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What do recent epidemiological studies tell us about the risk of cancer from radiation doses typical of diagnostic radiography?

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Abstract:

The last five years have seen unprecedented efforts to gain further understanding of the cancer risks following exposure to radiation doses below 100 mGy. Research has focused on occupationally exposed groups, populations exposed to elevated background radiation levels and children undergoing computed tomography scans. This review summarises the main findings of these studies and discusses the implications for diagnostic radiography. On balance, recent studies strengthen the association between radiation exposure at diagnostic dose levels and the risk of developing cancer at low doses. Although subject to considerable uncertainties, the risks to patients and staff from exposure to x-rays at diagnostic dose levels appear to be small, but non-zero. Despite the improved statistical power of recent studies, a number of shortcomings are apparent. These include dosimetric uncertainties and the potential confounding effects of cancer predisposing conditions and pre-existing tumours.

Introduction:

Radiation protection is primarily based on the known association between ionising radiation exposure and the increased lifetime risk of developing cancer. Until recently, epidemiological studies have lacked sufficient statistical power to demonstrate excess cancer risks at doses below around 100 milligray (mGy). Risk estimates are based on downward extrapolation of the risks at higher doses, assuming a linear relationship between dose and risk, without a threshold, below which there is no risk [1-3]. This so-called linear-no-threshold (LNT) approach remains controversial [4, 5], however, with authors claiming the model either underestimates [6], or overestimates [7, 8] the risks at low doses. The implications of this uncertainty for public health, the nuclear industry and healthcare are profound. Consequently, the last five years have seen major efforts to gain further understanding of

the risks at doses below 100 mGy, including updated studies of occupational exposures and populations residing in high background radiation areas, as well as new cohorts of children undergoing computed tomography (CT) scans. The aim of this review was to provide a concise summary of these studies and to discuss the implications of findings for radiation protection. Risks are presented in several forms, i.e. relative risk (RR), excess relative risk (ERR), incidence rate ratio (IRR), hazard ratio (HR) and standardised incidence ratio (SIR), along with respective 95% confidence intervals (CI). A short description of these measures is provided in the supplementary materials for this review.

Computed tomography studies:

CT scans deliver effective doses of approximately 1-15 mSv [9-12], depending on body part and patient age. Mean absorbed doses to organs within the exposed region are generally below 30 mGy for head scans and 20 mGy elsewhere [10-13]. These doses are thus towards the upper end of the range of doses encountered in diagnostic imaging. Since 2012, seven epidemiological studies investigating the cancer risks from CT scans have been published [14-20], based on five national cohorts. All have focused on children or young adults (under 22 years). The potential for adult studies has been assessed [21], though to date, none have been published.

Pearce *et al* [14] conducted a retrospective observational study of nearly 180,000 British children and adolescents receiving CT scans between 1985 and 2002. Neoplasms developing within 5 years (brain tumours) or 2 years (leukaemia) following exposure were excluded from the analysis. After around 15 years of follow-up, a significant association between radiation dose and incidence of leukaemia (ERR=0.036 mGy^{-1} 95% CI: 0.005, 0.120) and brain tumours (ERR=0.023 mGy^{-1}, 95% CI: 0.010, 0.049) was detected, in relation to red bone marrow and brain doses, respectively. For both diseases, the dose/risk relationship was best described by a linear model. The authors quote equivalent ERR figures from the 'Life Span Study' (LSS) of atomic bombing survivors in Hiroshima and Nagasaki of 0.045 mSv^{-1} for leukaemia (95% CI: 0.016, 0.188) and 0.0061 mSv^{-1} for brain tumours (95% CI: 0.0001, 0.639) in the 0-19 years age group, based on the same length of follow-up. However, the ERR quoted by Pearce *et al* for leukaemia includes myelodysplastic syndrome (MDS), which is not

usually regarded as a form of leukaemia [22] and not included in the LSS risk estimate. After excluding MDS from the results of Pearce *et al*, the ERR is reduced to 0.019 mSv^{-1} and no longer statistically significant. The risk of brain tumours was found to increase with increasing age at exposure, ranging from 0.005 Gy^{-1} at 0-5 years to 0.041 mGy^{-1} after 15 years. This finding, while not unprecedented, contrasts with the LSS [23] and studies of children irradiated for scalp ringworm (tinea capitis) [24] and skin haemangioma [25] in which the reverse pattern was found. There was a suggestion that females were at a greater risk than males of brain tumours following CT scans (ERR of 0.028 mSv^{-1}, versus 0.016, p=0.085). Again, the reverse pattern was observed among the LSS cohort (p=0.02) [23].

A second study by Matthews *et al* [15] involved a data linkage analysis of 680,211 Australian patients receiving CT scans before age 19 years, between 1985 and 2005, compared to 10,259,569 unexposed individuals. With a mean follow-up duration of 9.3 years and an exclusion period of just one year, cancer incidence in the exposed group was 24% greater than in the unexposed group (incidence rate ratio (IRR)= 1.24, 95% CI: 1.20, 1.29 for all cancers). This increase, the authors state, is 'mostly due to irradiation'. Increases for almost all cancer sites were found, including those with limited previous association with radiation, such as Hodgkin's lymphoma and melanoma [26, 27], but no increase was found for breast cancer (IRR= 0.99) and lymphoid leukaemia (0.96), both of which are strongly associated with radiation [28, 29] (the former finding is perhaps unsurprising given the short follow-up). Interestingly, the IRR for brain tumours was significantly raised following scans of regions other than the brain (1.51, 95% CI: 1.19, 1.91).

