Confounding of the Association between Radiation Exposure from CT Scans and Risk of Leukemia and Brain Tumors by Cancer Susceptibility Syndromes

Johanna M. Meulepas1, Cécile M. Ronckers2, Johannes Merks2, Michel E. Weijerman3, Jay H. Lubin4, and Michael Hauptmann1

Abstract

Background: Recent studies linking radiation exposure from pediatric computed tomography (CT) to increased risks of leukemia and brain tumors have shown elevated risks of leukemia and brain tumors (1–5) and other studies are underway (6, 7). These studies are record-linkage cohort studies on large numbers of patients collected from existing databases (health insurances and hospitals) with limited or no information on potential confounding factors, which may bias the radiation-cancer association. A confounder is associated with the exposure in the source population from which the cases arise and with the disease under study in the non-exposed population and is not on the causal pathway.

Results: We estimate that radiation-related RRs for leukemia are not meaningfully confounded by Down syndrome, Noonan syndrome, or other CSS. In contrast, RRs for brain tumors may be overestimated due to confounding by tuberous sclerosis complex (TSC) while von Hippel–Lindau disease, neurofibromatosis type 1, or other CSS do not meaningfully confound. Empirical data on the use of CT scans among CSS patients are urgently needed.

Conclusions: Our assessment indicates that associations with leukemia reported in previous studies are unlikely to be substantially confounded by unmeasured CSS, whereas brain tumor risks might have been overestimated due to confounding by TSC.

Impact: Future studies should identify TSC patients in order to avoid overestimation of brain tumor risks due to radiation exposure from CT scans. Cancer Epidemiol Biomarkers Prev; 25(1): 114–26. ©2015 AACR.

Introduction

Five epidemiologic studies on cancer following radiation exposure from pediatric computed tomography (CT) scans have shown elevated risks of leukemia and brain tumors (1–5) and other studies are underway (6, 7). These studies are record-linkage cohort studies on large numbers of patients collected from existing databases (health insurances and hospitals) with limited or no information on potential confounding factors, which may bias the radiation-cancer association. A confounder is associated with the exposure in the source population from which the cases arise and with the disease under study in the non-exposed population and is not on the causal pathway.

Concerns have been raised about a possible overestimation of radiation-related risks in studies of pediatric CT scans and cancer due to confounding by indication (also called reverse causation; refs. 8–13). Confounding by indication occurs if the reason for a CT scan is associated with cancer risk.

With regard to CT studies, the primary concern is about two sources of confounding by indication, namely subclinical tumors and cancer susceptibility syndromes (CSS). Cancer in a subclinical prodromal phase may cause symptoms that necessitate a CT scan. The CT radiation dose is solely associated with detection and not with disease causation. This source of confounding by indication is often amenable to evaluation through the use of an exclusion period. CSS, on the other side, are congenital disorders and are associated with increased cancer risk at one or more sites (14). The potential for confounding arises because CSS patients may have CT scans for early symptoms of the syndrome, diagnostic purposes, monitoring of disease progression, or associated comorbidities (15, 16). We focus on CSS because we believe that they are the potentially most important source of confounding by indication.

In the absence of empirical data, it appears plausible that CSS patients are more likely to have one or multiple CT scans than children without CSS. Because CT scans do not cause CSS, the observed increased risk of cancer following pediatric radiation exposure from diagnostic imaging might be partly due to

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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The largest studies published to date did not adjust their risk estimates for CSS. Such data are likely not available, because most countries do not have registries or other easily accessible resources to identify CSS patients. For CSS where the direction of the potential confounding is known but not its magnitude, we use plausible scenarios to assess the magnitude of possible bias in studies of radiation exposure from pediatric CT scans (17).

This report focuses on pediatric CT scans, because children are more radiosensitive than adults. The endpoints of primary concern are leukemia and brain tumors. These diseases are the most common radiogenic malignancies among children, adolescents, and young adults and are the primary focus of published and ongoing epidemiologic studies on cancer risk following pediatric CT scan exposure (18). Nevertheless, the results of our analyses provide guidance for all epidemiologic studies of diagnostic imaging and cancer risk.

**Materials and Methods**

In short, we identify CSS predisposing to leukemia or brain tumors and characterize: their prevalence in the general population, the strength of their association with leukemia and/or brain tumors, and their life expectancy. We then calculate the magnitude of CSS-related confounding of relative risk (RR) estimates for leukemia and brain tumors after diagnostic CT scans, under various assumptions for the association between CSS and the frequency of CT scans.

