

# Low-dose ionizing radiation and cancer risk: not so easy to tell

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Medical imaging has helped physicians in the diagnosis and treatment of numerous medical conditions. The widespread utilization of medical imaging particularly computed tomography and nuclear scans has led to increased exposure to ionizing radiation (1). Malignancy is certainly the most concerning late complication of diagnostic ionizing radiation and the lifetime attributable risk of having cancer is significantly higher when exposure is in the childhood (2). The international experts body recommends the doses must be "As Low As Reasonably Achievable (ALARA)" while maintaining the diagnostic image quality. Several dose reduction techniques have been suggested to follow the ALARA principle (3). While it is not possible to completely eliminate such diagnostic tests, it is recommended that physicians request such tests only when the benefits absolutely outweigh the risks (4).

Current data that support the risks of cancers due to ionizing radiation are from the studies of survivors of the atomic bombs in Japan (5). The study by Brenner *et al.* (6) showed the risk of lifetime cancer mortality is significantly higher from pediatric CT than from adult CT. In another study by Pearce *et al.* (7), the cumulative radiation doses more than 50 milliSieverts (mSv) in children could triple the risk of leukemia and brain cancer, although the cumulative absolute risks were small and there was high possibility of reverse causation (explained below). The use of CT scans in pediatric populations could potentially produce small cancer risk and should be used only when absolutely necessary.

The linear no-threshold (LNT) model evolved in the 1950s and is the basis of current regulation which suggests

there is no safe level of radiation doses, and that any amount of radiation carries some risk of cancer (linear with the dose) (8). However, the validity of LNT model has been challenged (9). In fact, low-dose exposures might stimulate immune responses and DNA repair (10,11), and the doseeffect relationship could be hormetic or biphasic with beneficial effects at low-doses and harmful effects at high doses (12,13). The mortality among medical professionals who are exposed to low-dose radiation was not found to be different compared to that among non-exposed (14,15). Similar results were found among workers in the nuclear industries (16-18). Populations living in areas of high-level radiation were not prone to high risk of health hazards than those living on low-level background radiation (19,20). Thus, many studies have now suggested that radiation exposures less than 100 mSv are too low to detect any statistically significant cancer excess in the presence of naturally occurring malignancies (21).

No epidemiological studies so far have presented convincing evidence that low-dose diagnostic ionizing radiation exposure causes cancer. The latest study in the field published recently suggested an association. In this paper by Hong *et al.* (22) "Association of exposure to diagnostic low-dose ionizing radiation with risk of cancer among youths in South Korea", the investigators reported increased incidence of overall cancer among young individuals exposed to diagnostic low-dose ionizing radiation than among non-exposed individuals. The cohort study included youths aged 0–19 years at baseline from South Korean National Health Insurance System (KNHIS)

claim records from January 1, 2006 to December 31, 2015. The KNHIS supports 90% of medical payments for cancer patients and thus the data was derived from large cohort of 49,570,064 individuals who filed medical claims from 2002 to 2015. The exposure to diagnostic low-dose ionizing radiation was classified as any that occurred on or after the entry date, when the participant was aged 0 to 19 years, on or before the exit date, and at least 2 years before any cancer diagnosis. Of 12,068,821 individuals 0-19 years old included for the analysis, 1,275,829 (10.6%) were exposed to diagnostic low-dose ionizing radiation between 2006-2015, and 10,792,992 (89.4%) individuals were not exposed. Among exposed individuals, 1,444 had cancer (0.11%). Among non-exposed individuals, 20,468 had cancer (0.19%). The authors concluded that the incidence rate ratio of cancer was greater among exposed individuals than among non-exposed individuals after adjusting for age and sex [incidence rate ratios (IRR), 1.64 (95% CI, 1.56-1.73), P<0.001).

Although the study is one of the largest population-based studies evaluating diagnostic medical radiation exposure and cancer risk and certainly the largest in an Asian cohort, there are several limitations:

(I) The study is a typical example of reverse causation, in which the suspicion for cancer leads physicians to order imaging tests which will indeed detect cancers. Thus, any subsequent incidence of cancer couldn't be attributed to the diagnostic low-dose ionizing radiation. In this study, there was lack of information regarding the reasons for obtaining a diagnostic imaging testing. Why would a 5-year old obtain computed tomography scan unless there is some suspicion of malignancy? The investigators considered this possibility of reverse causation and allowed at least a 2-year lag period between radiation exposure and cancer diagnosis. However, it takes at least 5-7 years for induction of leukemia and at least 10 years for solid tumors. The cancer listed in the study, therefore, most likely have occurred naturally rather than by diagnostic lowdose ionizing radiation exposure. The investigators also calculated risk in three different lag-period (1, 2, and 5 years). Interestingly, the IRR decreased with longer lag period-IRR was 1.72 for lag of 1 year, 1.64 for lag of 2 years, and 1.48 for a lag of 5 years. This finding again supports reverse causation. If the cancers were truly due to ionizing radiation, then the lag period of 5 years should

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have higher IRR compared to the lag period of 1 year, and not the other way around;

- (II) The incidence of cancer among exposed was 0.11 % and the incidence of cancer among non-exposed was 0.19%. Thus, it looks like the incidence of cancer is actually lower in the exposed group. However, the investigators adjusted for age and sex and calculated the IRR of 1.64 (95% CI, 1.56–1.73) to draw the conclusion. It is not clear to us how significant it is to adjust for age and sex in youths of 0–19 years because the authors have not provided unadjusted data of IRR, thus the possibility of overadjustment exists;
- (III) The investigators analyzed the risks of specific types of cancers among exposed and non-exposed groups and found the increased incidence rate ratio of solid neoplasms than of lymphoid/hematopoietic neoplasms (IRR 1.7 *vs.* 1.53 respectively). When there is a lag period of only 2 years between exposure to ionizing radiation and cancer diagnosis, we would expect a higher incidence of lymphoid/hematopoietic neoplasm. The current study reflects the opposite results according to the data presented in the paper;
- (IV) To overcome the issue of whether the CT (or other diagnostic imaging test) was done due to suspicion of cancer (brain cancer was more likely to be diagnosed after CT of the head), the authors could simply compare children who underwent head CT to people who underwent brain MR to see if there is an increase. It is highly doubtful, as children who undergo brain imaging most likely have significant headaches or neurologic findings that could be an early manifestation of cancer;
- (V) The present study lacks the data about radiation dosage and it further complicates the process to show any association of ionizing radiation with cancer risk.

Despite several limitations listed above, the study has raised awareness among readers about risks of cancer in young population associated with diagnostic ionizing radiation. The study could have potentially shown true evidence of causation if the follow-up period were at least 10–20 years after diagnostic low-dose ionizing radiation exposure. The results of epidemiological studies involving ionizing radiation and cancer risk should be interpreted with caution due to presence of several confounders. Finally, one should also bear in mind that over-estimating

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the harmful effects of ionizing radiation could falsely alarm physicians to not to order such imaging tests and could impose greater risk to patients than that associated with diagnostic radiation exposures (23).

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## Footnote

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