CT Scanning: Is the Contrast Material Enhancing the Radiation Dose and Cancer Risk as Well as the Image?¹

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In 2014, an estimated 81.2 million computed tomographic (CT) scans were performed in the United States, including 12.6 million chest CT examinations, and overall approximately 52% of these were performed with contrast material (1). CT scans can save lives and can enable unnecessary surgical procedures to be avoided; however, the very high levels of use, particularly in the United States, have raised questions about the associated risks and costs. One potential risk is the small possibility the patient will develop a radiation-related cancer. Two large cohorts of children who underwent CT provided some of the first direct evidence of a possible link to subsequent cancer risk (2,3). These findings still need additional replication, and deeper assessment of potential biases is ongoing; however, the size of the risks was broadly consistent with the Japanese atomic bomb studies, a finding that further supports the linear no-threshold assumption for radiation protection purposes (4).

It is difficult to study the cancer risks from low doses of radiation directly because of the very large sample size needed to detect small excess risks, and the long latency period for most radiation-related cancers means that decades of follow-up are needed (5). The two cohorts of pediatric patients who underwent CT scanning surmounted these difficulties via a retrospective cohort design achieved through the linkage of large electronic databases (2,3). A retrospective cohort is equally as valid as a prospective cohort and should not be confused with a retrospective case-control study, which can be subject to recall bias (6). The large scale of these studies, however, precludes assessment of more detailed questions, such as the effect of contrast medium, which was not necessarily routinely recorded in the electronic records. Another approach that can be used to indirectly assess the

potential cancer risks from specific procedures is to use an intermediate end point, such as the induction of DNA double-strand breaks (DSBs) (7). This was the approach adopted in the current study (8). Piechowiak et al assessed the effect of iodinated contrast agents on the formation of DNA DSBs after chest CT. They found that the γ H2AX foci levels were increased after CT scanning but that the increases were twice as high in the group that received contrast material. Contrast material-enhanced CT has been shown to increase the radiation dose to organs (9); however, Piechowiak et al took this a step further by providing evidence of damage at the DNA level.

To our knowledge, this is the largest study to date to investigate this question, with 245 patients in total (66 underwent only unenhanced CT, 179 underwent contrast-enhanced CT). The patients underwent scanning in the same hospital over a 2-year period with use of a standard protocol. Blood was taken immediately before and after CT. The foci levels were the same in the two groups of patients (contrast-enhanced CT group vs unenhanced CT group) before CT. Estimated radiation doses were slightly higher in the unenhanced CT group. The increase in foci levels after CT was significantly higher in the group that received contrast material, after adjustment for the lower radiation dose levels in the contrast-enhanced group (0.056 foci per cell vs 0.027 foci per cell). The magnitude of the increase was also broadly consistent with the estimated increase in radiation dose due to contrast material from a study that used change in attenuation (measured in Hounsfield units) (9). Three earlier studies reported similar findings of increased excess foci per cell, but these studies included fewer than 20 patients in each group (10–12). Although two other studies did not reveal increases due to contrast material at low doses (<0.1 Gy), they did

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reveal increases at doses higher than 1 Gy, but these were in vitro rather than in vivo studies (13,14).

Chromosome aberrations in peripheral lymphocytes are considered to be the reference standard of biomarkers of radiation exposure (15). They have been used as biomarkers of acute short-term exposures typically from accidents, as well as long-term exposures from occupational, environmental, or medical sources of radiation. Chromosomal aberration frequency also has been linked directly to subsequent cancer risk in a large pooled epidemiologic study of 22358 subjects from 11 countries (16). In this study, Bonassi et al found increased risk of cancer in the subjects with chromosome damage in the highest tertile compared with those in the lowest tertile. Unfortunately, it is challenging to use these reference standard biomarkers for very-low-dose exposures, such as CT scanning. Translocations, which are a marker of long-term radiation exposure, are not detectable in the low-dose range of CT scans, and dicentric, which are a marker of short-term exposure, cannot be used as reliable markers of past exposure. In contrast, γ H2Ax has been shown to be precise, sensitive, and simple to use, even to detect a few DSBs. Experimental evidence has shown that DSBs can be detected at doses as low as 1 mGy with a linear relationship of DSBs from 1 mGy up to 100 Gy (7).

The Piechowiak et al study uses γ H2Ax to measure DSBs but does not attempt to directly link the findings to subsequent cancer risk; rather, it stays within the realm of viewing this as a biodosimetry tool. The link between DSBs and subsequent cancer risk is mechanistically highly plausible but has yet to be shown convincingly in a large human study population (17). Several small studies of patients with cancer (bladder, lung, and esophageal) have shown increased levels of γ H2AX when compared with those in control subjects, indicating a higher susceptibility to DSBs in patients with cancer (18–20). The quantitative link between foci levels and cancer risk is also difficult to predict, given the large uncertainties

around levels of repair. In some of the previous studies, researchers assessed blood 24 hours after CT scanning and found that the excess foci per cell, both in those who received contrast material and in those who did not, had returned to pre-examination levels (10,11). This implies repair of the DSB damage in the peripheral lymphocytes or, alternatively, elimination of damaged cells by another mechanism, such as apoptosis. Experimental work has indicated that DNA repair of the damage is more efficient at higher doses than at lower doses and that repair is strongly compromised in the range of typical diagnostic radiation exposures of 1–10 mGy that can lead to lasting damage from persistent DSBs (7). The laboratory work-up is very expensive, but there seems to be a need to design an efficient study in a highly exposed population to test and quantify the link between DSBs and subsequent cancer risk directly.

There are other potential acute side effects from contrast material that also need to be considered, the most common being allergic reactions and nephrotoxicity. Thyroid disease (iodine-induced hyperthyroidism or thyrotoxicosis) and extravasation are much rarer side effects. Levels of injectable contrast material use in the United States appear to be decreasing, declining from 67% of examinations in 2007 to 52% in 2014 (1). American College of Radiology Appropriateness Criteria can be used to determine the clinical scenarios in which it is critical and those in which it is unnecessary. In one recent study, researchers evaluated the use of contrast material in abdominal and pelvic CT examinations performed in U.S. academic emergency departments and found that a substantial number of respondents deviated from the American College of Radiology recommendations (21). The most common deviation was use of contrast material when it was not indicated; however, there were also scenarios in this study in which contrast material was indicated but not used. In situations in which it is indicated, as for blunt chest trauma (22), the higher dose and potential risks will be outweighed by the benefits. There are many current efforts

to keep radiation dose from CT examinations as low as reasonably possible, especially in children (23); however, the use of contrast material has not been widely recognized as an important factor in these efforts. Given the expanding evidence about the effect on dose and potential cancer risk, further research into patterns of use and the potential adverse effects of contrast material use with CT now seems warranted.

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