Brain tumours have been previously associated with ionising radiation exposure, most notably following cranial radiotherapy for acute lymphoblastic leukaemia [30] or previous brain tumours [31]. The association appears to be somewhat stronger for benign tumours such as meningiomas and schwannomas, than for malignant gliomas [32, 33]. The latency period (i.e. the time between exposure and diagnosis) for meningioma development following radiotherapy is typically around 20 years, ranging from 10 to 30 [30, 34, 35], while for gliomas, the latency is around 10 years [31, 34-36]. Many such tumours are detected at an asymptomatic stage via screening programs in these

patient groups [30]. For other exposed populations, including children given radiotherapy for scalp ringworm (mean dose= 1.4 Gy) [37], skin haemangioma [25], or atomic bombing survivors [38], the latency period is longer still, at around 35-40 years. Yet the study by Mathews *et al* [15] reported a significantly raised IRR for brain tumours in the period 1-4 years following head CT scans (3.24, 95% CI: 2.61, 4.02), with declining IRR figures for the periods 5-9 (IRR=2.42), 10-14 (1.80) and >15 years (1.74). The appearance of brain tumours so soon after exposure is highly unusual and raises concerns that these diseases were present at the time of, or indeed were the indication for, the CT scan in the first place [39, 40]. Alternatively, the condition for which the patient underwent a CT scan may itself be a risk factor for developing cancer [29]. Examples include neurofibromatosis (NF) and tuberous sclerosis complex (TSC) [41, 42]. This so-called 'confounding by indication' has become one of the leading concerns among radiation epidemiologists and the dominant focus of more recent studies.

A re-examination of the British CT cohort, first reported by Pearce *et al* [14], was conducted by Berrington de González *et al* [19], who analysed pathology and radiologist reports and comments written in the radiology information system (RIS) to identify predisposing conditions and pre-existing tumours. Previous cancers and possible previous cancers, were found to have the largest impact, resulting in a reduction in ERR for brain tumours by around 57% (0.023 mGy^{-1} to 0.010) and for leukaemia by 44% (0.036 mGy^{-1} to 0.020). There was little evidence that patients with leukaemia pre-disposing conditions received higher bone marrow doses, meaning ERR figures were almost unchanged when these patients were excluded. Patients with CNS tumour predisposing conditions received slightly higher brain doses. Excluding these patients reduced the ERR by about 17% (0.023 mGy^{-1} to 0.019).

Huang and colleagues [16] studied cancer incidence ascertained from insurance records among 28,185 Taiwanese subjects undergoing CT head scans while aged under 18 years between 1998 and 2006, compared to 97,668 unexposed individuals. Patients with NF, hamartomas, multiple endocrine neoplasia and disorders of the adrenal gland were excluded, leaving a sample of 24,418 children. For all cancer types combined, based on an exclusion period of 2 years, no significant increase was seen among the exposed cohort (hazard ratio = 1.29, 95% CI: 0.90, 1.85). A significant increase in brain

tumours was found (HR=2.56, 95% CI: 1.44, 4.54), based on 19 cases, of which 14 were benign. The study has a number of limitations, including the lack of any dose estimation at all, and the failure to include non-head CT exposures in the analysis. Patients with a number of well-known cancer-predisposing conditions, such as TSC, ataxia telangiectasia (AT) or Li Fraumeni syndrome do not appear to have been excluded, thus may have confounded the results.

Journy *et al* [17] investigated cancer incidence among 67,274 French children receiving CT scans before the age of 10 years between 2000 and 2010. Patients with predisposing conditions, including NF, AT, organ transplantation, HIV/AIDS and other phacomatoses (including TSC) were identified from discharge notes. Dose estimates were based on examination protocols. Following a very short follow-up time (median= 4 years), the authors report a decrease in ERR after adjusting for predisposing conditions, falling from 0.022 mGy^{-1} to 0.012 for CNS tumours, from 0.057 mGy^{-1} to 0.047 for leukaemia, and from 0.018 mGy^{-1} to 0.008 for lymphoma. However, the ERR for children without such conditions appears to be higher than the unadjusted ERR for the whole cohort, while the ERR for children with predisposing conditions is close to zero. Responses by Cardis and Bosch de Basea [43] and Muirhead [44] argue that this implies the ERR was modified by predisposing factors rather than confounded. In a further analysis [20] of the same cohort using Cox proportional hazard models, a pattern of increasing risk of CNS tumours and leukaemia with increasing dose was seen (HR per 10 mGy: 1.07 and 1.17 respectively) in children without predisposing conditions, while for those with these conditions, the reverse pattern was seen (HR per 10 mGy: 0.80 and 0.57, respectively).

Krille *et al* [18] investigated cancer incidence among 44,584 German children undergoing 71,073 CT scans between 1980 and 2010. Again, efforts were made to identify subjects with cancer predisposing conditions or those examined for suspected cancer. After excluding these patients, a significantly raised standardised incidence ratio (SIR) was found for all cancer sites combined (SIR=1.54, 95% CI: 1.05, 2.19), along with a non-significantly raised SIR for leukaemia (1.79, 95 % CI: 0.92, 3.12) and CNS tumours (1.20, 95% CI: 0.44, 2.61). A dose response was obtained by calculating the hazard ratio for the whole cohort (including subjects with predisposing conditions). A significantly increased

HR was found for brain tumours (1.008 mGy^{-1}, 95% CI: 1.004, 1.013), but not for leukaemia (1.009, 95% CI: 0.981, 1.037) or for all tumours combined (0.986, 95% CI: 0.944, 1.030).

Dose estimates in the above studies [14-20], where provided, were non-individualised, based on age adjusted 'typical' doses for the equipment or year of scan. Future studies may utilise examination-specific metadata recorded in the image DICOM header [45, 46]. Potential reasons for underestimation of doses includes missing procedures (e.g. pre- and post-contrast head scan listed as simply 'CT head') or unrecorded repeat slices. Contrast agent administration could also result in higher absorbed doses than expected [47], although the overall impact of contrast agents on doses and associated risks is currently unknown. Potential for overestimation of doses includes RIS entries for scans that weren't conducted or 'scans' that were in fact multiplane reconstructions, scout images or non-radiological procedures carried out in the CT room. None of the above studies included doses from other forms of medical imaging, including nuclear medicine or fluoroscopy.

