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RADIOBIOLOGY SPECIAL FEATURE: COMMENTARY

What we know and what we don't know about cancer risks associated with radiation doses from radiological imaging

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ABSTRACT

Quantifying radiation-induced cancer risks associated with radiological examinations is not easy, which has resulted in much controversy. We can clarify the situation by distinguishing between higher dose examinations, such as CT, positron emission tomography-CT or fluoroscopically guided interventions, and lower dose "conventional" X-ray examinations. For higher dose examinations, the epidemiological data, from atomic bomb survivors exposed to low doses and from direct epidemiological studies of paediatric CT, are reasonably consistent, suggesting that we do have a reasonable quantitative understanding of the individual risks: in summary, very small but unlikely to be zero. For lower dose examinations, we have very little data, and the situation is much less certain, however, the collective dose from these lower dose examinations is comparatively unimportant from a public health perspective.

The debates about the cancer risks associated with very low-dose radiation exposures will surely not end soon. Even if we really could quantitate the risks (or lack of risks) associated with some very low radiation doses, we would immediately start to wonder about the risks associated with further lower doses. We will focus here on what we know (and what we do not know) about the cancer risks associated with doses from radiological imaging.

Almost all radiological doses are "small", in the context of, for example, radiotherapeutic doses; however, one can clearly distinguish between low radiological doses associated with many conventional examinations such as dental or chest examinations (organ doses typically <0.5 mGy) and higher radiological doses associated with CT, positron emission tomography (PET)-CT or fluoroscopically guided complex interventions (organ doses for a single examination or series of examinations typically between 5 and 100 mGy). As we shall discuss, this divide in dose ranges corresponds quite well to the dose range where we do know a good deal about radiation risks (5–100 mGy) and the dose range (<1 mGy) where we know far less.

We shall discuss briefly what we know and do not know in both these radiation dose ranges, but it is important to view these considerations in the context of the potential

benefits associated with the corresponding imaging procedure.¹ When a radiological examination of any sort is clinically justified, its benefits will almost always far outweigh any radiation risks. That being said, we still need to optimize radiological examinations (use the lowest dose consistent with obtaining the required information) and to justify radiological examinations (minimize clinically unnecessary procedures); however, the significance of such optimization and justification depends entirely on the magnitude (if any) of the associated radiation risks.^{1–3}

WHAT IS KNOWN AT HIGHER RADIOLOGICAL DOSES

In the organ dose range from 5 to 100 mSv, the evidence that cancer risk is slightly increased is now reasonably strong, although certainly not definitive. As always, we first turn to the atomic bomb (A-bomb) survivors because the numbers are large and the follow-up is long. A common comment about the A-bomb survivors is that it is a high-dose cohort and, therefore, one needs to extrapolate the risks to radiologically relevant doses. In fact, there are about 28 000 individuals in the well-studied Life Span Study (LSS) cohort, whose dose estimates are in the 5–100 mSv range, which is >60% of the total exposed cohort.⁴ Focusing only on the cohort members exposed to low doses,⁴ there is a statistically significant ($p = 0.01$) dose response for solid cancer incidence (compared with controls) when the analysis is restricted to LSS cohort members who received doses of

≤ 150 mSv, and a marginally significant dose response ($p = 0.08$) when the analysis was restricted to doses of ≤ 100 mSv. Similar results are seen for cancer mortality.⁵

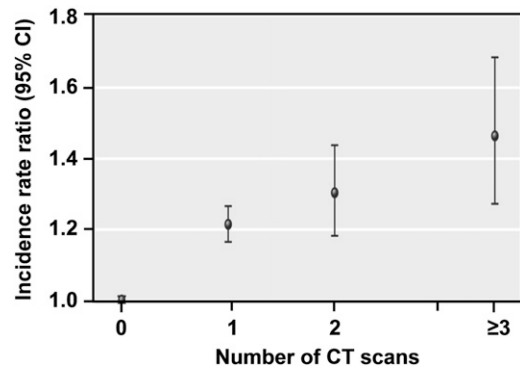
One important conclusion to draw from these p -values is that epidemiological studies on populations exposed to further lower doses (with presumably correspondingly lower risks) are unlikely to have enough significance to draw quantitative conclusions. Thus, for example, despite the large number of individuals studied (approximately 400 000), the major international epidemiological study of radiation workers exposed at low-dose rates to an average dose of 20 mGy has given quite equivocal results, consistent with zero risk and also consistent with risks derived from A-bomb survivors.⁶ In retrospect, this is not so surprising.

One approach to epidemiological assessment of risks at lower doses is to focus on scenarios where the signal-to-background ratio is likely to be higher than is the case overall. One example is the study of childhood cancers after *in utero* diagnostic imaging. Here, the absolute risk (the signal) is expected to be high because the subjects were exposed *in utero*, and the background is expected to be low because childhood cancers are rare, and, indeed, the Oxford Study of Childhood Cancers was able to detect a significant increase in paediatric cancer risk for a mean dose of only 6 mGy.⁷

The same logic, of tailoring the epidemiological study to improve the signal-to-background ratio, applies to two recently published epidemiological studies of cancer risks associated with paediatric exposure to CT scans, both with a relatively short mean follow-up of about 10 years.^{8,9} The relatively short follow-up after paediatric exposure allows radiation-induced cancers with short latency to be detected while limiting the background from cancers appearing in the “cancer-prone” years of late middle age. Both studies were very large and showed a statistically significant association between the number of CT scans and the increased cancer risk. For example, as illustrated in Figure 1, the second paediatric CT study⁹ reported a significant dose–response relation over the range from zero to more than three CT scans, with an increase in the cancer incidence rate ratio, relative to controls, of 0.16 (95% confidence interval: 0.13–0.19) for each additional CT scan.

