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

from computed tomography: results from a German cohort study. *Radiat Environ Biophys* **54**: 1–12.
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.
Muirhead RC (2015) Letter to the editor: ct scans and cancer risk – confounding or effect modification? *Br J Cancer* doi:10.1038/bjc.2015.106.
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 M-O Bernier; marie-odile.bernier@irsn.fr

BJC
British Journal of Cancer (2015) 112, 1844 | doi: 10.1038/bjc.2015.161

Hepatitis B virus infection and gastric cancer risk: pitfalls in the potential association

X-Z Chen[1,2], R Wang[3,4] and J-K Hu*[,1,2]

[1]*Department of Gastrointestinal Surgery, West China Hospital, Sichuan University, Chengdu, China;* [2]*Laboratory of Gastric Cancer, State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu, China and* [3]*Department of Gastroenterology, West China Hospital, Sichuan University, Chengdu, China*

Sir,

We read with great interests the retrospective case–control study by Wei *et al* (2015). As the authors Wei *et al* introduced that epidemiological study is the first one, which found a potential association between hepatitis B virus (HBV) serology and gastric cancer risk. This main finding is indeed surprising to readers. On the basis of the literature from Chinese CNKI journal database, the prevalence of HBV DNA in gastric cancer tissues is only 0–3% by PCR test. Therefore, to evidence the causality between HBV infection and gastric cancer risk, a qualified study with adequate statistical power requires a dramatically larger scale of sample size than that of the study by Wei *et al* (2015). In particular, direct detection of HBV DNA in gastric cancer cells by *in situ* hybridisation is the most convincing evidence to confirm that association.

As known, WHO has defined *Helicobacter pylori* as a class I human carcinogen for gastric cancer development (Fock *et al*, 2013). Besides, Epstein–Barr virus infection is also found to be associated with around 10% of gastric cancer (Murphy *et al*, 2009). However, in the study by Wei *et al* (2015), these two critical confounders were not considered in the logistic regression models. The investigated population in the study by Wei *et al* (2015) is also collected from an endemic region (Guangzhou Province) of both Helicobacter pylori and Epstein–Barr virus infections in mainland China (Wang and Chen, 2014). Therefore, the results are unable to rule out the confounding effects from these two kinds of infections.

Probably, the association between HBV infection and gastric cancer risk might be biased by chance, imbalance of prevalence of *H. pylori* and/or Epstein–Barr virus infection in stomach, or potentially indirect linkage between HBV and those two pathogens. Without the adjustment for those two co-infections, the results may have a risk of misleading readers. Thus, we would like to underline these pitfalls behind interpreting the results to readers and practitioners.

Critically, the epidemiological study Wei *et al* provides some information about the potential association between HBV infection and gastric cancer risk, but the obvious defect in covariate modelling makes the results still far from public health policy and clinical practice. Despite of that, the interesting findings also suggest further investigations with large scale and well-adjusted model to rule out potential biases.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

Fock KM, Graham DY, Malfertheiner P (2013) Helicobacter pylori research: historical insights and future directions. *Nat Rev Gastroenterol Hepatol* **10**(8): 495–500.
Murphy G, Pfeiffer R, Camargo MC, Rabkin CS (2009) Meta-analysis shows that prevalence of Epstein-Barr virus-positive gastric cancer differs based on sex and anatomic location. *Gastroenterology* **137**(3): 824–833.
Wang R, Chen XZ (2014) High mortality from hepatic, gastric and esophageal cancers in mainland China: 40 years of experience and development. *Clin Res Hepatol Gastroenterol* **38**(6): 751–756.
Wei XL, Qiu MZ, Jin Y, Huang YX, Wang RY, Chen WW, Wang DS, Wang F, Luo HY, Zhang DS, Wang FH, Li YH, Xu RH (2015) Hepatitis B virus infection is associated with gastric cancer in China: an endemic area of both diseases. *Br J Cancer* **112**(Suppl): 1283–1290.

*Correspondence: Dr J-K Hu; E-mail: hujkwch@126.com
[4]This author co-first senior author.
Published online 12 May 2015