EDITORIAL

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Editorial

Risks from CT scans—what do recent studies tell us?

Substantial effort is now under way to identify and follow up patients who have received a computed tomography (CT) scan, to determine whether any increased risk of cancer resulting from exposure to ionising radiation during a scan can be detected. CT scans are becoming an increasingly popular and effective diagnostic tool, and their usage has risen dramatically in economically developed countries (UNSCEAR 2010). Each CT scan delivers an effective dose of between several mSv and a few tens of mSv, depending on the type of scan (UNSCEAR 2010). The radiation risk models that have been developed from the epidemiological study of groups receiving moderate and high doses (such as the Japanese survivors of the atomic-bombings of Hiroshima and Nagasaki) imply that the excess risk of cancer resulting from the low doses received during a CT scan is small, so that large and carefully designed and conducted studies are necessary to discern this predicted small additional risk. Such studies are important because of the direct evidence that they can potentially provide on the levels of risk resulting from low doses of radiation. The findings of large studies of patients who have experienced a CT scan at a young age are starting to become available—studies of infants, children and adolescents are a sensible starting point because the risk of radiation-induced cancer is generally greater at younger ages at exposure (UNSCEAR 2013).

Pearce et al (2012) reported the results of a cohort study of around 180,000 patients in Great Britain, identified from hospital records as having been first examined with CT while \( \leq 21 \) years of age during 1985–2002. Cases of leukaemia and brain tumours in the cohort, diagnosed during 1985–2008, were identified by linkage to national cancer registry records. They studied the incidence of leukaemia and brain tumours, because of the known radiosensitivity of the former and the influence upon the latter of the two-thirds of the CT scans included in their study that were of the head. Pearce et al (2012) noted, ‘to avoid inclusion of CT scans related to cancer diagnosis, follow-up for leukaemia began 2 years after the first CT and for brain tumours 5 years after the first CT’, and added that these periods are also the conventional minimum latencies for these cancer types. Using estimates of the absorbed doses delivered to the red bone marrow and the brain during a CT scan, and taking those patients receiving tissue/organ doses \(<5\) mGy during a scan as the reference groups, the excess relative risk (ERR) per mGy was 0.036 (95% confidence interval (CI): 0.005, 0.120) for leukaemia (including myelodysplastic syndromes, MDS) and 0.023 (95% CI: 0.010, 0.046) for brain tumours (including benign tumours). Dose–response slopes were statistically significantly positive for acute lymphoblastic leukaemia and for MDS, but although positive, not significantly so for acute myeloid leukaemia or for all leukemias excluding MDS (the ERR/mGy for which was 0.019 (95% CI: –0.012, 0.079), demonstrating the influence of MDS in the study). The ERR/mGy estimate for leukaemia (with or without MDS) is compatible with
equivalece estimates derived from the Life Span Study (LSS) of the Japanese atomic-bomb survivors, but the ERR/mGy for brain tumours appears to be somewhat high when a similar comparison is made, although the difference is not significant (Pearce et al 2012).

However, the difficulties of reliably interpreting the results of CT scan studies are illustrated by the recent findings of Mathews et al (2013). They reported the results of a record linkage study of cancer incidence among a cohort of almost eleven million people in Australia who were <20 years of age at the start of 1985 or born during 1985–2005. About 60 500 cases of cancer incident in the cohort during 1985–2007 were identified from national records. Using the Australian Medicare database, around 680 000 members of the cohort were identified as first undergoing CT scans in Australia during 1985–2005 while <20 years of age. Cancer incidence rates for this ‘exposed’ cohort were compared with rates among the remaining members of the cohort (the ‘unexposed’ cohort) having no record of a CT scan during 1985–2005 while <20 years of age, to give incidence rate ratios (IRRs). Mathews et al (2013) studied all types of cancer and, somewhat surprisingly, calculated risk in a period beginning just one year after first exposure for each cancer type. For all cancers combined, the incidence rate in the exposed cohort was 24% greater than the rate in the unexposed cohort, a highly statistically significant excess; the authors concluded that ‘the increased incidence of cancer after CT scan exposure in this cohort was mostly due to irradiation’.

