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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Abstract

Background: Recent studies linking radiation exposure from pediatric computed tomography (CT) to increased risks of leukemia and brain tumors lacked data to control for cancer susceptibility syndromes (CSS). These syndromes might be confounders because they are associated with an increased cancer risk and may increase the likelihood of CT scans performed in children.

Methods: We identify CSS predisposing to leukemia and brain tumors through a systematic literature search and summarize prevalence and risk estimates. Because there is virtually no empirical evidence in published literature on patterns of CT use for most types of CSS, we estimate confounding bias of relative risks (RR) for categories of radiation exposure based on expert opinion about the current and previous patterns of CT scans among CSS patients.

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.

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 under way (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...
confounding by CSS. 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 Acknowledgements 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 scans). 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

Bias = \frac{RR_{OBS}/RR_{ADJ}}{= [RR_{CD}/p_{HI} + (1 - p_{HI})]/[RR_{CD}/p_{LO} + (1 - p_{LO})]} (1)

where \(RR_{OBS}\) is the RR of cancer comparing arbitrarily defined high- and low-exposure groups without adjustment for CSS, \(RR_{CD}\) is the corresponding RR adjusted for the CSS, \(RR_{ADJ}\) is the RR of cancer among CSS patients compared with others in the reference population, \(p_{HI}\) is the CSS prevalence in the high exposed group, \(p_{LO}\) is the CSS prevalence in the low exposed group. Let \(g = p_{HI}/p_{LO}\) and \(f = p_{CD}/p_{ADJ}\) where \(p_{0}\) is the CSS prevalence in the general population, so that the CSS prevalence in the high exposed group is a multiple of the prevalence in the low exposed (reference) group \((p_{HI} = g \cdot p_{LO})\), while the prevalence in the low exposed group is a multiple of that in the general population \((p_{LO} = f \cdot p_{0})\) (19). If a CSS does not increase cancer risk \((RR_{CD} = 1)\), or if CT use is unrelated to CSS occurrence \((p_{CD} = p_{HI})\), there is no bias (bias = 1). An evaluation of potential bias for comparison of children with any CT scans compared with the general population [standardized incidence ratio (SIR)] can be carried out by setting \(p_{LO} = p_{0}\) i.e., \(f = 1\).

We use values of 1, …5 for \(f\) and 1, …8 for \(g\). For example, one scenario assumes that the prevalence of a particular CSS among low exposed subjects is twice the general population prevalence \((f = 2)\), while the CSS prevalence among high exposed subjects is 5-fold that among the low exposed \((g = 5)\), i.e., 10-fold the general population prevalence \((p_{HI} = 2 \cdot 5 \cdot p_{LO})\). Because \(p_{0}\) 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>Synonym</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>Ataxia telangiectasia</td>
<td>AT 1-3/100,000 (15)</td>
<td>20-49 y (44)</td>
<td>Case series of 78 AT patients (45), case report of 1 patient (46), 1 patient (47)</td>
<td>1× T-CLL/1× T-PLL/5× ALL</td>
<td>1 Astrocytoma 1 Medulloblastoma</td>
<td>–</td>
</tr>
<tr>
<td>Biallelic Lynch syndrome</td>
<td>Mismatch repair-deficiency-syndrome Lynch syndrome 3</td>
<td>&lt;1/100,000 (48)</td>
<td>Case series of 92 patients (48)</td>
<td>6 ALL 3 AML 1 CML 1 AL</td>
<td>32 Glioblastoma 5 Neuroectodermal tumor 4 Medulloblastoma 3 Unspecified</td>
<td>–</td>
</tr>
<tr>
<td>Bloom syndrome</td>
<td>BS, BLM</td>
<td>&lt;1/100,000 (50)</td>
<td>BLM Registry with 129 BS patients and 205 neoplasms (50)</td>
<td>12 ALL/25 AML neoplasms</td>
<td>32 Glioblastoma 5 Neuroectodermal tumor 4 Medulloblastoma 3 Unspecified</td>
<td>–</td>
</tr>
<tr>
<td>Cardiofaciocutaneous syndrome</td>
<td>&lt;1/100,000 (51)</td>
<td>Shortened lifespan due to cardiac involvements (51)</td>
<td>Case reports (52, 53)</td>
<td>2 ALL</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Cowden syndrome</td>
<td>&lt;1/100,000 (54)</td>
<td>Shortened lifespan due to cancer risk (55)</td>
<td>Case reports of 2 patients (56), 1 patient (57), 3 patients (59)</td>
<td>6 Cerebellar dysplastic gangliocytoma (Lhermitte-Duclos disease) 1 Meningioma</td>
<td>–</td>
<td>–</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>
<td>SIR = 2.0±</td>
<td>–</td>
<td>++</td>
</tr>
<tr>
<td>Down syndrome</td>
<td>Trisomy 21</td>
<td>160/100,000 (20)</td>
<td>Retrospective cohort with 2,841 patients (21)</td>
<td>All leukemia 0-4 y SIR 56.4 15-19 y SIR 9.88 All ages SIR 17.6</td>
<td>–</td>
<td>++</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>
<td>1 Leukopenia 1 Agranulocytosis 2 Pancytopenia 1 ALL</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Fanconi anemia</td>
<td>FA</td>
<td>&lt;1/100,000 (66)</td>
<td>Review with 1300 FA patients (67), prospective study with 754/279 patients (68, 69) cross sectional study 145 patients (70) and case reports (71, 72)</td>
<td>Leukemia 6%–8.9%; SIR &gt;40 MDS 6.8%–10%</td>
<td>2 Medulloblastoma 1 Glioma (second primary after NHL)</td>
<td>+</td>
</tr>
<tr>
<td>Fetal alcohol syndrome</td>
<td>FAS</td>
<td>50-200/100,000 (73)</td>
<td>Normal (74)</td>
<td>Review with 13 patients with cancer (73), 1 patient (75)</td>
<td>1 Leukemia</td>
<td>1 Medulloblastoma</td>
</tr>
<tr>
<td>Gardner's syndrome</td>
<td>Familial colorectal polyposis</td>
<td>6/100,000 (76)</td>
<td>Normal (77)</td>
<td>Pooled registry with published reports: 56 families and 213 individuals (78)</td>
<td>Brain tumors: OR = 3.7 Medulloblastoma: OR = 13.1</td>
<td>–</td>
</tr>
</tbody>
</table>