Occupational exposure studies:

Occupationally exposed individuals make suitable subjects in radiation epidemiology studies due to widespread dose monitoring, potentially large sample sizes and the protracted nature of exposures. A study published in 2005, involving a pooled analysis of cancer mortality among 407,391 nuclear industry workers in 15 countries [48], exposed to an average cumulative dose of 19.4 mSv, reported a significantly increased risk for all cancers except leukaemia (ERR=0.97 Sv^{-1}, 95% CI: 0.14, 1.97) and a non-significantly raised risk for leukaemia (ERR=1.93, 95% CI: <0, 8.47). The study has drawn comment concerning the potential confounding effect of smoking and the unusually high ERR among Canadian workers [49, 50]. A reanalysis of the Canadian data was conducted by Zablotska *et al* [51], who reported a much greater solid cancer ERR among workers employed between 1956 and 1964 (7.78 Sv^{-1}, 95% CI: 1.88, 19.5) than for those employed after 1964 (-1.20, 95% CI: -1.47, 2.39). Excluding the Canadian data from the 15-country study, the ERR for solid cancers was reduced to 0.58 Sv^{-1} (95% CI: -0.10, 1.39) [52], which is reasonably close to the linear ERR mortality estimate from the LSS of 0.32 Sv^{-1} [3]. A more recent analysis was conducted by Leuraud *et al* [53] on a subset

of the 15-country study called INWORKS (International Nuclear Workers Study), focusing on 308,297 radiation-monitored workers in the UK, USA and France, receiving a mean yearly bone marrow dose of 1.1 mGy (cumulative mean= 15.9 mGy, cumulative median= 2.1 mGy). Mortality was significantly raised for leukaemia (ERR=2.96 Gy^{-1}, 95 CI: 1.17, 5.21), but not for non-Hodgkin's lymphoma (ERR=0.47 Gy^{-1}, 95% CI: -0.76, 2.03). The INWORKS cohort was subject to a further analysis by Richardson *et al* [54] examining cancer mortality for all sites except leukaemia, based on a mean cumulative colon dose of 20.9 mGy (median= 4.1 mGy). A significantly elevated risk was found (ERR=0.48 Gy^{-1}, 95% CI: 0.2, 0.79). This risk is 50% lower than reported in the above-mentioned study by Cardis *et al* [52], though still a little higher than that of the LSS. Despite the reduced sample size, compared to the 15-country study, the longer follow-up and larger number of deaths of the INWORKS cohort yield much greater statistical power. Limitations include the potential confounding effect of smoking, considerable dosimetric uncertainties and limited information on neutron dose or internal radionuclides [55].

Two recent studies have focused on the offspring of female workers at the Mayak nuclear facility in Russia, providing the opportunity to assess the lifetime cancer risks following *in utero* exposures. The median estimated *in utero* dose from gamma radiation for those with a dose greater than zero was 18.7 mSv (max= 945 mSv) [56]. Doses due to plutonium were extremely low. No significant association was found by Schonfeld *et al* [57] for mortality for solid cancers (ERR= −0.1 Gy^{-1}, 95% CI: <−0.1, 4.1) or leukaemia (ERR= −0.8 Gy^{-1}, 95% CI: <−0.8, 46.9). The solid cancer ERR was raised, however, for attained ages below 15 years (ERR= 50 Gy^{-1}). Though based on only 2 cases and with an exceptionally wide confidence interval (-0.1, 1334), this latter finding is similar to that of the Oxford Survey or Childhood Cancers (OSCC) (ERR of 51 Gy^{-1}) [58]. A later study by Tsareva and colleagues [56] focused on solid cancer incidence, with the advantage of longer follow-up and a greater number of cases. Again, no association with radiation exposure was found (ERR= -1.0 Gy^{-1}, 95% CI: N/A, 0.5). These findings, while surprising, are subject to considerable statistical imprecision, thus are not incompatible with those of the OSCC and should not be interpreted as conclusive evidence that *in utero* exposure does not increase cancer risk.

Previous studies of medical radiation workers, including the US Radiologic Technologists Study [59], have found evidence of increased rates of leukaemia and cancers of the skin and breast among those employed before 1950, but mixed evidence for those employed thereafter [60-62]. A recent update of a cohort study of 27,011 Chinese diagnostic x-ray workers [63] exposed to a mean cumulative colon dose, estimated from badge readings, of 86 mGy (median= 42 mGy) found a significantly increased incidence of solid cancer (ERR= 0.87 Gy^{-1}, 95% CI: 0.48, 1.45) compared to 25,782 non-exposed physicians. The potential socioeconomic differences in these two groups, along with substantial dosimetric uncertainties are acknowledged limitations. The doses received by most x-ray staff have decreased markedly, with mean estimated cumulative breast dose falling from 560 mGy for US technologists first employed in the 1930s, to 2.8 mGy in the 1990s [64]. The associated risks, therefore, are likely to be small.