That the CT scan cohort experienced a risk of cancer incidence 24% greater than that of the unexposed cohort during the period of follow-up, and the attribution of this excess largely to exposure to radiation during a scan, is an inference of some concern. There are, however, some disturbing features of this study that cast doubt on a causal explanation of the excess cancer incidence in terms of radiation exposure. First, Mathews et al (2013) did not give reasons for the choice of 1985 for the start of the periods of CT examinations and follow-up. About half of the persons in the cohort entered at the start of follow-up with ‘unknown’ CT exposure status, but were classified as ‘unexposed’. The authors discussed this exposure misclassification bias and stated that it would have led to a ‘small downward bias in our estimates of the cancer risks from CT’, but did not justify this statement or quantify the potential impact of bias. The statement is evidently based on the assumption that those with a CT examination post-1984 were no more likely to have had a CT examination pre-1985 than those who had no post-1984 CT examination; this assumption may be questionable. The authors could have verified and strengthened their results by conducting an analysis restricted to persons born after 1985. Even after 1985, several sources of CT exposure were missed including: ‘nearly all CT scans in state-based tertiary hospitals’ (because no individual bills for these were in the Medicare administration system); CT examinations after the age of 19 years (the number of which may have been appreciable, since follow-up sometimes extended past an age of 40 years); and the extra doses when patients had retake scans (e.g., because of patient movement, especially during the long scan times required during the earlier calendar years). Mathews et al (2013) did not include details of their dose estimation procedures, and estimates of direct and scatter tissue/organ doses received during paediatric CT examinations in the 1980s and 1990s are sparse; their estimates may have largely reflected ‘best practices’ rather than representative practices at the time. Considering the variety of limitations, the estimates of cumulative doses probably have considerable uncertainty and may be biased downwards.

Of some importance to interpretation is the pattern of the IRRs for various types of cancer. For all but two reported IRRs, raised ratios were found, some of which were increased to a statistically significant extent. These included melanoma, IRR = 1.12 (95% CI: 1.04, 1.20), and Hodgkin’s lymphoma, IRR = 1.15 (95% CI: 1.01, 1.32), for both of which there is little evidence for a link with exposure to ionising radiation (UNSCEAR 2008). For brain cancer after a brain CT scan, the IRR was a highly significant 2.44 (95% CI: 2.12, 2.81), and after
a CT scan other than of the brain it was 1.51 (95% CI: 1.19, 1.91); the IRR for all cancers except brain cancer after a brain CT scan was 1.20 (95% CI: 1.15, 1.24). The two types of cancer for which the IRR was (non-significantly) less than unity are breast cancer and acute lymphoblastic leukaemia, for both of which there is strong evidence of a link with radiation exposure, particularly at a young age at exposure (UNSCEAR 2008).

However, these IRRs include all cancers diagnosed more than one year after first exposure. Mathews et al (2013) presented results for various periods following first CT scan, which are of some interest. So, for brain cancer after a brain CT scan the IRR for the period 1–4 years after first exposure was 3.24 (2.61, 4.02); it is difficult to believe that so high and statistically significant an IRR occurring so shortly after first exposure is not largely due to a latent brain tumour producing symptoms that led to the CT scan. But this phenomenon is more widespread: during the period 1–4 years after first exposure, the IRR for brain cancer after a CT scan other than of the brain was 2.08 (95% CI: 1.47, 2.92), for all solid cancers except brain cancer it was 1.23 (95% CI: 1.12, 1.35), for lymphoid and hematopoietic cancers other than leukemias and MDS it was 1.25 (95% CI: 1.05, 1.49), and it is only for leukemias and MDS that the IRR of 1.20 (95% CI: 0.98, 1.48) was not significantly raised. The one grouping of cancers for which the risk might be expected, a priori, to be significantly increased within five years of first exposure is the only one that is not.

Unfortunately, difficulties of interpretation are not confined to data for the period 1–4 years after first exposure. For brain cancer after a CT scan of the brain, the IRRs for 1–4, 5–9, 10–14 and ≥15 years after first exposure were 3.24 (95% CI: 2.61, 4.02), 2.42 (95% CI: 1.88, 3.12), 1.80 (95% CI: 1.29, 2.51) and 1.74 (95% CI: 1.17, 2.59), respectively: there is a highly significant (p < 0.001) downward trend of IRR with time since first CT scan, but the significantly elevated risk that was manifest 1–4 years following first exposure persists for more than 15 years. For all solid cancers except brain cancer, the IRRs for 1–4, 5–9, 10–14 and ≥15 years after first exposure were 1.23 (95% CI: 1.12, 1.35), 1.17 (95% CI: 1.09, 1.27), 1.14 (95% CI: 1.05, 1.24) and 1.24 (95% CI: 1.14, 1.35), respectively: there is no trend of IRR with time since first CT scan, and the significantly raised risk for the period 1–4 years after first exposure persists at around the same level during the later periods. Unlike Mathews et al (2013), Pearce et al (2012) only began follow-up for brain tumours five years after first exposure (a period that would presumably also have been applied for other solid cancers, if they had been studied), in an attempt ‘to avoid inclusion of CT scans related to cancer diagnosis’. However, the key question posed by the pattern of risks with time since first exposure apparent in the results of Mathews et al (2013) is: how long and to what extent does the influence persist of ‘CT scans related to cancer diagnosis’? One would expect, on the basis of prior evidence, that the risk of radiation-induced leukaemia and solid cancers would start to appear around two and five years after exposure, respectively, but there is no assurance that excess cancers occurring after these minimum latent periods are unassociated with the underlying reason for the CT scan, only that this effect would be expected to diminish with time. For example, the IRR for all solid cancers except brain cancer is significantly raised in all four periods of time since first exposure (see above) and the excess does not differ significantly between periods; how is any radiation effect to be reliably distinguished from the persistence, for some unknown length of time and to some unknown degree, of a residual effect of the underlying reason for the CT examination beyond the minimum latent period?