**Identification and characterization of CSS**

We identified CSS that are associated with increased risk of either leukemia, or brain tumors, or both, at any age based on two major sources of information: (i) a table of genetic syndromes predisposing to childhood cancer from a thorough systematic review of the literature by a pediatric oncologist who specializes in these syndromes (J. Merks, ref. 14) and (ii) a systematic overview of familial cancer syndromes (15). Third, we consulted with physicians specializing in genetic syndromes at three university hospitals (see the Acknowledgments section) to identify any other rare eligible CSS. Then, the pediatric oncologist (J. Merks) assessed the likelihood of medical radiation exposures for screening or health care for each of the CSS. Finally, we queried the MEDLINE database for each CSS to determine prevalence risk of leukemia and brain tumors, life expectancy, and the likelihood of diagnostic imaging (in particular CT scan). We included articles regardless of study design, as well as book chapters and systematic reviews. Articles were identified by name of the syndrome combined with [epidemiology OR life expectancy OR systematic review OR leukemia OR CNS tumor OR brain tumors]. We typically reviewed the most recent reports and focused on large studies with adequate methodology. Because empirical data on the role of imaging in the diagnosis and monitoring of CSS patients were extremely sparse, we relied on expert opinion to inform scenarios concerning use of CTs among CSS patients for those CSS with the highest potential of confounding within the relevant timeframe from 1990 to 2012.

**Quantitative assessment of confounding bias**

Most previous and ongoing epidemiologic studies include patients who received at least one pediatric CT scan. We assume that all study participants receive some exposure and thus evaluate potential confounding for higher exposure compared with lower exposure. We estimate bias of the RR of leukemia or brain tumors by CT-related radiation exposure due to unmeasured confounding by a particular CSS as

$$\text{Bias} = \frac{\text{RR}_{\text{OBS}}}{\text{RR}_{\text{ADJ}}} = \left[\frac{\text{RR}_{\text{CD}}p_{\text{HI}} + (1 - p_{\text{HI}})}{\text{RR}_{\text{CD}}p_{\text{LO}} + (1 - p_{\text{LO}})}\right]$$

where $\text{RR}_{\text{OBS}}$ is the RR of cancer comparing arbitrarily defined high- and low-exposure groups without adjustment for CSS, $\text{RR}_{\text{ADJ}}$ is the corresponding RR adjusted for the CSS, $\text{RR}_{\text{CD}}$ is the RR of cancer among CSS patients compared with others in the reference population, $p_{\text{HI}}$ is the CSS prevalence in the high exposed group, $p_{\text{LO}}$ is the CSS prevalence in the low exposed group. Let $g = p_{\text{HI}}/p_{\text{LO}}$ and $f = p_{\text{LO}}/p_{\text{HI}}$, where $p_{\text{HI}}$ is the CSS prevalence in the general population, so that the CSS prevalence in the high exposed group is a multiple of that in the low exposed group. Let $p_{\text{LO}} = f p_{\text{HI}}$ where $p_{\text{LO}}$ is the prevalence of a particular CSS in the low exposed subjects is 5-fold that among the low exposed ($g = 5$), i.e., 10-fold the general population prevalence ($p_{\text{HI}} = f p_{\text{LO}}$). Because $p_{\text{HI}}$ is small, this is equivalent to CSS patients being 2-fold and 10-fold more likely to be in the low and high exposed groups, respectively, compared with subjects without the CSS.

We also calculated collective bias from all CSS predisposing to leukemia (and/or brain tumors) by summing their prevalences and calculating the corresponding cancer risk as the mean of CSS-specific risks weighted by CSS prevalence. Finally, we considered life expectancy of all CSS. If life expectancy was severely limited, confounding would also be limited because the contribution of person-years from CSS patients would be very small and cancer events would not contribute to the high exposed categories due to commonly used lagging of exposure metrics by several years in this type of research.

**Results**

**Identification and characterization of CSS**

We identified 31 CSS (Table 1), 16 of which are characterized by population prevalence ($p_0$) and estimated risk of leukemia or brain tumors (Table 2). In decreasing order of prevalence, Down syndrome, fetal alcohol syndrome, Noonan syndrome, cystic fibrosis and neurofibromatosis type 1 (NF1) are the most common syndromes in the general population (range, 39-160/100,000). Down syndrome, Li–Fraumeni syndrome (LFS), NF1, tuberous sclerosis complex (TSC), and von Hippel–Lindau disease (VHL) carry the highest risks for leukemia or brain tumors. Childhood mortality from these syndromes is generally low, so they cannot be ruled out as potential confounders based on life expectancy (Table 1).
**Table 1.** Cancer susceptibility syndromes with an increased risk of leukemia or brain tumors

