Editorial Commentary

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 dose-effect 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 low-dose 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 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 over-adjustment 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 neoplasms than that of solid 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 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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References

1. Fazel R, Krumholz HM, Wang Y, Ross JS, Chen J, Ting HH, Shah ND, Nasir K, Einstein AJ, Nallamothu BK. Exposure to low-dose ionizing radiation from medical imaging procedures. N Engl J Med 2009;361:849-57.
2. Einstein AJ, Henzlova MJ, Rajagopalan S. Estimating risk of cancer associated with radiation exposure from 64-slice computed tomography coronary angiography. JAMA 2007;298:317-23.
3. Tamm EP, Rong XJ, Cody DD, Ernst RD, Fitzgerald NE, Kundra V. Quality initiatives: CT radiation dose reduction: how to implement change without sacrificing diagnostic quality. Radiographics 2011;31:1823-32.
4. Budoff M. Cardiac CT: benefits outweigh the risks. J Cardiovasc Comput Tomogr 2011;5:275-6.
5. Preston DL, Ron E, Tokuoka S, Funamoto S, Nishi N, Soda M, Mabuchi K, Kodama K. Solid cancer incidence in atomic bomb survivors: 1958-1998. Radiat Res 2007;168:1-64.
6. Brenner D, Elliston C, Hall E, Berdon W. Estimated risks of radiation-induced fatal cancer from pediatric CT. AJR Am J Roentgenol 2001;176:289-96.
7. Pearce MS, Salotti JA, Little MP, McHugh K, Lee C, Kim KP, Howe NL, Ronckers CM, Rajaraman P, Sir Craft AW, Parker L, Berrington de González A. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. Lancet 2012;380:499-505.
8. Calabrese EJ. How the US National Academy of Sciences misled the world community on cancer risk assessment: new findings challenge historical foundations of the linear dose response. Arch Toxicol 2013;87:2063-81.
9. Vaiserman A, Koliada A, Zabuga O, Socol Y. Health Impacts of Low-Dose Ionizing Radiation: Current Scientific Debates and Regulatory Issues. Dose Response 2018;16:1559325818796331.
10. Cohen BL. Dose-response relationship for radiation carcinogenesis in the low-dose region. Int Arch Occup Environ Health 1994;66:71-5.
11. Cui J, Yang G, Pan Z, Zhao Y, Liang X, Li W, Cai L. Hormetic Response to Low-Dose Radiation: Focus on the Immune System and Its Clinical Implications. Int J Mol Sci 2017. doi: 10.3390/ijms18020280.
12. Calabrese EJ. Biphasic dose responses in biology, toxicology and medicine: accounting for their generalizability and quantitative features. Environ Pollut 2013;182:452-60.
13. Calabrese EJ, Dhawan G, Kapoor R, Iavicoli I, Calabrese V. What is hormesis and its relevance to healthy aging and longevity? Biogerontology 2015;16:693-707.
14. Linet MS, Kitahara CM, Ntowe E, Kleinerman RA, Gilbert ES, Naito N, Lipner RS, Miller DL, Berrington de Gonzalez A; Multi-Specialty Occupational Health Group. Mortality in U.S. Physicians Likely to Perform Fluoroscopy-guided Interventional Procedures Compared with Psychiatrists, 1979 to 2008. Radiology 2017;284:482-94.
15. Mohan AK, Hauptmann M, Freedman DM, Ron E, Matanoski GM, Lubin JH, Alexander BH, Boice JD Jr, Doody MM, Linet MS. Cancer and other causes of mortality among radiologic technologists in the United States. Int J Cancer 2003;103:259-67.
16. Iwasaki T, Murata M, Ohshima S, Miyake T, Kudo S, Inoue Y, Narita M, Yoshimura T, Akiba S, Tango T, Yoshimoto Y, Shimizu Y, Sobue T, Kusumi S, Yamagishi C, Matsudaira H. Second analysis of mortality of nuclear industry workers in Japan, 1986-1997. Radiat Res 2003;159:228-38.
17. Kendall GM, Muirhead CR, MacGibbon BH, O'Hagan JA, Conquest AJ, Goodill AA, Butland BK, Fell TP, Jackson DA, Webb MA. Mortality and occupational exposure to radiation: first analysis of the National Registry for Radiation Workers. BMJ 1992;304:220-5.
18. Muirhead CR, O'Hagan JA, Haylock RG, Phillipson MA, Willcock T, Berridge GL, Zhang W. Mortality and cancer incidence following occupational radiation exposure: third analysis of the National Registry for Radiation Workers. Br J Cancer 2009;100:206-12.
19. Dobrzynski L, Fornalski KW, Feinendegen LE. Cancer Mortality Among People Living in Areas With Various

Levels of Natural Background Radiation. Dose Response 2015;13:1559325815592391.
20. Hendry JH, Simon SL, Wojcik A, Sohrabi M, Burkart W, Cardis E, Laurier D, Tirmarche M, Hayata I. Human exposure to high natural background radiation: what can it teach us about radiation risks? J Radiol Prot 2009;29:A29-42.
21. American Association of Physicists in Medicine. AAPM Position Statement on Radiation Risks from Medical Imaging Procedures. Available line: https://www.aapm.org/org/policies/details.asp?id=318&type=PP&current=true
22. Hong JY, Han K, Jung JH, Kim JS. Association of exposure to diagnostic low-dose ionizing radiation with risk of cancer among youths in South Korea. JAMA Netw Open 2019;2:e1910584.
23. Siegel JA, Pennington CW, Sacks B. Subjecting Radiologic Imaging to the Linear No-Threshold Hypothesis: A Non Sequitur of Non-Trivial Proportion. J Nucl Med 2017;58:1-6.

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