Background radiation studies:

Residents of a number of areas are exposed to elevated radiation levels as a result of natural radioactivity or industrial pollution. Previous studies of these populations have produced mixed results, hindered by dose uncertainties and small sample sizes [65]. A recent case-control study with reasonably high statistical power was conducted by Kendall and colleagues [66] who matched 27,447 children living in Great Britain who developed cancer with 36,793 cancer-free controls. Radiation doses were estimated based on the mother's residence at the time of the child's birth and a national survey of natural background radiation levels [67]. For leukaemia, a significantly raised relative risk of 1.12 per mSv cumulative bone marrow dose from gamma radiation was found (95% CI: 1.03, 1.22). Relative risk increased monotonically with increasing cumulative bone marrow dose, becoming significantly raised above around 4 mGy. The trend was driven by lymphoid leukaemia (RR=1.13, 95% CI: 1.02, 1.24), with lower risks for myeloid leukaemia (RR=1.05, 95% CI: 0.87, 1.28). For all cancers except leukaemia, risks were non-significantly negative up to cumulative doses of around 12 mGy, above which they were positive. Lest this be interpreted as evidence of hormesis (i.e. the theory that low doses reduce risk), it should be noted that these doses were protracted. Thus, if a hormesis

effect or low dose threshold does exist, it is likely to be in the region of a few nanogray and of little significance in medical imaging. Another new background radiation study, based in Switzerland, was conducted by Spycher *et al* [68], involving 2,093,660 children aged under 16 years. A significant increase in incidence was reported for all cancers combined (HR = 1.64, 95% CI:1.13, 2.37) and leukaemia (HR= 2.04, 95% CI: 1.11, 3.74) for children residing in areas with background dose rates of greater than 200 nSv per hour (≈1.75 mSv per year) compared to less than 100 nSv per hour (≈0.88 mSv per year). No corresponding increase was found for lymphoma (HR=0.91, 95% CI: 0.29, 2.86). Otherwise, the negative risks for low-to-moderate dose rates found in the study by Kendall *et al* described above were not seen in the Swiss study.

Implications for patients and staff:

Practical radiation protection is primarily based on the assumed association between radiation exposure and increased cancer risk. Recent epidemiological studies have, on balance, strengthened this association. While no significant change to practice is warranted, a number of recent findings have potentially important implications. Firstly, dose limits for members of the public and radiation workers are based on risk estimates calculated by the ICRP of 5.5% per Sv (effective dose) [2] that assume risks, per unit dose, at low doses (<200 mGy) or dose rates (<0.1 mGy per minute) are reduced by a factor of 2.0 compared to higher doses or dose rates [2]. These risk estimates impact room design considerations such as shielding requirements and designation of controlled and supervised areas. The results of studies of nuclear workers [69], including the new INWORKS analyses [53, 54], appear to challenge this assumption, suggesting a DDREF closer to 1.0. This, in turn, suggests dose limits should be reduced by 50%. Nuclear workers are exposed to different photon energies and radionuclides to medical imaging staff, including beta emitters such as strontium-90 or alpha emitters such as plutonium. The transferability of these findings, if true, between occupational groups is unclear.

Secondly, findings of increased risk of leukaemia among children receiving CT scans, occupationally exposed workers or children living in high background radiation areas ought to encourage greater

focus on bone marrow dose reduction. This is especially significant for staff given the reported lack of adequate coverage provided by often ill-fitting lead aprons [70]. Around 15% of active bone marrow is found in the arms and head of the average 40-year-old [71].

Thirdly, recent studies have provided more information on the modifying effect of age-at-exposure, suggesting the relationship is somewhat less clear cut than often assumed. For example, brain tumour risk was found to increase with increasing age-at-exposure in the CT study by Pearce *et al* [14]. A recent review [72] considered children to be clearly more sensitive to radiation-induced cancers than adults for 25% of sites, equally sensitive for 15% and less sensitive for 10%. For the remaining sites, the evidence was insufficient to draw conclusion, or there is little evidence of increased risk at any age. The majority of studies investigating the risks from low dose medical radiation have focussed on exposures during childhood, mainly due to the suitability of young people for epidemiological analysis. ERR figures from paediatric CT studies should not be directly compared with ERR figures from adult studies (e.g. nuclear workers) due to the different levels of follow-up. The failure to find new evidence of increased cancer risks following *in utero* exposures does not invalidate previous research (i.e. the Oxford Survey) nor justify abandoning current radiation protection practices for pregnant patients.

Conclusion:

Table 1 summarises the site specific risk of radiation induced cancer based on current evidence. Recent epidemiological studies, combined with existing knowledge, have strengthened the evidence that ionising radiation, at diagnostic dose levels, increases the risk of developing cancer. The findings of significantly increased cancer risks following protracted exposures among nuclear workers and individuals exposed to elevated background radiation levels, do not suggest the presence of a low dose threshold below which there is no risk. The magnitude of the risks and the shape of the dose-risk relationship at low doses remain very uncertain, however. It may never be possible to demonstrate the risks for procedures delivering localised doses below 1 mGy, such as chest or extremity radiographs, with adequate statistical power, nor may it be possible to rule out the possibility that the risks are zero. Future research, including extended background radiation studies, cohorts of children undergoing

cardiac catheterizations [73] and Europe-wide pooling of CT cohorts with improved dosimetry, taking account of confounding conditions, should improve risk estimates.

References:

1. Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation. Health Risks from Exposures to Low Levels of Ionizing Radiation: BEIR VII Phase 2. Washington D.C: National Research Council of the National Academies2006.
2. International Commission on Radiological Protection (ICRP). ICRP Publication 103. The 2007 recommendations of the International Commission on Radiological Protection.2007.
3. Gilbert ES. Ionising radiation and cancer risks: What have we learned from epidemiology? International Journal of Radiation Biology. 2009;85(6):467-82.
4. Little MP, Wakeford R, Tawn EJ, Bouffler SD, Berrington de Gonzalez A. Risks associated with low doses and low dose rates of ionizing radiation: why linearity may be (almost) the best we can do. Radiology. 2009;251(1):6-12.
5. Tubiana M, Feinendegen LE, Yang C, Kaminski JM. The linear no-threshold relationship is inconsistent with radiation biologic and experimental data. Radiology. 2009;251(1):13-22.
6. Gofman JW. Radiation from Medical Procedures in Pathogenesis of Cancer and Ischemic Heart Disease: Dose-Response Studies with Physicians per 100,000 Population: Committee Nuclear Responsibility, 1999.
7. Aurengo A, Averbeck D, Bonnin A, Le Guen B, Masse R, Monier R, et al. Dose-effect relationships and estimation of the carcinogenic effects of low doses of ionizing radiation: Académie des Sciences [Academy of Sciences] - Académie nationale de Médecine [National Academy of Medicine]2005.
8. Siegel JA, Welsh JS. Does Imaging Technology Cause Cancer? Debunking the Linear No-Threshold Model of Radiation Carcinogenesis. Technology in cancer research & treatment. 2016;15(2):249-56.
9. Mettler FA, Jr., Huda W, Yoshizumi TT, Mahesh M. Effective doses in radiology and diagnostic nuclear medicine: a catalog. Radiology. 2008;248(1):254-63.
10. Miglioretti DL, Johnson E, Williams A, Greenlee RT, Weinmann S, Solberg LI, et al. The use of computed tomography in pediatrics and the associated radiation exposure and estimated cancer risk. JAMA pediatrics. 2013;167(8):700-7.
11. Bernier MO, Rehel JL, Brisse HJ, Wu-Zhou X, Caer-Lorho S, Jacob S, et al. Radiation exposure from CT in early childhood: a French large-scale multicentre study. Br J Radiol. 2012;85(1009):53-60.
12. Smith-Bindman R, Moghadassi M, Wilson N, Nelson TR, Boone JM, Cagnon CH, et al. Radiation Doses in Consecutive CT Examinations from Five University of California Medical Centers. Radiology. 2015;277(1):134-41.
13. Lee C, Pearce MS, Salotti JA, Harbron RW, Little MP, McHugh K, et al. Reduction in radiation doses from paediatric CT scans in Great Britain. Br J Radiol. 2016;89(1060):20150305.
14. 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(9840):499-505.
15. 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 or adolescence: data linkage study of 11 million Australians. BMJ (Clinical research ed). 2013;346:f2360.
16. Huang WY, Muo CH, Lin CY, Jen YM, Yang MH, Lin JC, et al. Paediatric head CT scan and subsequent risk of malignancy and benign brain tumour: a nation-wide population-based cohort study. Br J Cancer. 2014.
17. Journy N, Rehel JL, Ducou Le Pointe H, Lee C, Brisse H, Chateil JF, et al. Are the studies on cancer risk from CT scans biased by indication? Elements of answer from a large-scale cohort study in France. Br J Cancer. 2015;112(1):185-93.
18. Krille L, Dreger S, Schindel R, Albrecht T, Asmussen M, Barkhausen J, et al. Risk of cancer incidence before the age of 15 years after exposure to ionising radiation from computed tomography: results from a German cohort study. Radiat Environ Biophys. 2015;54(1):1-12.

19. Berrington de González A, Salotti J, McHugh K, Little M, Harbron R, Lee C, et al. The Relationship Between Pediatric CT Scans and Subsequent Risk of Leukemia and Brain Tumors: Assessment of The Impact of Underlying Conditions. British Journal of Cancer. 2016;114:388-94.
20. Journy N, Roue T, Cardis E, Le Pointe HD, Brisse H, Chateil JF, et al. Childhood CT scans and cancer risk: impact of predisposing factors for cancer on the risk estimates. Journal of radiological protection : official journal of the Society for Radiological Protection. 2016;36(1):N1-7.
21. Shuryak I, Lubin JH, Brenner DJ. Potential for adult-based epidemiological studies to characterize overall cancer risks associated with a lifetime of CT scans. Radiat Res. 2014;181(6):584-91.
22. Leukaemia & Lymphoma Research. Myleodysplastic Syndromes (MDS) (patient information leaflet). Available online at https://leukaemialymphomaresearch.org.uk/booklet/myelodysplastic-syndromes-mds2012.
23. Preston DL, Ron E, Tokuoka S, Funamoto S, Nishi N, Soda M, et al. Solid cancer incidence in atomic bomb survivors: 1958-1998. Radiat Res. 2007;168(1):1-64.
24. Sadetzki S, Chetrit A, Freedman L, Stovall M, Modan B, Novikov I. Long-term follow-up for brain tumor development after childhood exposure to ionizing radiation for tinea capitis. Radiat Res. 2005;163(4):424-32.
25. Karlsson P, Holmberg E, Lundell M, Mattsson A, Holm LE, Wallgren A. Intracranial tumors after exposure to ionizing radiation during infancy: a pooled analysis of two Swedish cohorts of 28,008 infants with skin hemangioma. Radiat Res. 1998;150(3):357-64.
26. Braam KI, Overbeek A, Kaspers GJ, Ronckers CM, Schouten-van Meeteren AY, Van Dulmen-Den Broeder E, et al. Malignant melanoma as second malignant neoplasm in long-term childhood cancer survivors: a systematic review. Pediatr Blood Cancer. 2012;58(5):665-74.
27. Guerin S, Dupuy A, Anderson H, Shamsaldin A, Svahn-Tapper G, Moller T, et al. Radiation dose as a risk factor for malignant melanoma following childhood cancer. Eur J Cancer. 2003;39(16):2379-86.
28. United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). UNSCEAR 2006 Report - Effects of ionizing radiation Annex A: United Nations, 2006.
29. Boice JD, Jr. Radiation epidemiology and recent paediatric computed tomography studies. Ann ICRP. 2015;44(1 Suppl):236-48.
30. Goshen Y, Stark B, Kornreich L, Michowiz S, Feinmesser M, Yaniv I. High incidence of meningioma in cranial irradiated survivors of childhood acute lymphoblastic leukemia. Pediatr Blood Cancer. 2007;49(3):294-7.
31. Broniscer A, Ke W, Fuller CE, Wu J, Gajjar A, Kun LE. Second neoplasms in pediatric patients with primary central nervous system tumors: the St. Jude Children's Research Hospital experience. Cancer. 2004;100(10):2246-52.
32. Berrington de González A, Gilbert E, Curtis R, Inskip P, Kleinerman R, Morton L, et al. Second solid cancers after radiation therapy: a systematic review of the epidemiologic studies of the radiation dose-response relationship. International journal of radiation oncology, biology, physics. 2013;86(2):224-33.
33. Braganza MZ, Kitahara CM, Berrington de Gonzalez A, Inskip PD, Johnson KJ, Rajaraman P. Ionizing radiation and the risk of brain and central nervous system tumors: a systematic review. Neuro-oncology. 2012;14(11):1316-24.
34. Walter AW, Hancock ML, Pui CH, Hudson MM, Ochs JS, Rivera GK, et al. Secondary brain tumors in children treated for acute lymphoblastic leukemia at St Jude Children's Research Hospital. J Clin Oncol. 1998;16(12):3761-7.
35. Galloway TJ, Indelicato DJ, Amdur RJ, Morris CG, Swanson EL, Marcus RB. Analysis of dose at the site of second tumor formation after radiotherapy to the central nervous system. International journal of radiation oncology, biology, physics. 2012;82(1):90-4.
36. Carret AS, Tabori U, Crooks B, Hukin J, Odame I, Johnston DL, et al. Outcome of secondary high-grade glioma in children previously treated for a malignant condition: a study of the Canadian