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Prevalence</th>
<th>Life expectancy*</th>
<th>Risk of cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study design and population</strong></td>
<td></td>
<td></td>
<td><strong>Leukemia</strong></td>
</tr>
<tr>
<td>Ataxia telangiectasia (AT)</td>
<td>1-3/100,000 (15)</td>
<td>20-49 y (44)</td>
<td>Leukemia: ALL 1 (45), T-PLL 5 (44)</td>
</tr>
<tr>
<td>Biallelic Lynch syndrome</td>
<td>&lt;1/100,000 (48)</td>
<td>1-19 y (49)</td>
<td>Life expectancy: 20-49 y (44)</td>
</tr>
<tr>
<td>Bloom syndrome (BS, BLM)</td>
<td>&lt;1/100,000 (50)</td>
<td>20-49 y (50)</td>
<td>Brain tumors: Medulloblastoma 12 (50)</td>
</tr>
<tr>
<td>Cardiofaciocutaneous syndrome</td>
<td>&lt;1/100,000 (51)</td>
<td>Shortened lifespan due to cardiac involvements (51)</td>
<td>Leukemia: ALL 1 (52, 53)</td>
</tr>
<tr>
<td>Cowden syndrome</td>
<td>&lt;1/100,000 (54)</td>
<td>Shortened lifespan due to cancer risk (55)</td>
<td>Leukemia: ALL 1 (56, 57, 58, 59)</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>40/100,000 (60)</td>
<td>50-69 y (61)</td>
<td>Clinical study with follow-up of 14,888 patients (62)</td>
</tr>
<tr>
<td>Down syndrome (Trisomy 21)</td>
<td>160/100,000 (20)</td>
<td>20-49 y (63)</td>
<td>Retrospective cohort with 2,841 patients (21)</td>
</tr>
<tr>
<td>Dubowitz syndrome</td>
<td>&lt;1/100,000 (64)</td>
<td>Shortened lifespan (65)</td>
<td>Case series with 141 patients (65)</td>
</tr>
<tr>
<td>Fanconi anemia (FA)</td>
<td>&lt;1/100,000 (66)</td>
<td>20-49 y (66)</td>
<td>Review with 1300 FA patients (67), prospective study with 754/279 patients (68, 69)</td>
</tr>
<tr>
<td>Fetal alcohol syndrome (FAS)</td>
<td>50-200/100,000 (73)</td>
<td>Normal (74)</td>
<td>Review with 15 patients with cancer (73)</td>
</tr>
<tr>
<td>Gardner's syndrome (Familial cololectal polyposis)</td>
<td>6/100,000 (76)</td>
<td>50-69 y (77)</td>
<td>Review with published reports: 56 families and 215 individuals (78)</td>
</tr>
</tbody>
</table>

(Continued on the following page)
Table 1. Cancer susceptibility syndromes with an increased risk of leukemia or brain tumors (Cont’d)

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Prevalence</th>
<th>Life expectancy</th>
<th>Study design and population</th>
<th>Leukemia</th>
<th>Brain tumors</th>
<th>Credibility/validity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gorlin syndrome</td>
<td>1/100,000 (76)</td>
<td>&gt;70 y (79)</td>
<td>Case series of 175 patients (80), case reports with 1 patient (81–85)</td>
<td>3% of the 175 patients had medulloblastoma, case reports reported 5 medulloblastoma and 1 meningioma</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Incontinentia pigmentia</td>
<td>1/100,000 (86)</td>
<td>Normal (87)</td>
<td>Case report of 4 females in three generations (88), Case report (89)</td>
<td>Pseudoplatelets, Acute myeloid leukemia</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Li–Fraumeni syndrome</td>
<td>2-5/100,000 (90)</td>
<td>Shortened lifespan due to cancer risk (91)</td>
<td>Studies with 24 families (92), 28 families (93) and 24 families (94)</td>
<td>4 Leukemia OR = 6.0</td>
<td>32 Brain tumors OR = 35 (95% CI: 19–60)</td>
<td>+</td>
</tr>
<tr>
<td>Neurofibromatosis type 1</td>
<td>39/100,000 (87)</td>
<td>70+ y (87)</td>
<td>Clinicopathologic study of 100 patients (95), longitudinal study of 176 patients (96), retrospective study 104 patients (97), population based study on &gt; 3700 deaths of people (98), multicentre collaboration of 2108 patients (99), population based study of 135 patients (100), case reports (101, 102)</td>
<td>15%–20% of children with NF1 develop OPG +</td>
<td>1 Medulloblastoma</td>
<td></td>
</tr>
<tr>
<td>Neurofibromatosis type 2</td>
<td>2/100,000 (87)</td>
<td>50–69 y (79)</td>
<td>Cross sectional study of 120 patients (103, 104), clinical spectrum 48 patients (105), population based study of 41 patients (107), clinical study of 82 patients (108), retrospective study of 285 patients (109, 110)</td>
<td>Bilateral vestibular schwannomas 90%–95% +</td>
<td>1 Medulloblastoma</td>
<td></td>
</tr>
<tr>
<td>Nijmegen breakage syndrome</td>
<td>1/100,000 (111)</td>
<td>Shortened lifespan due to cancer risk and infections (112)</td>
<td>Registry of 55 patients (112), case series of 8 patients (113), case reports (114–116)</td>
<td>3 T-cell precursor ALL</td>
<td>2 Medulloblastoma</td>
<td></td>
</tr>
<tr>
<td>Noonan syndrome</td>
<td>40–100/100,000 (117)</td>
<td>Normal (118)</td>
<td>Retrospective cohort of 235 patients and 62 family members (119), Retrospective cohort of 735 patients (120)</td>
<td>10% Myelodysplastic disorder, 3 precursor B-ALL, 4 acute myelogenous leukemia, 3 ALL, 2 CMML</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Rubinstein–Taybi syndrome</td>
<td>&lt;1–1/100,000 (122)</td>
<td>Normal (122)</td>
<td>Case reports (123, 124)</td>
<td>1 ALL</td>
<td>1 Medulloblastoma</td>
<td></td>
</tr>
<tr>
<td>Severe congenital neutropenia</td>
<td>&lt;1/100,000 (87)</td>
<td>NM</td>
<td>Registry with 82 patients (125)</td>
<td>MDS and AML</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

