of cancer patients. Fewer than 4% of the children in the cohort of Journy *et al* had a predisposing factor and the correspondence percentage for the general population is likely to be lower still, given that children with a predisposing factor may be more likely to receive CT scans than other children. On that basis, the ERR estimates specific to children without a predisposing factor would seem to be much more relevant to the general population than the adjusted estimates of Journy *et al*.

In view of the small number of cases in this study, inferences are limited. Further follow-up of this cohort and results from other studies that collect information on predisposing factors (e.g., Meulepas *et al*, 2014) would be valuable in providing further insights. Nevertheless, the findings of Journy *et al* do not indicate that the association between cancer risk and radiation exposure from CT scans has been confounded by predisposing factors for cancer.

## REFERENCES


Journy N, Rehel JL, Ducou Le Pointe H, Lee C, Brisse H, Chateil JF, Caer-Lorho S, Laurier D, Bernier MO (2015) 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* **112**(1): 185–193.

Mathews JD, Forsythe AV, Brady Z, Butler MW, Goergen SK, Byrnes GB, Giles GG, Wallace AB, Anderson PR, Guiver TA, McGale P, Cain TM, Dowty JG, Bickerstaffe AC, Darby SC (2013) Cancer risk in 680,000 people exposed to computed tomography scans in childhood or adolescence: data linkage study of 11 million Australians. *BMJ* **346**: f2360.

Meulepas JM, Ronckers CM, Smets AM, Nievelstein RA, Jahnen A, Lee C, Kieft M, Lameris JS, van Herk M, Greuter MJ, Jeukens CR, van Straten M, Visser O, van Leeuwen FE, Hauptmann M (2014) Leukemia and brain tumors among children after radiation exposure from CT scans: design and methodological opportunities of the Dutch Pediatric CT Study. *Eur J Epidemiol* **29**(4): 293–301.

Pearce MS, Salotti JA, Little MP, McHugh K, Lee C, Kim KP, Howe NL, Ronckers CM, Rajaraman P, Craft AW, Parker L, Berrington de Gonzalez A (2012) Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. *Lancet* **380**(9840): 499–505.

Walsh L, Shore R, Auvinen A, Jung T, Wakeford R (2014) Risks from CT scans–what do recent studies tell us? *J Radiol Prot* **34**(1): E1–E5.


*Correspondence: Dr CR Muirhead; E-mail: Colin.Muirhead@Newcastle.ac.uk


BJC

British Journal of Cancer (2015) 112, 1842–1843 | doi: 10.1038/bjc.2015.155

# 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

E Cardis*[,1,2,3] and M B de Basea[1,2,3]

[1]*Center for Research in Environmental Epidemiology (CREAL), Barcelona, Spain;* [2]*Universitat Pompeu Fabra (UPF), Barcelona, Spain and* [3]*CIBER Epidemiología Salud Pública (CIBERESP), Barcelona, Spain*

**Sir,**

The paper by Journy *et al* (2015) presents the first results of a very carefully conducted cohort study of paediatric computerised tomography (CT) patients from France, part of the European collaborative study 'EPI-CT' (Bosch de Basea *et al*, submitted). Because of criticisms raised about the results of previous studies of CT patients (Pearce *et al*, 2012; Mathews *et al*, 2013; Huang *et al*, 2014), the authors made particular efforts to collect information on potential factors which could invalidate estimates of radiation risks in these studies. The current paper emphasises, in particular, the potential impact of predisposing factors (PFs) for leukaemia, central nervous system (CNS) tumours and lymphoma, the outcomes under study in this paper. For this study, a list of PFs was developed by paediatric oncologists based on the literature, and hospitalised discharge records of cohort members were searched to identify cohort members with PFs. These included familial adenomatous polyposis, multiple endocrine neoplasia, retinocytoma, Fanconi anaemia, ataxia telangiectasia, neurofibromatosis, other phacomatoses, xeroderma pigmentosum, Down syndrome, Noonan syndrome, Klinefelter syndrome and Bloom syndrome as well as immune deficiencies (HIV/AIDS, severe combined immune deficiency, Wiskott–Aldrich syndrome, common variable immune deficiency and organ transplantation). The frequency of PFs for CNS tumours in the cohort was 0.54%; it was 1.7% and 1.6%, respectively, for PFs of leukaemia and lymphoma. The most frequent PFs were organ transplantation (observed in 749 of the 67 274 members of the cohort − 1.11%), HIV/AIDS (0.36%), Down syndrome (0.3%), neurofibromatosis types 1 and 2 (0.16%) and other phacomatoses (0.29%). These percentages, though low, are greater than in the general population and their presence appears to be related to a slightly increased frequency and slightly decreased age at CT examinations, thus potentially confounding the association between radiation from CTs and risks of the aforementioned neoplasms.