Pediatric Brain Tumour Consortium. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2006;81(1):33-8.
37. Sadetzki S, Flint-Richter P, Ben-Tal T, Nass D. Radiation-induced meningioma: a descriptive study of 253 cases. Journal of neurosurgery. 2002;97(5):1078-82.
38. Sadamori N, Shibata S, Mine M, Miyazaki H, Miyake H, Kurihara M, et al. Incidence of intracranial meningiomas in Nagasaki atomic-bomb survivors. International journal of cancer Journal international du cancer. 1996;67(3):318-22.
39. Walsh L, Shore R, Auvinen A, Jung T, Wakeford R. Risks from CT scans-what do recent studies tell us? Journal of radiological protection : official journal of the Society for Radiological Protection. 2014;34(1):E1.
40. Harvey HB, Brink JA, Frush DP. Informed Consent for Radiation Risk from CT Is Unjustified Based on the Current Scientific Evidence. Radiology. 2015;275(2):321-5.
41. Evans DG. Neurofibromatosis type 2 (NF2): a clinical and molecular review. Orphanet journal of rare diseases. 2009;4:16.
42. Yates JR. Tuberous sclerosis. European journal of human genetics : EJHG. 2006;14(10):1065-73.
43. Cardis E, de Basea MB. Comment on 'Are the studies on cancer risk from CT scans biased by indication? Elements of answer from a large-scale cohort study in France'-Evidence of confounding by predisposing factors unclear. Br J Cancer. 2015;112(11):1842-3.
44. Muirhead CR. Response to 'Are the studies on cancer risk from CT scans biased by indication? Elements of answer from a large-scale cohort study in France'. Br J Cancer. 2015;112(11):1841-2.
45. Thierry-Chef I, Dabin J, Friberg EG, Hermen J, Istad TS, Jahnen A, et al. Assessing organ doses from paediatric CT scans--a novel approach for an epidemiology study (the EPI-CT study). International journal of environmental research and public health. 2013;10(2):717-28.
46. Jahnen A, Kohler S, Hermen J, Tack D, Back C. Automatic computed tomography patient dose calculation using DICOM header metadata. Radiat Prot Dosimetry. 2011;147(1-2):317-20.
47. Amato E, Salamone I, Naso S, Bottari A, Gaeta M, Blandino A. Can contrast media increase organ doses in CT examinations? A clinical study. AJR Am J Roentgenol. 2013;200(6):1288-93.
48. Cardis E, Vrijheid M, Blettner M, Gilbert E, Hakama M, Hill C, et al. Risk of cancer after low doses of ionising radiation - Retrospective cohort study in 15 countries. British Medical Journal. 2005;331(7508):77-80.
49. Wakeford R. Nuclear worker studies: promise and pitfalls. Br J Cancer. 2014;110(1):1-3.
50. Wakeford R. Radiation in the workplace-a review of studies of the risks of occupational exposure to ionising radiation. Journal of radiological protection : official journal of the Society for Radiological Protection. 2009;29(2A):A61-79.
51. Zablotska LB, Lane RS, Thompson PA. A reanalysis of cancer mortality in Canadian nuclear workers (1956-1994) based on revised exposure and cohort data. Br J Cancer. 2014;110(1):214-23.
52. Cardis E, Vrijheid M, Blettner M, Gilbert E, Hakama M, Hill C, et al. The 15-Country Collaborative Study of Cancer Risk among Radiation Workers in the Nuclear Industry: estimates of radiation-related cancer risks. Radiat Res. 2007;167(4):396-416.
53. Leuraud K, Richardson DB, Cardis E, Daniels RD, Gillies M, O'Hagan JA, et al. Ionising radiation and risk of death from leukaemia and lymphoma in radiation-monitored workers (INWORKS): an international cohort study. Lancet Haematol. 2015;2(7):e276-e81.
54. Richardson DB, Cardis E, Daniels RD, Gillies M, O'Hagan JA, Hamra GB, et al. Risk of cancer from occupational exposure to ionising radiation: retrospective cohort study of workers in France, the United Kingdom, and the United States (INWORKS). BMJ (Clinical research ed). 2015;351:h5359.
55. Little MP. Ionising radiation in the workplace. BMJ (Clinical research ed). 2015;351:h5405.
56. Tsareva Y, Deltour I, Sokolnikov M, Okatenko P, Vostrotin VV, Schonfeld SJ, et al. Risk of solid cancer in the offspring of female workers of the Mayak nuclear facility in the Southern Urals, Russian Federation. Radiat Environ Biophys. 2016.