(Continued on the following page)
<table>
<thead>
<tr>
<th>Synonym/Abbreviation</th>
<th>Prevalence</th>
<th>Life expectancy</th>
<th>Risk of cancer</th>
<th>Study design and population</th>
<th>Credibility/validity</th>
</tr>
</thead>
<tbody>
<tr>
<td>101x99</td>
<td>82x99</td>
<td><strong>Table 1.</strong> Cancer susceptibility syndromes with an increased risk of leukemia or brain tumors (Cont’d)</td>
<td>82x99</td>
<td>82x99</td>
<td>82x99</td>
</tr>
<tr>
<td>Silver-Russell syndrome</td>
<td>1/100,000 (126)</td>
<td>Normal (127)</td>
<td>Leukemia</td>
<td>Case reports (126, 129)</td>
<td>Low (–)</td>
</tr>
<tr>
<td>Sotos syndrome</td>
<td>1/14,000 (87)</td>
<td>Normal</td>
<td>Leukemia</td>
<td>Case series with 224 patients (130) and 27 patients (131)</td>
<td>Low (–)</td>
</tr>
<tr>
<td>Sturge-Weber syndrome</td>
<td>25/100,000 (132)</td>
<td>Normal (133)</td>
<td>Brain tumors</td>
<td>Retrospective study with 55 patients (134, 135)</td>
<td>Low (–)</td>
</tr>
<tr>
<td>Trisomy 8 mosaicism</td>
<td>1/100,000 (139)</td>
<td>NM</td>
<td></td>
<td>15%-20% develop leukemia, syndrome often detected at leukemia diagnosis</td>
<td>Low (–)</td>
</tr>
<tr>
<td>Trisomy 13</td>
<td>Patau syndrome</td>
<td>4/100,000 (137)</td>
<td>Leukemia</td>
<td>Case report (139)</td>
<td>Low (–)</td>
</tr>
<tr>
<td>Tuberous sclerosis complex</td>
<td>TSC</td>
<td>8/100,000 (26, 140)</td>
<td>Shortened (141)</td>
<td>Review (87, 141), retrospective cross-sectional study with 285 patients (127)</td>
<td>Average (+)</td>
</tr>
<tr>
<td>Turcot syndrome</td>
<td>Glioma polyposis</td>
<td>10/100,000 (87)</td>
<td>Unknown</td>
<td>Registry with 14 families (142)</td>
<td>Average (+)</td>
</tr>
<tr>
<td>Turner syndrome</td>
<td>50/100,000 females (143)</td>
<td>NM</td>
<td>Leukemia</td>
<td>Cohort study with 3,425 patients (145), case report (144)</td>
<td>Average (+)</td>
</tr>
<tr>
<td>von Hippel-Lindau disease</td>
<td>VHL</td>
<td>2-3/100,000 (30)</td>
<td>50-69 y (79)</td>
<td>Follow-up study of 225 patients with VHL-related CNS hemangioblastoma (131)</td>
<td>Average (+)</td>
</tr>
<tr>
<td>Werner syndrome</td>
<td>&lt;1/100,000 (145)</td>
<td>Short but depends on type</td>
<td>Leukemia and preleukemia</td>
<td>Literature review with 189 patients from case reports (146)</td>
<td>Average (+)</td>
</tr>
<tr>
<td>Xeroderma pigmentosum</td>
<td>XP</td>
<td>&lt;1/100,000 (146)</td>
<td>Shortened lifespan due to neurologic abnormalities (147) and/or skin cancer (148)</td>
<td>Case report of 4 patients (149), case reports of 132 patients (150), systematic study of 830 cases (148)</td>
<td>Average (+)</td>
</tr>
</tbody>
</table>