Two caveats are important for these epidemiological studies of radiation risks associated with CT scans. The first is the possibility that the reason for a paediatric CT might also be the cause of subsequent cancer; for example, an undiagnosed brain tumour might have been the cause of symptoms for which the patient had a CT scan; a head trauma might have been the reason for a CT scan, but perhaps might itself be linked to increased cancer risks; or epilepsy might have been the cause of symptoms that prompted the CT scan and might be linked with increased cancer risks. Broadly termed “reverse causality”,¹⁰ in the CT context, these issues relate primarily to brain tumours after head CT scans, with fewer possible such scenarios for leukaemia. So, it is important to understand whether these risks remain if brain tumours after head CT scans are removed from the analyses; in fact, the relative risks stay much the same,⁹ so it seems unlikely that reverse causality is a major effect.

Figure 1. Cancer incidence rate ratios for all cancers in individuals who received CT scans vs those who did not. The right most data point refers to ≥ 3 CT scans, with the mean number of CT scans being 3.5. The data shown here are for a lag period (exclusion period before cancer diagnosis) of 1 year; similar results were reported⁹ for lag periods of 5 or 10 years. Reproduced with permission from BMJ Publishing Group and originally published in⁹. CI, confidence interval.



A second caveat relates to the fact that radiation-induced latency periods can be many decades;⁴ because the paediatric CT studies^{8,9} have fairly short follow-up times (of the order of 10 years), they cannot directly estimate lifetime cancer risks; rather, they provide only a snapshot of the overall risk. However, when corrected for follow-up, CT risks previously estimated from A-bomb survivors are, in fact, quite similar to the epidemiological results.¹¹ So, the paediatric CT risk estimates do provide some validation that we have a reasonable understanding of the overall cancer risks associated with CT and PET/CT exposures: in short, very small individual risks but unlikely to be zero.

WHAT IS KNOWN AT LOWER RADIOLOGICAL DOSES

At organ doses < 1 mGy, typical of “conventional” radiological examinations, the short answer is that we have little or no reliable data. The natural background cancer risk in humans of $> 40\%$ is too large for a realistic reasonably powered epidemiological study when the expected risks are, at most, much less than 0.1%. These same considerations apply to laboratory animal studies, where even when using mice with very low background cancer rates, radiation-induced cancer studies at these doses are not feasible.¹² A further problem is the absence of credible *in vitro* models for radiation-induced cancer: although many low-dose studies have been reported using genomic changes, including changes in gene expression, DNA strand breaks, mutations or chromosome aberrations, there is no convincing quantitative/mechanistic connection between any of these end points and radiation-induced cancer, which is of course a much later end point.¹³ Perhaps, the most plausible *in vitro* model for radiation-induced cancer is *in vitro* oncogenic transformation, but, even for this, end point studies at doses ≤ 1 mGy are not feasible.^{14,15}

The absence of data at these low doses is unfortunate and inevitably leads to uncertainty and controversy. As an example, three studies^{16–18} of historical mortality risks in radiologists concluded that there was a statistically significant increase in

risk,¹⁶ a statistically significant decrease in risk,¹⁷ or that there was no significance difference compared with other physicians.¹⁸ This diversity is not surprising given the limited power of such studies, and interpretation of *all* results at very low doses, whether *in vitro* or *in vivo*, should be undertaken with much caution.

From the radiological perspective, however, the collective dose from lower dose examinations is comparatively unimportant compared with that from higher dose studies, such as CT or PET-CT.¹⁹ However, these issues are extremely important in other contexts, such as understanding the public health significance of the exposures at Chernobyl and Fukushima.

CONCLUSION

Quantifying radiation-induced cancer risks associated with radiological examinations is not easy. For higher dose examinations, the epidemiological data, from A-bomb survivors exposed to low doses and from direct epidemiological studies of paediatric CT, are reasonably consistent, suggesting that we do have a reasonable quantitative understanding of the individual risks; in summary, very small but unlikely to be zero. For lower dose

examinations, we have very little data and the situation is much less certain, but the collective dose from these lower dose examinations is comparatively unimportant from a public health perspective.

Historically, the radiation doses for which we have quantitative information about cancer risks have steadily decreased with time. Around 1980, for example, almost nothing was known about cancer risks associated with a 100 mGy dose.²⁰ This has clearly changed in the past 30 years. We have probably reached a limit in terms of what can be done using classical epidemiological techniques, and the future must surely lie in augmenting epidemiology with radiobiological concepts.²¹ As one obvious example, if a definitive “fingerprint” of a radiation-induced tumour could be found, many of the issues associated with our high-background cancer rate would disappear, and epidemiological studies at lower doses would become more feasible.

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