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LETTER TO THE EDITOR

Estimates of cardiovascular disease risk from CT scans may be premature

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Martin *et al* [1] have published the results of an interesting study in which the mortality risk of cardiovascular disease (CVD) from computed tomography (CT) scans was estimated for a sample of patients in clinical practice, based on excess absolute risk (EAR) figures calculated by Little *et al* [2]. The results suggest an important radiation-related CVD burden from diagnostic imaging, especially for patients receiving high cumulative doses from multiple scans. In the case of patients receiving multiple head scans, the risk of mortality from cerebrovascular disease (CeVD) may exceed that from cancer (all sites) by an order of magnitude. While these findings need to be taken seriously, I would like to draw the attention of readers to some potential limitations of the study methodology and also to clarify the interpretation of the results.

The figures presented by Martin *et al* [1] represent mortality among a group of 100 000 patients, only a small proportion of whom would exceed the postulated threshold dose for an increased risk of CVD of 100 mGy. For example, of the 65 394 individuals in their sample ($n = 105\,574$) who underwent 'body scans', only 1545 received an estimated cumulative dose to the heart of >100 mGy. In this sub-group, the estimated number of deaths from ischaemic heart disease (IHD) is approximately 1.5 (this can be seen by summing the blue columns in figure 1(a) [1] for dose ranges 100–200, 200–300 and >300 mGy). This figure was then normalised to give 'predicted excess mortality per 100 000 patients' by multiplying by 100 000/65 394. The 2.2 excess deaths from IHD in table 4 [1] does not represent risk of IHD per 100 000 individuals who all receive a dose of >100 mGy, rather the expected burden of IHD deaths among 100 000 individuals who undergo CT body scans at the same frequency as the study sample, with most receiving cumulative cardiac doses well below 100 mGy. A similar method was applied for estimating cancer mortality risk. Martin *et al* [1] report that 0.68% of patients in their sample received a cumulative effective dose of greater than 100 mSv. The figures in the lower half of table 4 [1] therefore represent the expected burden of cancer deaths among 0.68% of 100 000 patients receiving a cumulative effective dose of >100 mSv.

Restricting analysis to patients only receiving cumulative doses above 100 mGy is not the same as applying a 'no risk' dose threshold, below which no effect is observed. In the study by Martin *et al* [1], doses between zero and 100 mGy still contribute to the risk of CVD, but only for patients with a cumulative dose above 100 mGy. This means the risk suddenly 'switches on' when the cumulative dose reaches 100 mGy, with the EAR jumping from zero to 0.233% for all CVD (based on an EAR of 2.33% per Gy). In this way, patients in the 100–200 mGy dose range make the largest contribution to the total excess mortality from radiation-related CVD, while those with cumulative doses below 100 mGy (even at 99 mGy) make no contribution at all. This does not necessarily result in under- or over-estimation of CVD risk, however, because the nature of the threshold (in addition to the dose level) is not known. The threshold dose, as defined by the ICRP [3], is a 'practical' threshold at which 1% of individuals would be observed to develop the disease. In this sense, the number of patients with cumulative doses below the threshold may contribute more to the overall disease burden, even if less than 1% of them develop CVD. Alternatively, one may consider the possibility that the threshold is higher (e.g. 500 mGy) in which case the number of CT-related CVD deaths would be lower than predicted by Martin *et al* [1].

The calculations performed by Martin *et al* [1] are unmodified by age-at-exposure, attained age or the expected length of remaining life among individuals in the sample. Currently, there is limited information on the latency between exposure and onset of CVD. Even with a relatively short latency period, it is likely that many of the individuals receiving high cumulative doses would not live long enough to develop

radiation-related CVD. The cancer mortality risks estimated by Martin *et al* [1] using the ICRP 147 methodology do, however, account for age-at-exposure and latency. This means that comparisons between estimated risks for CVD and cancer, and the conclusion that the risk of CVD may be higher than cancer, may not be appropriate. It is unfortunate that Martin *et al* [1] have chosen to make this comparison only for the cancer burden from patients exceeding a threshold effective dose of either 20 mSv or 100 mSv and not the zero-dose threshold commonly assumed in practical radiological protection. This is especially significant for head scans, in which the effective dose is quite low.

There are also potential limitations of the dose estimates used by Martin *et al* [1]. The target organ/tissue for CVD is uncertain, although the vessel wall, in particular the endothelium, has been suggested [4]. The available evidence suggests the carotid arteries, rather than the brain, are the target for CeVD [2]. These vessels (especially at the site of bifurcation) may be partially or wholly excluded from both head and chest scans, meaning the use of brain dose likely overestimates CeVD risk. Martin *et al* [1] acknowledge this, making it strange that they chose to base CeVD estimates on brain dose in the first place.

In normal circumstances, the average absorbed dose to the heart would closely approximate the dose to cardiac vessels. However, in many cases, CT scans are performed following administration of iodinated contrast media (ICM). These ICM molecules act as a source of secondary electrons, which would mainly deposit their energy in the blood and the first few micrometres of the vessel wall. In this case, the use of mean heart dose would underestimate dose to the vessel wall. It is also unfortunate that Martin *et al* [1] have chosen to use Radimetrics to estimate doses, given its use of simplistic 'Cristy/Eckerman' phantom models. In table 5 [1], the authors appear to have used the simplification that organ dose and volumetric CTDI ($CTDI_{vol}$) are approximately equal. In reality, it is likely $CTDI_{vol}$ would overestimate brain dose, while underestimating heart dose.

The paper by Martin *et al* [1] should encourage the radiological protection community to consider non-cancer outcomes as part of the overall potential burden from diagnostic medical exposures (one may also add Parkinson's disease, given recent findings from the Million Person Study [5]). My main concern is that the authors have attempted to estimate the number of CT-related CVD deaths before the science has properly developed and models for estimating lifetime attributable risk of CVD have been defined. The uncertainties in risk estimates come not only from the underlying epidemiological data and the threshold dose (as the authors acknowledge), but also in the how factors such as sex, age-at-exposure, attained age, latency, the effect of fractionation and the nature of a dose threshold are modelled. At this stage, estimates of CVD related to CT scans appear to be premature and need to be interpreted with caution.

Data availability statement

No new data were created or analysed in this study.

Conflict of interest

The author declares no conflicts of interest.

Disclaimer

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