**Abbreviations:** AL, acute leukemia; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; CML, chronic myelogenous leukemia; MDS, myelodysplastic syndrome; NM, not mentioned; OPG, optic pathway gliomas; OR, odds ratio; RR, relative risk; T-CLL, T-cell chronic lymphocytic leukemia; T-PLL, T-cell prolymphocytic leukemia; y, years; CI, confidence interval; SIR, standardized incidence ratio; NHL, non-Hodgkin lymphoma; CNS, central nervous system.

*Reported life expectancies vary greatly with length of follow-up, study inclusion criteria, follow-up methods for medical outcomes and vital status, as well as the calendar period covered by the study. Therefore, reported values in single studies should be interpreted with caution. Where feasible, we classified all values as <1, 1-19, 20-49, 50-69, >70; normal; if little information on shortened lifespan was available, we reported “shortened.”

*Nontransplanted CF patients or before transplantation for transplanted patients.

*Slightly increased number of SEGAS for recent years due to screening.

*Preleukemia: Myelofibrosis, myelodysplasia, refractory anemia with excess blasts.

**Credibility/validity**
- **High (+++)**: large cohort studies (>1,000 population) with adequate follow-up methods and CCS case ascertainment.
- **Average (+):** large cohort studies with either incomplete follow-up or incomplete case ascertainment methods OR small cohort studies (<1,000 population).
- **Low (–):** case series, case reports; physician surveys; reviews of case series/case reports.
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Table 2. Selected CSS by general population prevalence and relative risk of leukemia and brain tumors

<table>
<thead>
<tr>
<th>RR (CSS-Cancer)</th>
<th>General population prevalence of CSS (per 100,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;1</td>
</tr>
<tr>
<td>Low</td>
<td>AT&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Trisomy 8&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Gorlin&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Medium</td>
<td>Blallic Lynch&lt;sup&gt;1,1&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>—</td>
</tr>
<tr>
<td>High</td>
<td>—</td>
</tr>
<tr>
<td>Very high</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>VHL&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>TSC&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

NOTE: Syndromes lacking a quantitative estimate of prevalence or RR are not included in the table, see discussion.

Abbreviations: AT, ataxia telangiectasia; CF, cystic fibrosis; NF, neurofibromatosis; VHL, von Hippel-Lindau disease; TSC, tuberous sclerosis complex; CSS, cancer susceptibility syndrome; RR, relative risk.

<sup>1</sup>Low, RR = 1-2; medium, RR = 2-15; high, RR = 15-50; very high, RR > 50 with a maximum RR of 20,000.

<sup>2</sup>Risk of leukemia.

<sup>3</sup>Risk of brain tumors.

Example: Based on the literature, the prevalence of Down syndrome in the general population is about 160 per 100,000 and the RR for leukemia among patients with Down syndrome is considered very low. Based on a conservative quantification of this information, if 20% of all children with Down syndrome undergo one additional chest CT during their childhood of this information, if 20% of all children with Down syndrome could maximally bias leukemia RRs about 2.0-fold in the general population. Therefore, the potential bias of the SIR (p<sub>H</sub> = p<sub>O</sub> and p<sub>HI</sub> = 4p<sub>O</sub>) and no appreciable bias of the RR because the prevalence of Down syndrome is not increasing further with exposure level because several CT scans due to Down syndrome are very unlikely (Fig. 1A).

For Noonan syndrome and leukemia, the unadjusted RR over-estimated the adjusted RR by maximally 30% (Fig. 1B). Other CSS were either less prevalent or their association with leukemia was weaker, or both, resulting in bias of 10% or less.

Confounding of leukemia risk due to specific CSS

Down syndrome is a genetic disorder caused by the presence of all or part of a third copy of chromosome 21 and has a prevalence of about 160/100,000 (20). It is typically associated with physical growth delays, characteristic facial features, and mild-to-moderate intellectual disability. Leukemia risk among patients with Down syndrome is about 50-fold higher than that in the general population (21). Ignoring confounding from Down syndrome could maximally bias leukemia RRs about 2.0-fold (p<sub>HI</sub>/p<sub>O</sub> = 4; p<sub>O</sub>/p<sub>HI</sub> = 0.25; Fig. 1A).

