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COMMENTARY

Does iodinated contrast medium amplify DNA damage during exposure to radiation

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ABSTRACT

There is a recognized increased risk of cancer following exposure of humans to ionizing radiation; this is felt to be most likely due to damage to DNA strands during exposure. Damage to DNA strands can be demonstrated microscopically following exposure to X-rays, and new evidence is emerging that this effect may be compounded by administration of iodinated contrast agents.

INTRODUCTION

It is widely accepted that there is an increased risk of cancer following exposure to ionizing radiation. The primary source of information is the Life Span Study, an epidemiological study of survivors of the atomic bombs at Hiroshima and Nagasaki. There were an excess number of deaths from leukaemia in the early follow-up years. Most recent figures published in 2011 indicate an excess relative risk for solid tumours of between 0.5 and 0.8 for doses between 5 and 200 mGy.¹ A study published in 2004 estimated that 0.9% of the cumulative cancer risk to individuals in the USA could be attributable to diagnostic X-ray exposure, equivalent to 5695 cases of newly diagnosed cancer per annum.² Diagnostic X-rays are the largest man-made source of radiation exposure. More complex examinations, and interventional procedures are increasing in number and average dose annually throughout the developed world. In the UK in 2008, CT accounted for 7% of the total number of medical and dental examinations but 68% of their resultant total collective dose.³ Quantification of cancer risk is difficult owing to the large sample size required to determine small excess risk and the long latency period involved. Some evidence of a possible link between diagnostic radiation exposure and cancer risk has emerged recently with the publication of studies of two large cohorts of children undergoing CT examination, and results were similar to the Japanese atomic bomb figures.^{4,5}

DNA STUDIES

The conventional view is that damage to DNA in the nucleus is the main initiating event by which radiation causes long-term harm to organs and tissues in the body. Among the different types of lesions induced in cells by ionizing

radiation, single-radiation tracks have been shown to result in DNA double-strand breaks (DSBs).⁶ When this occurs, both strands of the double helix are severed. DNA repair is error prone and can lead to genome rearrangements which in turn may lead to tissue damage although no direct causal link to tumorigenesis has been demonstrated. Chromosome aberrations following radiation exposure were initially described in the 1960s.⁷ It is possible to quantify DSBs using an antibody specific to the phosphorylated form of the histone variant H2AX (γ H2AX).⁸ Immunofluorescence analysis of this focus yield in lymphocytes enables visualization of the number of DSBs *in vivo* after medical X-ray exposure, and it is felt that a subsequent decrease in the number of foci indicates DSB repair. CT data have shown that the yield of γ H2AX depends linearly on the dose-length product.⁹ Giesel et al¹⁰ demonstrated an increase in DNA DSBs following both CT examination and percutaneous transluminal angioplasty (PTA) and showed an even greater increase in yield of γ H2AX in samples taken from the leg directly exposed during PTA.

Iodinated contrast media

It is well recognized that iodinated contrast media have a cytotoxic effect, and this is felt to be one of the mechanisms responsible for contrast-induced nephrotoxicity.¹¹

Small studies^{10,12} have suggested an association between contrast media and increased DNA DSBs in individuals exposed to low-dose radiation but not necessarily high-dose radiation.

Grudzenski et al¹² demonstrated an increased number of γ H2AX foci following X-irradiation with 10 or 500 mGy in

the presence of iodinated contrast media *in vitro* in both fibroblasts and lymphocytes. This effect was neither observed when the cells were exposed to contrast media after being irradiated nor was it observed when exposed to high-energy γ -irradiation in the presence of contrast media. They also demonstrated that the injection of contrast medium prior to CT scanning enhanced the yield of γ H2AX foci to a lesser extent but numbers studied were small.

A recent study by Piechowiak et al.¹³ has investigated the effect of contrast media on DNA DSBs in a larger population than previous studies,^{10,12} in patients investigated by CT scan for clinical indications. A total of 179 patients had contrast-enhanced CT examination and 66 patients underwent unenhanced CT. Radiation dose parameters between the groups did differ significantly [dose-length product (DLP) for unenhanced CT $342 \text{ mGy cm}^{-1} \pm 116$; DLP for contrast-enhanced CT $301 \text{ mGy cm}^{-1} \pm 120$; $p = 0.02$]. Blood samples were taken pre- and post-scanning and lymphocytes separated by centrifugation prior to incubation with anti-phospho-histone H2AX antibody. Numbers of γ H2AX foci post-irradiation were counted by eye using immunofluorescence microscopy. γ H2AX foci levels were increased in both

groups, but the increase in the contrast media group was 107% higher than that in the unenhanced group. They conclude that application of iodinated contrast media leads to an increase in the extent of DNA damage following irradiation for diagnostic imaging purposes. Whilst contrast media administration can result in an increase in the dose during CT examination in this study, the dose was actually lower in the contrast media group.

