OXFORD

JNCI J Natl Cancer Inst (2019) 111(9): djz062

doi: 10.1093/jnci/djz062
First published online April 12, 2019
Response

Response to Wollschläger, Blettner, and Pokora

Johanna M. Meulepas, Cecile M. Ronckers, Anne M. J. B. Smets, Rutger A. J. Nievelstein, Patrycja Gradowska, Choonsik Lee, Andreas Jahnen, Marcel van Straten, Marie-Claire Y. de Wit, Bernard Zonnenberg, Willemijn M. Klein, Johannes H. Merks, Otto Visser, Flora E. van Leeuwen, Michael Hauptmann

See the Note section for the full list of authors' affiliations.

Correspondence to: Michael Hauptmann, PhD, Department of Epidemiology and Biostatistics, Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, the Netherlands (e-mail: m.hauptmann@nki.nl).

We thank the editor for the opportunity to respond to the potential issues raised by Wollschläeger et al. Unreported cancers can indeed bias radiation-related risks upward, but we showed that this was not the case for our brain tumor results (1). It was also not the case for our leukemia results, which were null. When we excluded 2281 children born before 1973, who contributed 61 200 person-years and two leukemia cases, relative risks for bone marrow doses of 5–10 mGy, 10–17 mGy, and 17 mGy or more were 1.13, 0.65, and 0.50 compared with bone marrow doses less than 5 mGy. The excess relative risk per 100 mGy was 0.12 and not statistically significant ($P > .5$). Restricting leukemia analyses to children born in 1989 or later leaves 26 cases and relative risks (cases) of 1.0 (12), 0.76 (5), 0.55 (5), and 0.84 (4), respectively.

The elevated cancer incidence in our cohort compared with the general population is in line with other computed tomography (CT) studies. A higher or lower overall cancer incidence in a cohort compared with the general population does not mean that an observed dose-response is biased. We evaluated internal (exclusion of children with tuberous sclerosis complex, different exclusion periods) and external evidence for indication bias (2–4) and found no reason to believe that indication bias explains the entire observed association in the absence of a radiation effect. Recent evidence, although in adults, also supports the notion that the reason for a CT scan does not substantially bias radiation-related risks for certain solid cancers (5). It is common for observational studies to investigate and observe dose-response relationships on background cancer risks that differ from the general population (6,7).

We respectfully disagree with the statement by Wollschläeger et al. that organ doses from CT scanning are "probably too low to make a causal link reconcilable with current knowledge." Recent reviews concluded that epidemiological data support the linear no-threshold model for cancer risk from low-dose radiation exposure. At least four projection studies have estimated substantial excess numbers of cancer cases and deaths due to CT-related radiation exposure. These studies used realistic data on frequency and dose of CT scans as well as radiation risk models reflecting current empirical evidence.

Apparent similarities in Table 1 (1) are due to rounding, and this is as expected-time since first exposure is counted from the first CT irrespective of when subjects start to be at risk. Our statements about the end of exposure follow-up are correct and not conflicting. We collected CTs up to 2014, but CTs after 2012 were not included in analyses due to lagging of the cumulative dose metric.

Wollschläeger et al. are correct in noting that we did not ascertain leukemia incidence among cohort members in the attained age range 15–17 years before 1989. This subgroup contributed 1673 person-years at risk (0.14% of all person-years in the main leukemia analysis), during which 0.06 leukemia cases would be expected. In conclusion, we believe the points raised by Wollschläeger et al. do not modify the main findings and conclusions in our report (1).

Note

Affiliations of authors: Department of Epidemiology and Biostatistics, Netherlands Cancer Institute, Amsterdam, the Netherlands (JMM, PG, FEL, MH); Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands (CMR, JHM); Department of Radiology, Academic Medical Center Amsterdam, Amsterdam, the Netherlands (AMJBS); Department of Radiology, University Medical Center Utrecht, the Netherlands (RAJN); Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, Rockville, MD (CL); Luxembourg Institute of Science and Technology (LIST), Esch-sur-Alzette, Luxembourg (AJ); Department of Radiology and Nuclear Medicine, Erasmus MC, Rotterdam, the Netherlands

Received: March 29, 2019; **Revised:** April 4, 2019;

(MS); Department of Neurology and Paediatric Neurology, Erasmus MC, Sophia Children's Hospital, Rotterdam, the Netherlands (MCYW); Department of Internal Medicine, University Medical Center Utrecht, the Netherlands (BZ); Department of Radiology and Nuclear Medicine, Radboud University Medical Center, Nijmegen, the Netherlands (WMK); Department of Paediatric Oncology, Emma Children's Hospital, Academic Medical Center Amsterdam, Amsterdam, the Netherlands (JHM); Dutch Childhood Oncology Group, the Hague, the Netherlands (JHM); Department of Registration, Netherlands Comprehensive Cancer Organisation, Utrecht, the Netherlands (OV).

References

1. Meulepas JM, Ronckers CM, Smets A, et al. Radiation exposure from pediatric CT scans and subsequent cancer risk in the Netherlands. *J Natl Cancer Inst*. 2019;111(3):256–263.
2. Journy N, Rehel JL, Ducou Le Pointe H, 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):185–193.
3. Berrington de Gonzalez A, Salotti JA, McHugh K, et al. The relationship between pediatric CT scans and subsequent risk of leukemia and brain tumors: assessment of the impact of underlying conditions. *Br J Cancer*. 2016;114(4):388–394.
4. Meulepas JM, Ronckers CM, Merks J, Weijerman ME, Lubin JH, Hauptmann M. Confounding of the association between radiation exposure from CT scans and risk of leukemia and brain tumors by cancer susceptibility syndromes. *J Radiol Prot*. 2016;36(4):953–974.
5. Meulepas JM, Hauptmann M, Lubin JH, Shuryak I, Brenner DJ. Is there unmeasured indication bias in radiation-related cancer risk estimates from studies of computed tomography? *Radiat Res*. 2018;189(2):128–135.
6. Hauptmann M, Lubin JH, Stewart PA, Hayes RB, Blair A. Mortality from lymphohematopoietic malignancies among workers in formaldehyde industries. *J Natl Cancer Inst*. 2003;95(21):1615–1623.
7. Teepen JC, van Leeuwen FE, Tissing WJ, et al.; on behalf of the DCOG LATER Study Group. Long-term risk of subsequent malignant neoplasms after treatment for childhood cancer in the DCOG LATER study cohort: role of chemotherapy. *J Clin Oncol*. 2017;35(20):2288–2298.