Results for Down syndrome indicate that the potential for confounding depends on the excess frequency of CT scans among Down syndrome patients. Based on a recent review (22) imaging modalities other than CT were adequate for Down syndrome patients in most clinical situations (Supplementary Table S1). In the absence of quantitative data from the literature, we interviewed a Down syndrome expert (M.E. Weijerman, pediatrician and head of the Down Center Netherlands), a pediatrician (Dr. Jost Frenkel, University Medical Center Utrecht), and an experienced primary care physician (Dr. Bart Meijman, Amster-
dam). They indicated that about 30% of children with Down syndrome suffer lung problems, such as hyperplasia or cysts, and a fraction of those might have gotten one diagnostic chest CT since 1990. For cardiac problems, which occur in about 44% of Down syndrome patients (23), ultrasound is the imaging modality of choice, except for a small fraction of children who need an interventional procedure. Abdominal problems (e.g., 8% have duodenal atresia or Hirschsprung's disease; ref. 24) are usually referred to the absence of quantitative data from the literature, we inter-
viewed a Down syndrome expert (Dr. Joost Frenkel, University Medical Center Utrecht), and an

Confounding of brain tumor risk due to specific CSS

TSC is an autosomal-dominant neurocutaneous disorder with a prevalence of about 8/100,000 (26). It is characterized by tumors involving many organ systems, including the brain, heart, kidneys, and skin, as well as other organ dysfunction and mental retardation. Subependymal giant cell tumors (SEGA), which develop in 9% to 14% of patients and almost always occur before 20 to 25 years of age (27), are a major feature specific for TSC (15). Bias can be up to 4-fold (Fig. 2A). In the past, screening for SEGAs was recommended among children with TSC using CT or magnetic resonance imaging (MRI) of the head every 1 to 3 years (28). MRI appears to be the preferred modality in more recent years (29) and has been used almost exclusively in the Netherlands since at least 2000 (personal communication: Drs. Bernard Zonne-

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VHL disease is an autosomal-dominant disorder that causes hemangioblastomas of the retina and the central nervous system, renal cell carcinomas, pancreatic cysts and tumors, among other manifestations. At a prevalence of 2–3/100,000 (30), 60% to 90% of patients with VHL disease develop hemangioblastomas of the cerebellum or the brain stem (31). VHL disease biased brain tumor risk by up to 6-fold (Fig. 2B).

Figure 1.

A, estimated potential bias of the relative risk of leukemia among high versus low exposed subjects by failure to adjust for Down syndrome. Bias = \( \frac{R_{\text{OBS}}}{R_{\text{ADJ}}} = \frac{R_{\text{CD}} p_{\text{HI}} + (1 - p_{\text{HI}})}{R_{\text{CD}} p_{\text{LO}} + (1 - p_{\text{LO}})} \), where \( R_{\text{OBS}} \) is the RR of leukemia comparing arbitrarily defined high and low (reference) exposure groups without adjustment for Down syndrome, \( R_{\text{ADJ}} \) is the corresponding RR adjusted for Down syndrome, \( R_{\text{CD}} \) is the RR of leukemia due to Down syndrome in the reference population, and \( p_{\text{HI}}, p_{\text{LO}}, \) and \( p_{0} \) are the prevalences of Down syndrome in the high exposed, low exposed, and general population, respectively (19). For example, under the assumption that the prevalence of Down syndrome among low exposed subjects is 5 times the general population prevalence (\( p_{\text{LO}} / p_{0} = 5 \)), and among the high exposed subjects is twice that in the low exposed group (\( p_{\text{HI}} = 2 p_{\text{LO}} = 2 / 5 p_{0} \), i.e., 10 times the general population prevalence), the RR of leukemia not adjusted for Down syndrome overestimates the RR adjusted for Down syndrome by 13%. B, estimated potential bias of the relative risk of leukemia among high versus low exposed subjects by failure to adjust for Noonan syndrome.
Academic Medical Center Amsterdam; Dr. Theo van Os, Academic Medical Center Amsterdam; Prof. Thera Links, University Medical Center Groningen; Dr. Frederik Hes, University Medical Center Leiden). It is therefore unlikely that a relevant number of VHL disease patients are included in an epidemiologic study on CT scanning and most of those would not have received several head CTs during childhood due to VHL disease.

NF1 is an autosomal-dominant disorder characterized by the development of multiple benign tumors of nerves and skin (neurofibromas) and areas of hypo- or hyperpigmentation of the skin. The most severe confounding bias caused by NF1 was about 25% (Supplementary Fig. S1).

Other CSS were either less prevalent or their association with brain tumors was weaker, or both. As a consequence, bias was 10% or less.

Confounding bias due to combined CSS

Combining all CSS predisposing to leukemia resulted in a potential confounder with a prevalence of 282/100,000 and a RR for leukemia of 14.8. This combination of prevalence and RR resulted in no additional confounding besides that from Down syndrome (data not shown). Any CSS predisposing to brain tumors were prevalent at 113/100,000 and carried a 713-fold elevated brain tumor risk, which resulted in confounding of the same magnitude as VHL disease alone (data not shown).