During the study period, 27 CNS tumours, 25 leukaemia and 21 lymphoma were observed in the cohort; of these 7, 5 and 7, respectively, had a PF for CNS, leukaemia or lymphoma. In Table 5 of their paper, the authors show that adjustment for PFs reduced the excess relative risk estimates related to cumulative doses from CT scans (Table 1). This led them to conclude 'This study suggests that the indication for examinations, whether suspected cancer or PF management, should be considered to avoid overestimation of the cancer risks associated with CT scans'. Results shown in their Supplementary Table 6, however, focusing on the ERR/mGy among subjects with and without PF, challenge, in our opinion, this interpretation.

Indeed, risk estimates among subjects with no PF are similar to—although slightly higher than—the unadjusted risk estimates for brain tumours and lymphoma (see Table 1). This observation suggests that PFs are not, in fact, confounders of the association between cumulative organ radiation dose from CT and risk of these tumours, but rather possible effect modifiers. Though the authors conducted tests of homogeneity of risks between subjects with and without PFs, they were based on small numbers of subjects and hence the power to formally identify effect modification was very limited. For leukaemia, the ERR/mGy among subjects without PF are

**Table 1. Number of cases (*N*) and ERR per mGy for tumours of the CNS, leukaemia and lymphoma, crude or adjusted for the presence of PFs and by patient's characteristics regarding presence of factors predisposing specifically to cancer at the site specified (PF)**

| | All cases (2-year exclusion period) | | | Subgroups | | | |
|---|---|---|---|---|---|---|---|
| | | Unadjusted | Adjusted for PF | Without PF | | With PF | |
| | *N* | ERR/mGy (95% CI) | ERR/mGy (95% CI) | *N* | ERR/mGy[a] | *N* | ERR/mGy[a] |
| CNS tumours | 22 | 0.022 (−0.016; 0.061) | 0.012 (−0.013; 0.037) | 15 | 0.028 | 7 | −0.005 |
| Leukaemia | 17 | 0.057 (−0.079; 0.193) | 0.047 (−0.065; 0.159) | 12 | 0.187 | 5 | −0.012 |
| Lymphoma | 19 | 0.018 (−0.068; 0.104) | 0.008 (−0.057; 0.073) | 12 | 0.025 | 7 | −0.005 |

Abbreviations: CNS = central nervous system; ERR = excess relative risks; PF = predisposing factor.
[a]Confidence intervals not provided.

substantially higher (but quite uncertain given the small number of cases) than the unadjusted estimates, again suggesting effect modification.

Numbers of cases with PFs are, unfortunately, too small to allow the study of the radiation effect associated with different types of PFs. For brain tumours, the majority of cases with PFs had neurofibromatosis; for lymphomas, organ transplantation, whereas for leukaemia there was a mixture of Down syndrome, primary immunodeficiency and organ transplantation (Journy, 2014). As the mechanism and the magnitude of the increased cancer risk differ for these different types of PFs, it is somewhat surprising that they would all have a similar effect on the risk estimates when adjustment is made for PFs in the analysis. The observation that, among subjects with PFs, the ERRs/mGy for all three outcomes were very close to 0, suggests instead that any effect of low doses of radiation would be too small to detect given the already very high cancer risk among these subjects in the absence of radiation. This would strengthen the argument that PFs are effect modifiers and not confounders of the association between CT radiation dose and risk of cancer.

This finding, if it can be replicated in other larger cohorts, is very important as information on PFs is not available in many cohorts and lack of information about predisposing factors is one of the main criticisms of published studies on the carcinogenic effect of radiation from CT scans in paediatric patients.

As the goal of EPI-CT and other similar studies is to estimate directly the risk of cancer associated with radiation exposure from CT scan examinations in the general paediatric population (where the proportion of PF is relatively low), the findings of Journy and collaborators suggest that the unadjusted ERR/mGy may be a reasonable (and unconfounded) estimate of the true risk, particularly since the frequency of PFs in this cohort is high, due to the inclusion in the study of a number of specialised referral hospitals (Journy, 2014).

## REFERENCES

Huang W-Y, Muo C-H, Lin C-Y, Jen Y-M, Yang M-H, Lin J-C, Sung F-C, Kao C-H (2014) Paediatric head CT scan and subsequent risk of malignancy and benign brain tumour: a nation-wide population-based cohort study. *Br J Cancer* **110**: 2354–2360.

Journy N (2014) Analyse de la relation entre l'exposition aux rayonnements ionisants lors d'examens de scanographie et la survenue de pathologie tumorale au sein de la cohorte Enfant scanner. PhD Thesis, UNIVERSITÉ PARIS-SUD, Paris.

Journy N, Rehel J-L, Ducou Le Pointe H, Lee C, Brisse H, Chateil J-F, Caer-Lorho S, Laurier D, Bernier M-O (2015) Are the studies on cancer risk from CT scans biased by indication? Elements of answer from a largescale cohort study in France. *Br J Cancer*. **112**: 185–193.

Mathews JD, Forsythe AV, Brady Z, Butler MW, Goergen SK, Byrnes GB, Giles GG, Wallace AB, Anderson PR, Guiver TA, McGale P, Cain TM, Dowty JG, Bickerstaffe AC, Darby SC (2013) Cancer risk in 680 000 people exposed to computed tomography scans in childhood or adolescence: data linkage study of 11 million Australians. *BMJ* **346**: f2360.

