Radiography xxx (2016) 1–6

Contents lists available at ScienceDirect

Radiography

journal homepage: www.elsevier.com/locate/radi

Review Article

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

R.W. Harbron [a, b, *]

[a] Institute of Health and Society, Newcastle University, Royal Victoria Infirmary, Queen Victoria Road, Newcastle-upon-Tyne, NE1 4LP, UK
[b] NIHR Health Protection Research Unit in Chemical and Radiation Threats and Hazards, Newcastle University, UK

ARTICLE INFO

Article history:
Received 2 June 2016
Received in revised form
2 August 2016
Accepted 18 August 2016
Available online xxx

Keywords:
Epidemiology
Cancer
Radiation protection

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 pre-disposing 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.

Abbreviations: AT, ataxia telangiectasia; CI, confidence interval; CNS, central nervous system; ERR, excess relative risk; HR, hazard ratio; ICRP, International Commission on Radiological Protection; INWORKS, International Nuclear Workers Study; IRR, incidence rate ratio; LNT, linear-no-threshold; LSS, Life Span Study; MDS, myelodysplastic syndrome; NF, neurofibromatosis; SIR, standardised incidence ratio; SMR, standardized mortality ratio; TSC, tuberous sclerosis complex.

* Institute of Health and Society, Newcastle University, Royal Victoria Infirmary, Queen Victoria Road, Newcastle-upon-Tyne, NE1 4LP, UK.
E-mail address: r.w.harbron@ncl.ac.uk.

http://dx.doi.org/10.1016/j.radi.2016.08.007
1078-8174/

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/MDS 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 1.16 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.

Please cite this article in press as: Harbron RW, What do recent epidemiological studies tell us about the risk of cancer from radiation doses typical of diagnostic radiography?, Radiography (2016), http://dx.doi.org/10.1016/j.radi.2016.08.007