Discussion

Our evaluation suggests that leukemia-predisposing CSS do not substantially confound the association between radiation exposure from pediatric CT scans and leukemia risk because they are too rare and/or too weakly associated with leukemia or, in the case of Down syndrome, CT uptake is only moderately elevated among patients, if at all. Brain tumor risks might be substantially confounded by TSC, while other brain tumor-predisposing CSS are unlikely to cause meaningful confounding. Because these conclusions are based on assumptions about CT use among CSS patients, robust empirical data are urgently needed.
Confounding by TSC can be controlled through adjustment for TSC or exclusion of subjects with TSC. The most promising source of such data for linkage with epidemiologic cohorts might be lists of TSC patients from hospitals treating TSC patients, which are usually limited to a few highly specialized medical centers. In contrast, hospital discharge registries or registries of congenital disorders might not be complete for TSC since hospitalization is often not required and most diagnoses do not occur perinatally (35). If individuals with TSC cannot be identified, it might be possible to identify children who developed SEGAs based on cancer incidence data from cancer registries. We are currently investigating practical aspects of linkage with TSC patient listings. Also, several cancer registries in Europe register non-malignant brain tumors, such as SEGAs, but little information regarding coverage/completeness by country or region and calendar period is available. The Dutch cancer registry records SEGAs since 1999, with most of them (93%) pathologically confirmed (personal communication: Dr. Otto Visser, Netherlands Comprehensive Cancer Organization). Exclusion of subjects who developed SEGAs will remove confounding; however, limiting follow-up to post-1999 will substantially compromise the statistical power of our study.

A relevant question is whether bias due to CSS can create a dose–response relationship in the absence of a causal association between radiation and cancer. We did not directly evaluate bias of the linear excess relative risk per Gray (ERR/Gy), the commonly used measure of the strength of a dose–response relationship between radiation exposure and cancer, because we are not aware of a published formula for the relative bias due to confounding. However, our results show that bias due to CSS can create increasing RR estimates for categories of increasing radiation exposure in the absence of a causal association, but only in very specific circumstances. If CT scanning among patients with a particular CSS is such that the prevalence of CSS patients increases across categories of increasing dose, bias of RRs comparing subjects exposed at different levels with the same reference level will then also increase with exposure level, leading to a positive ERR/Gy. This does not require the cancer risk due to CSS to increase with radiation exposure.

Two studies with some information on indication for CT scanning have recently been published. The first study included 67,274 children who received at least one CT scan before age 10 years between 2000 and 2010 in one of 21 French hospitals and who were followed for, on average, 4.4 years, with cancer diagnosed before age 15 years as the outcome of interest (35). ERRs for leukemia or brain tumors were not or only mildly attenuated after adjustment for Down syndrome or neurofibromatosis, respectively, based on hospital discharge information. More substantial attenuation of the brain tumor ERR was observed for the group of so-called other phakomatoses, which includes TSC. A note of caution in interpreting these findings is warranted, though. First, because of the small sample size and short follow-up, all confidence intervals were wide and included unity, and attenuation for any of the evaluated (groups of) CSS was less than about 10% of the confidence interval width. Second, ERRs were not attenuated when patients with relevant CSS were excluded from analysis (36–38). Third, very high prevalences were observed for several CSS, most likely owing to overrepresentation of referral centers among participating hospitals, which limits the generalizability of these results for nation-wide samples. The second study followed 44,584 children who received at least one CT scan before age 15 years in the period 1980 to 2010 in one of 20 German hospitals for, on average, 3.6 years and ascertained cancers diagnosed before age 15 years (4). Standardized incidence ratios were nonsignificantly elevated for leukemia and brain tumors. Radiology reports, which were available for most of the 12 leukemias and 7 brain tumors, respectively, indicated potential confounding by indication for one brain tumor case. Exclusion of that case slightly attenuated the brain tumor SIR.