57. Schonfeld SJ, Tsareva YV, Preston DL, Okatenko PV, Gilbert ES, Ron E, et al. Cancer mortality following in utero exposure among offspring of female mayak worker cohort members. Radiation Research. 2012;178(3):160-65.
58. Wakeford R, Little MP. Risk coefficients for childhood cancer after intrauterine irradiation: A review. International Journal of Radiation Biology. 2003;79(5):293-309.
59. National Cancer Institute, University of Minnesota. The US Radiologic Technologist Study. Available from: http://radtechstudy.nci.nih.gov/.
60. Linet MS, Kim KP, Miller DL, Kleinerman RA, Simon SL, Berrington de Gonzalez A. Historical review of occupational exposures and cancer risks in medical radiation workers. Radiat Res. 2010;174(6):793-808.
61. Liu JJ, Freedman DM, Little MP, Doody MM, Alexander BH, Kitahara CM, et al. Work history and mortality risks in 90,268 US radiological technologists. Occup Environ Med. 2014;71(12):819-35.
62. Samerdokiene V, Atkocius V, Valuckas KP. The risk of cancer among Lithuanian medical radiation workers in 1978-2004. Medicina (Kaunas, Lithuania). 2009;45(5):412-8.
63. Sun Z, Inskip PD, Wang J, Kwon D, Zhao Y, Zhang L, et al. Solid cancer incidence among Chinese medical diagnostic x-ray workers, 1950-1995: Estimation of radiation-related risks. International journal of cancer Journal international du cancer. 2016;138(12):2875-83.
64. Simon SL, Preston DL, Linet MS, Miller JS, Sigurdson AJ, Alexander BH, et al. Radiation organ doses received in a nationwide cohort of U.S. radiologic technologists: methods and findings. Radiat Res. 2014;182(5):507-28.
65. Hendry JH, Simon SL, Wojcik A, Sohrabi M, Burkart W, Cardis E, et al. Human exposure to high natural background radiation: what can it teach us about radiation risks? Journal of radiological protection : official journal of the Society for Radiological Protection. 2009;29(2a):A29-42.
66. Kendall GM, Little MP, Wakeford R, Bunch KJ, Miles JC, Vincent TJ, et al. A record-based case-control study of natural background radiation and the incidence of childhood leukaemia and other cancers in Great Britain during 1980-2006. Leukemia. 2013;27(1):3-9.
67. Wrixon AD, Green BMR, Lomas PR, Miles JCH, Cliff KD, EA F, et al. Report No: NRPB-R190: Natural Radiation Exposure in UK Dwellings. : National Radiological Protection Board:1998.
68. Spycher BD, Lupatsch JE, Zwahlen M, Roosli M, Niggli F, Grotzer MA, et al. Background ionizing radiation and the risk of childhood cancer: a census-based nationwide cohort study. Environ Health Perspect. 2015;123(6):622-8.
69. Jacob P, Ruhm W, Walsh L, Blettner M, Hammer G, Zeeb H. Is cancer risk of radiation workers larger than expected? Occup Environ Med. 2009;66(12):789-96.
70. Cremen SA, McNulty JP. The availability of appropriately fitting personal protective aprons and jackets for angiographic and interventional radiology personnel. Radiography. 20(2):126-30.
71. Cristy M. Active bone marrow distribution as a function of age in humans. Phys Med Biol. 1981;26(3):389-400.
72. United Nations Scientific Committee on Atomic Radiation (UNSCEAR). Sources, effects and risks of Ionizing radiation, Volume II, Annex B: Effects of radiation exposure of children. New York: United Nations2013.
73. Baysson H, Réhel J, Boudjemline Y, Petit J, Girodon B, Aubert B, et al. Risk of cancer associated with cardiac catheterization procedures during childhood: a cohort study in France. BMC Public Health 2013, 13:266. 2013;13:266.
74. Richardson D, Sugiyama H, Nishi N, Sakata R, Shimizu Y, Grant EJ, et al. Ionizing radiation and leukemia mortality among Japanese Atomic Bomb Survivors, 1950-2000. Radiat Res. 2009;172(3):368-82.
75. Krestinina LY, Davis FG, Schonfeld S, Preston DL, Degteva M, Epifanova S, et al. Leukaemia incidence in the Techa River Cohort: 1953-2007. Br J Cancer. 2013;109(11):2886-93.
76. Veiga LH, Holmberg E, Anderson H, Pottern L, Sadetzki S, Adams MJ, et al. Thyroid Cancer after Childhood Exposure to External Radiation: An Updated Pooled Analysis of 12 Studies. Radiat Res. 2016;185(5):473-84.