Other concerns are raised by the reported pattern of brain cancer risk and by the solid cancer risk estimates. For all CT examinations other than those of the brain, Mathews et al (2013) reported an IRR for brain cancer of 1.51 (95% CI: 1.19, 1.91), including an IRR of 2.21 (95% CI: 1.22, 4.00) after abdomen/pelvis CT scans and 1.56 (95% CI: 0.95, 2.55) after CT examinations of the extremities. These values seem implausibly high given the small brain
doses received from indirect irradiation and suggest background differences in cancer risk between the exposed and unexposed groups due to factors that were not accounted for in the study. For all solid cancers other than brain cancer after a CT scan of the brain, Mathews et al. (2013) reported an ERR/mGy estimate of 0.027 (95% CI: 0.017, 0.037), which contrasts with the corresponding estimate based on the LSS of the atomic-bomb survivors of 0.003 (95% CI: 0.002, 0.006), a notable difference.

Mathews et al. (2013) state that their risk estimates for leukaemia are similar to those obtained from the LSS of survivors of the atomic-bombings. However, the leukaemia risks from the Australian CT scan study show no excess for the group of patients who had a first CT examination before the age of 10 years, then a statistically significant excess for the group having a first exposure between 10 and 19 years of age. Indeed, the trend of IRR across the four five-year groups of age at first exposure is positive with increasing age at first CT scan and is of borderline statistical significance ($p = 0.06$). This age at exposure pattern is notably different from that reported from the LSS, where the relative risk is greatest for those exposed at younger ages (Hsu et al. 2013, UNSCEAR 2013, Wakeford 2013).

Serious consideration must be given to the possibility that reverse causation (also known as confounding by indication) is playing an important role in the findings of CT scan studies, a point made recently by UNSCEAR (2013). Reverse causation implies that it is the early symptoms of undetected cancer, or of factors that predispose to cancer, that are the indications for the CT scans, rather than the CT scans per se that are causing the apparent excess risk of cancer. The findings of Mathews et al. (2013) reinforce concern over this possibility, including: the appearance within five years of first CT scan of a significant excess of solid cancers, especially the high risk of brain cancer after a CT scan of the brain; the excess risk of brain cancer following a CT scan of parts of the body remote from the brain; and the significant excesses of cancers known to be, at best, only weakly associated with exposure to radiation while there is no excess of radiosensitive breast cancer or of leukaemia among those exposed while less than 10 years of age. It would be of interest to know if similar patterns are present in the British data, since this cannot be determined fully from the paper by Pearce et al. (2012), which reported results from a different study design from that of Mathews et al. (2013) and only considered leukaemia and brain tumours.

In conclusion, recently published reports of CT scan studies indicate that their findings need to be interpreted with caution because of the potential for reverse causation. It will be difficult to design and conduct such studies if a reliable explanation of their results is to be achieved, and researchers need to be fully aware of this problem in their approach to study design. It could take quite an effort to extract any signal of the risk of radiation exposure during a CT scan from what appears to be the considerable background of extraneous factors related to the reasons for the CT scan being conducted. Hopefully, CT studies that are now under way, such as the ‘EPI-CT’ study in Europe (see www.epi-ct.iarc.fr), will shed additional light on historical paediatric CT doses, have fewer ‘missed doses’, and be better able to address issues of possible risk factor confounding and reverse causation by, for example, establishing the reason(s) for an examination. If the reasons for the CT examinations were known, sub-group analyses of persons, say, undergoing CT either after an accident or for routine screening, could help in the further investigation of the potential effects of reverse causation. Meanwhile, it would be prudent to assume that the low dose of radiation received during a CT scan produces a small additional risk of cancer compatible with the predictions of conventional risk models, and clinical practice should be guided by this assumption.
References

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