Our study has a number of limitations. Although patients with CSS suffer from a diverse spectrum of health complaints (15) for which CT scans are an appropriate diagnostic imaging modality (16), actual quantitative health care utilization data are scarce and therefore we had to rely on subjective scenarios. For illustration, with 5% to 7% of all children in the Netherlands receiving at least one CT before their 18th birthday, a 10-fold higher proportion among patients with a particular CSS implies that about 50% to 70% of CSS patients receive at least one CT. Second, for some of the CSS evaluated here, there is evidence of increased radiosensitivity (e.g., AT, Xeroderma pigmentosum, and LFS; ref. 15). For those CSS, we might have underestimated bias because the CSS-related cancer risk increases with the level of radiation exposure. However, these CSS are very rare. Also, affected families and medical professionals are well aware of the radiosensitivity, which likely implies a prevalence of CT use lower than that of the general population. Therefore, these syndromes are very unlikely to be potent confounders. Third, expert opinions on the use of CT scans among patients with CSS reflect clinical practice in the Netherlands. We believe this does not limit the generalizability because diagnostic and therapeutic situations, as evidenced by the fact that most fields in the lower right part of Table 2 are populated. Besides CSS, other predisposing conditions can confound CT-related cancer risk. For instance, leukemogenic drugs or total body irradiation prior to stem cell transplantation for non-malignant diseases, such as Fanconi anemia, aplastic anemia, immune system deficiencies, or congenital malformations in the nervous and circulatory system (41). Confounding by these conditions, although not the objective of this report, can be easily assessed by assigning the condition to one of the cells in Table 2. For example, common variable immune deficiency has a prevalence of approximately 1 in 30,000 live births (42) and an increased risk of leukemia (43), although the magnitude is not known. Based on our results, even if leukemia risk was substantially increased, confounding bias would be negligible given the low prevalence.

In conclusion, our assessment of confounding of CT-related cancer risks indicates that associations with leukemia reported in previous studies (1–5) are unlikely to be substantially confounded by unmeasured CSS, whereas brain tumor risks might have been overestimated due to confounding by TSC. Robust empirical data on the use of CT among CSS patients are needed in order to
inform the interpretation of previous and future studies of the subject.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The funders had no involvement in the study design, data collection, analysis and interpretation, the writing of the report, or the decision to submit the paper for publication.

Authors’ Contributions

Conception and design: J.M. Meulepas, C.M. Ronckers, J. Merks, M. Hauptmann
Development of methodology: J.M. Meulepas, C.M. Ronckers, J.H. Lubin, M. Hauptmann
Acquisition of data (provisioned animals, acquired and managed patients, provided facilities, etc.): J.M. Meulepas, C.M. Ronckers, M. Hauptmann
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.M. Meulepas, C.M. Ronckers, J. Merks, J.H. Lubin, M. Hauptmann
Writing, review, and/or revision of the manuscript: J.M. Meulepas, C.M. Ronckers, J. Merks, M.E. Weijerman, J.H. Lubin, M. Hauptmann
Study supervision: M. Hauptmann

References

19. Weijerman ME, van Furth AM, Vonk Noordegraaf A, van Wouwe JP, Broers AM, et al. Radiation exposure from computerized tomography and to optimize doses. Netteke Schouten Center Groningen) and Peter Vandertop (VU University Medical Center Amsterdam and Academic Medical Center Amsterdam) for providing their expertise.

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Retraction: Confounding of the Association between Radiation Exposure from CT Scans and Risk of Leukemia and Brain Tumors by Cancer Susceptibility Syndromes

The article titled, "Confounding of the association between radiation exposure from CT scans and risk of leukemia and brain tumors by cancer susceptibility syndromes," which was published in the January 2016 issue of Cancer Epidemiology, Biomarkers & Prevention (1), is being retracted at the request of the authors.

The authors recently reported analytical errors that drastically change the published article conclusions. The error is explained in detail below.

The authors calculated, separately for a series of cancer susceptibility syndromes (CSS), the bias of radiation risks for leukemia and brain tumors from computed tomography (CT) scanning in children due to confounding by CSS, based on Axelsson’s formula. Values of the factors in the formula were chosen based on literature when available and based on assumptions otherwise. The error occurred in the calculation of bias for syndromes tuberous sclerosis complex (TSC) and von Hippel–Lindau (VHL) and brain tumor risk. More specifically, the error occurred in the calculation of the relative risk of brain tumors among patients with TSC or VHL disease compared with the general population (RR_CD in the formula). Because of the error, the estimates for these two relative risks were too high, 2,500 and 28,000, respectively, when they should have been 125 and 142. Because of the large (and incorrect) relative risks used, bias of TSC and VHL disease was substantial for several scenarios. As a result, the authors concluded that TSC is a potentially important confounder for brain tumor risks in CT studies. The authors originally concluded that, "associations with leukemia reported in previous studies are unlikely to be substantially confounded by unmeasured CSS, whereas brain tumor risks might have been overestimated due to confounding by TSC" (1). In light of the analytical error, the reassessment indicates that associations with leukemia and brain tumors reported in previous studies are unlikely to be substantially confounded by unmeasured CSS.

The authors regret the error and seek, in good faith, to update the scientific record by issuing this retraction.

Reference

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### Confounding of the Association between Radiation Exposure from CT Scans and Risk of Leukemia and Brain Tumors by Cancer Susceptibility Syndromes

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