Pearce MS, Salotti JA, Little MP, McHugh K, Lee C, Kim KP, Howe NL, Ronckers CM, Rajaraman P, Sir Craft AW, Parker L, Berrington de González A (2012) Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. *Lancet* **380**: 499–505.

*Correspondence: Professor E Cardis; E-mail: ecardis@creal.cat
Published online 12 May 2015


BJC

British Journal of Cancer (2015) 112, 1843–1844 | doi: 10.1038/bjc.2015.105

# 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

N Journy[1], D Laurier[1] and M-O Bernier*[,1]

[1]*Laboratory of Epidemiology, Institute for Radiological Protection and Nuclear Safety, BP 17, 92262 Fontenay-aux-Roses, France*

**Sir,**

In response to our publication in the *BJC* (Journy *et al*, 2015), Dr. Colin R. Muirhead gave insightful comments for the interpretation of the potential impact of predisposing factors (PF) for cancer in estimating radiation-related cancer risks from CT scans (Muirhead, 2015). He pointed out that the possibility of an effect modification by the presence of PF, which was reported in the published study, should be considered for providing relevant CT-related risk estimates.

The paper's results indicated that PFs (i.e., some genetic disorders and immune deficiencies) might be a confounding factor (Journy *et al*, 2015). In the cohort, PFs were, as expected, associated with high relative cancer risks, but also with specific patterns of CT exposures. However, as underlined by Dr. Muihead, the excess relative risks (ERRs) related to CT exposure differed in individuals with or without PF. In particular, CT exposure was associated with reduced cancer risks in children with PFs, and the risk estimates in patients without PF were equal to or greater than unadjusted ERRs in the overall cohort, for each of the three cancer sites of interest.

Biological processes, leading to reduced radiation sensitivity in presence of genetic disorders and/or immune deficiencies, are not likely to have been involved in such an effect modification observed with various PFs. From further analyses conducted in the cohort (Journy, 2014), the reduced radiation-related risks in children with PFs might rather be explained by competing events initiated or promoted by PFs, that is, cancer or death. Finally, we agree that the decrease in ERRs with adjustment for PFs reflected, at least partly, an effect modification by PFs.

From our paper's results, Dr. Muihead stated that risk estimates adjusted for the presence of PFs – expressing averaged risks in a population of patients with or without PF – are not relevant for public health purposes, as they are driven by the ERRs in predisposed individuals. Indeed, adjusted ERRs in all exposed individuals might be appropriate to correct the estimations for a potential confounding bias, provided that CT-related risks are homogeneous in the studied population. In the cohort, however, adjusted risk coefficients would represent underestimated risk estimates for children without PFs who accounted for the great majority of patients exposed to CT scans (97% of the cohort). Joining Dr. Muihead's conclusion, these results thus suggest that the most relevant risk coefficients for radiation protection concerns are estimates excluding patients with PFs.

In epidemiological studies on cancer risk after CT scans, in which information on PF is most often inaccessible, a central question is to determine to which extent risk estimates without considering PFs at all might be biased or not. In our study, the results suggested an effect modification without totally excluding the possibility of a confounding bias. It should be noted that issues on reverse causation (Walsh *et al*, 2014) might also differ according to PFs, with enhanced medical surveillance for cancer and early cancer detection in predisposed patients. Our results should nevertheless be interpreted with much caution owing to the small numbers of cases, especially in the subgroup analyses. Indeed, the estimated ERRs were imprecise, and not interpretable for leukemia in children without PF. The duration of follow-up was another major limitation given the latency time between radiation exposure and stochastic health effects. Longer follow-up of this cohort, as well as of other studies that benefit from clinical information (Meulepas *et al*, 2014; Krille *et al*, 2015), will allow a better assessment of the impact of PFs on CT-related risk estimates.

## REFERENCES

Journy N (2014) *Analysis of the Relation Between Ionizing Radiation Exposure from Computed Tomography Scans in Childhood and Cancer Incidence, Within the "Cohorte Enfant Scanner" Study (Unpublished Doctoral Dissertation)*. Paris Sud University: Le Kremlin Bicêtre, France.

Journy N, Rehel JL, Ducou Le Pointe H, Lee C, Brisse H, Chateil JF, Caer-Lorho S, Laurier D, Bernier MO (2015) 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* **112**(1): 185–193.

Krille L, Dreger S, Schindel R, Albrecht T, Asmussen M, Barkhausen J, Berthold JD, Chavan A, Claussen C, Forsting M, Gianicolo EA, Jablonka K, Jahnen A, Langer M, Laniado M, Lotz J, Mentzel HJ, Queißer-Wahrendorf A, Rompel O, Schlick I, Schneider K, Schumacher M, Seidenbusch M, Spix C, Spors B, Staatz G, Vogl T, Wagner J, Weisser G, Zeeb H, Blettner M (2015) Risk of cancer incidence before the age of 15 years after exposure to ionising radiation