77. Ozasa K, Shimizu Y, Suyama A, Kasagi F, Soda M, Grant EJ, et al. Studies of the mortality of atomic bomb survivors, report 14, 1950-2003: An overview of cancer and noncancer diseases. Radiation Research. 2012;177(3):229-43.
78. Ron E, Lubin JH, Shore RE, Mabuchi K, Modan B, Pottern LM, et al. Thyroid cancer after exposure to external radiation: a pooled analysis of seven studies. Radiat Res. 1995;141(3):259-77.
79. Preston DL, Mattsson A, Holmberg E, Shore R, Hildreth NG, Boice JD, Jr. Radiation effects on breast cancer risk: a pooled analysis of eight cohorts. Radiat Res. 2002;158(2):220-35.
80. Sokolnikov ME, Gilbert ES, Preston DL, Ron E, Shilnikova NS, Khokhryakov VV, et al. Lung, liver and bone cancer mortality in Mayak workers. International journal of cancer Journal international du cancer. 2008;123(4):905-11.
81. Morton LM, Dores GM, Curtis RE, Lynch CF, Stovall M, Hall P, et al. Stomach cancer risk after treatment for hodgkin lymphoma. J Clin Oncol. 2013;31(27):3369-77.
82. Tukenova M, Diallo I, Anderson H, Hawkins M, Garwicz S, Sankila R, et al. Second malignant neoplasms in digestive organs after childhood cancer: a cohort-nested case-control study. International journal of radiation oncology, biology, physics. 2012;82(3):e383-90.
83. Anderson JK, Alanee S, Lindgren B, Slaton J. The risk of bladder cancer in patients diagnosed with other primary neoplasms: analysis of the SEER database. Urologic oncology. 2013;31(6):862-5.
84. Ron E, Preston DL, Kishikawa M, Kobuke T, Iseki M, Tokuoka S, et al. Skin tumor risk among atomic-bomb survivors in Japan. Cancer Causes Control. 1998;9(4):393-401.
85. Morton LM, Gilbert ES, Stovall M, van Leeuwen FE, Dores GM, Lynch CF, et al. Risk of esophageal cancer following radiotherapy for Hodgkin lymphoma. Haematologica. 2014;99(10):e193-6.
86. United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). Hereditary effects of radiation. New York, NY, 2001.
87. Travis LB, Hauptmann M, Gaul LK, Storm HH, Goldman MB, Nyberg U, et al. Site-specific cancer incidence and mortality after cerebral angiography with radioactive thorotrast. Radiat Res. 2003;160(6):691-706.
88. Schneider AB, Lubin J, Ron E, Abrahams C, Stovall M, Goel A, et al. Salivary gland tumors after childhood radiation treatment for benign conditions of the head and neck: dose-response relationships. Radiat Res. 1998;149(6):625-30.
89. Boukheris H, Stovall M, Gilbert ES, Stratton KL, Smith SA, Weathers R, et al. Risk of salivary gland cancer after childhood cancer: a report from the Childhood Cancer Survivor Study. International journal of radiation oncology, biology, physics. 2013;85(3):776-83.
90. Schwartz B, Benadjaoud MA, Clero E, Haddy N, El-Fayech C, Guibout C, et al. Risk of second bone sarcoma following childhood cancer: role of radiation therapy treatment. Radiat Environ Biophys. 2014;53(2):381-90.
91. Henderson TO, Whitton J, Stovall M, Mertens AC, Mitby P, Friedman D, et al. Secondary sarcomas in childhood cancer survivors: a report from the Childhood Cancer Survivor Study. J Natl Cancer Inst. 2007;99(4):300-8.
92. Dores GM, Curtis RE, van Leeuwen FE, Stovall M, Hall P, Lynch CF, et al. Pancreatic cancer risk after treatment of Hodgkin lymphoma. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO. 2014;25(10):2073-9.
93. Kim CJ, Freedman DM, Curtis RE, Berrington de Gonzalez A, Morton LM. Risk of non-Hodgkin lymphoma after radiotherapy for solid cancers. Leukemia & lymphoma. 2013;54(8):1691-7.
94. Lundell M, Holm LE. Risk of solid tumors after irradiation in infancy. Acta oncologica (Stockholm, Sweden). 1995;34(6):727-34.

Cancer site:	Strength of Evidence:	Comments:	Key references
Leukaemia	Very strong	Assumed to follow exposure to bone marrow. Increased risks following acute and protracted exposures.	[14, 15, 17, 19, 66, 74, 75]
Thyroid	Very strong	Strongly associated with radioiodine intake. Risk is much higher for young children and infants.	[76-78]
Breast	Very strong	Associated with both acute and fractionated exposures.	[79]
Lung	Strong	Strong link with occupational exposures. Risks appear to be higher for exposures in adulthood.	[77, 80]
Stomach	Strong	Large excess among LSS cohort, though problems arise transferring risk estimates to non-Japanese populations.	[77, 81]
Colon	Strong	Increased risks in LSS and radiotherapy cohorts with linear dose response.	[77, 82]
Bladder	Strong	Increased risks demonstrated in LSS and radiotherapy studies.	[77, 83]
Skin	Strong	Risks are high for basal cell carcinoma. Some evidence of increased melanoma risk after radiotherapy.	[26, 84]
Brain/CNS	Moderate	Recent findings of large risks following CT scans. Radiation-induced tumours tend to be benign.	[14-20, 24, 25, 33]
Oesophagus	Moderate	Large level of uncertainty in ERR and effect of age.	[77, 85]
Ovary	Moderate	Increased rates among LSS cohort, though mixed evidence from other studies. Highly uncertain ERR. Evidence of hereditary effects is inconclusive.	[77, 86]
Liver	Moderate	Strong association with internal emitters such as plutonium or thorium. Modifying effect of age at exposure is unclear.	[77, 80, 87]
Salivary glands	Moderate	Excesses seen among the LSS cohort and patients treated with radiotherapy. Dose response is unclear, however. Tumours tend to be benign.	[77, 88, 89]
Bone/soft tissue sarcoma	Weak	Very well established risk following high dose radiotherapy, though limited evidence of risks at doses below 0.5-1 Gy.	[90, 91]
Pancreas	Weak	Some evidence of increased risk after radiotherapy.	[92]
Non-Hodgkin's Lymphoma	Weak	A few studies show non-significantly raised rates. Immunosuppression is a major confounding factor.	[53, 77, 93]
Hodgkin's lymphoma, testes, kidneys, prostate, cervix, small intestine, rectum, eyes.	Possibly absent/no evidence	These sites are often omitted from analyses. Increased risks are sometimes observed following high dose radiotherapy. At low doses, cancer risks are likely to be small, if present at all. Evidence of hereditary effects following exposure of the testes is inconclusive. The eyes are sensitive to cataract induction.	[77, 86, 94]

Table 1: Site-specific risk of cancer from ionising radiation exposure. LSS= Life Span Study (Hiroshima and Nagasaki cohort).