude some cellular injury, especially one that can be measured with sensitive biomarkers such as in the current study, but adequate repair mechanisms may mitigate obvious stochastic effects. The paper by Nguyen et al. (8) did not find DNA damage or apoptosis below 7 mSv radiation, whereas both of these cellular effects increased with increasing dose beyond that threshold. If this is true, it might shed some light on the possibility of a linear threshold in cardiac imaging even in terms of sensitive assays for DNA damage. This is consistent with other emerging evidence that tissue damage after radiation may indeed have dose thresholds (14). With increasing attention to imaging wisely and newer CT machines bringing down radiation to the sub-1 mSv to 5 mSv range, the fear of radiation may be far outweighed by the benefits of thoughtful imaging.

This report by Nguyen et al. (8) is not the definitive study, but despite many limitations, it adds credence to the importance of optimization of radiation dose reduction in everyday laboratory practice for CT. Future studies may show what could possibly be a safe harbor radiation level. The PROMISE trial showed that CT, as a diagnostic modality, was associated with similar clinical outcomes compared with functional imaging with stress electrocardiography, echocardiography, or myocardial perfusion imaging (11). Coupled with optimized dose reduction and appropriate test selection, the evidence has become quite compelling that CT should be supported as an important tool for diagnosis of cardiovascular disease. Having said that, it is also important to consider this report by Nguyen et al. (8) as preliminary, and one should not read far too much into the safe threshold in this study. Use of radiation principles such as *image gently, image wisely and as low as reasonably achievable (ALARA)* must still remain the cornerstone of good practice.

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