CONCLUSION

The use of biomarkers to assess DNA damage following both diagnostic and therapeutic radiology procedures provides us with an insight into how radiation might lead to an increased risk of cancer induction. Whilst a direct causal link between DNA DSBs and cancer induction has not been demonstrated, it must certainly be considered as one of the potential mechanisms.

The fact that the extent of such damage may be enhanced by administration of iodinated contrast media will make the imaging community consider in more detail whether contrast-enhanced studies are truly necessary although in the majority of cases the benefit will hopefully outweigh the risk.

REFERENCES

1. Douple EB, Mabuchi K, Cullings HM, Preston DL, Kodama K, Shimizu Y, et al. Long-term radiation-related health effects in a unique human population: lessons learned from the atomic bomb survivors from Hiroshima and Nagasaki. *Disaster Med Public Health Prep* 2011; 5: S122–33. doi: [10.1001/dmp.2011.21](https://doi.org/10.1001/dmp.2011.21)
2. Berrington de Gonzles A, Darby S. Risk of cancer from diagnostic X-rays: estimates for the UK and 14 other countries. *Lancet* 2004; 363: 345–51.
3. Hart D, Wall BF, Hillier MC, Shrimpton PC. *Frequency and collective dose for medical and dental X-ray examinations in the UK 2008. Report HPA-CRCE-012*. Didcot, UK: HPA; 2010.
4. Mathews JD, Forsythe AV, Brady Z, Butler MW, Goergen SK, Byrnes GB, et al. Cancer risk in 680,000 people exposed to computed tomography scans in childhood and adolescence: data linkage study of 11 million Australians. *BMJ* 2013; 346: f2360. doi: [10.1136/bmj.f2360](https://doi.org/10.1136/bmj.f2360)
5. Pearce MS, Salotti JA, Little MP, McHugh K, Lee C, Kim KP, et al. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. *Lancet* 2012; 380: 499–505. doi: [10.1016/S0140-6736\(12\)60815-0](https://doi.org/10.1016/S0140-6736(12)60815-0)
6. Charles M. UNSCEAR report 2000: sources and effects of ionizing radiation. United Nations Scientific Committee on the effects of atomic radiation. *J Radiol Prot* 2001; 21: 83.
7. Bloom AD, Tjio JH. *In vivo* effects of diagnostic X-irradiation on human chromosomes. *N Eng J Med* 1964; 270: 1341–4. doi: [10.1056/NEJM196406182702504](https://doi.org/10.1056/NEJM196406182702504)
8. Rogakou EP, Boon C, Redon C, Bonner WM. Megabase chromatin domains involved in DNA double-strand breaks *in vivo*. *J Cell Biol* 1999; 146: 905–16. doi: [10.1083/jcb.146.5.905](https://doi.org/10.1083/jcb.146.5.905)
9. Lbrich M, Rief N, Khne M, Heckmann M, Fleckenstein J, Rbe C, et al. *In vivo* formation and repair of DNA double-strand breaks after computed tomography examinations. *Proc Natl Acad Sci USA* 2005; 102: 8984–9. doi: [10.1073/pnas.0501895102](https://doi.org/10.1073/pnas.0501895102)
10. Giesel D, Heverhagen JT, Kalinowski M, Wagner HJ. DNA double-strand breaks after percutaneous transluminal angioplasty. *Radiology* 2008; 248: 852–9. doi: [10.1148/radiol.2483071686](https://doi.org/10.1148/radiol.2483071686)
11. Haller C, Hizoh I. The cytotoxicity of iodinated radiocontrast agents on renal cells *in vitro*. *Invest Radiol* 2004; 39: 149–54. doi: [10.1097/01.rli.0000113776.87762.49](https://doi.org/10.1097/01.rli.0000113776.87762.49)
12. Grudzenski S, Kuefner MA, Heckmann MB, Uder M, Lbrich M. Contrast medium-enhanced radiation damage caused by CT examinations. *Radiology* 2009; 253: 706–14. doi: [10.1148/radiol.2533090468](https://doi.org/10.1148/radiol.2533090468)
13. Piechowiak EI, Peter JF, Kleb B, Klose KJ, Heverhagen JT. Intravenous iodinated contrast agents amplify DNA radiation damage at CT. *Radiology* 2015; 275: 692–7. doi: [10.1148/radiol.14132478](https://doi.org/10.1148/radiol.14132478)