(Continued on the following page)
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Synonym</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>Nevoid basal-cell carcinoma syndrome</td>
<td>&lt;1/100,000 (76)</td>
<td>&gt;70 y (79)</td>
<td>Case series of 173 patients</td>
<td>3% of the 173 patients had medulloblastoma,</td>
<td>1 ALL</td>
<td>–</td>
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<td></td>
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<td>(80), case reports with 1</td>
<td>case reports reported 5 medulloblastoma and 1</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>patient (81–85)</td>
<td>meningioma</td>
<td></td>
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</tr>
<tr>
<td>Incontinentia pigmentia</td>
<td>Bloch-Sulzenberger syndrome</td>
<td>&lt;1/100,000 (86)</td>
<td>Normal (87)</td>
<td>Case report of 4 females in</td>
<td>Pseudoplatelets, Acute granulocytic leukemia</td>
<td></td>
<td>–</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>three generations (88),</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Case report (89)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Studies with 24 families (92,</td>
<td>4 Leukemia OR = 6.0</td>
<td>32 Brain tumors OR = 35 (95% CI: 19–60)</td>
<td>+</td>
</tr>
<tr>
<td>Li–Fraumeni syndrome</td>
<td></td>
<td>2–5/100,000 (90)</td>
<td>Shortened lifespan</td>
<td>24 families (93) and 24</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>due to cancer risk (91)</td>
<td>families (94)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurofibromatosis type 1</td>
<td>NF1/von Recklinghausen disease</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 NFI develop OPG</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Neurofibromatosis type 2</td>
<td>NF2/multiple inherited schwannoma, meningiomas and ependymomas syndrome</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), 63 patients (106), population based study of 406 patients (107), clinical study of 83 patients (108), retrospective study of 283 patients (109, 110)</td>
<td>Bilateral vestibular schwannomas 90%–95%</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Nijmegen breakage syndrome</td>
<td>NBS</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>10% Myeloproliferative disorder, 3 precursor B-ALL, Juvenile myelomonocytic leukemia, 3 ALL, 2 CMML</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noonan syndrome</td>
<td></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% Myeloproliferative disorder, 3 precursor B-ALL, Juvenile myelomonocytic leukemia, 3 ALL, 2</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Rubinstein–Taybi syndrome</td>
<td>Broad thumb-hallux</td>
<td>&lt;1–1/100,000 (121)</td>
<td>Normal (122)</td>
<td>Case reports (123, 124)</td>
<td>1 ALL MDS and AML</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe congenital neutropenia</td>
<td>SCN</td>
<td>&lt;1–1/100,000 (87)</td>
<td>NM</td>
<td>Registry with 82 patients (125)</td>
<td>1 Meningioma</td>
<td></td>
<td>–</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>Synonym</th>
<th>Prevalence</th>
<th>Life expectancy&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Study design and population</th>
<th>Leukemia</th>
<th>Brain tumors</th>
<th>Credibility/validity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silver-Russel syndrome</td>
<td>1/100,000 (126)</td>
<td>Normal (127)</td>
<td>Case reports (128, 129)</td>
<td>1</td>
<td>Cranioopharyngioma</td>
<td>–</td>
</tr>
<tr>
<td>Sotos syndrome</td>
<td>1/4,000 (87)</td>
<td>Normal</td>
<td>Case series with 224 patients (130) and 27 patients (133)</td>
<td>3 ALL</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Sturge-Weber syndrome</td>
<td>2-5/100,000 (132)</td>
<td>Normal (133)</td>
<td>Retrospective study with 55 patients (134, 135)</td>
<td>3 Ipsilateral leptomeningeal angioma</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Trisomy 8 mosaicism</td>
<td>1/100,000 (136)</td>
<td>NM</td>
<td>15%-20% develop leukemia, syndrome often detected at leukemia diagnosis</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Trisomy 13</td>
<td>4/100,000 (137)</td>
<td>&lt;1 y (158)</td>
<td>Case report (139)</td>
<td>1 Pilocytic astrocytoma</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Tuberous sclerosis complex</td>
<td>8/100,000 (26, 140)</td>
<td>Shortened (141)</td>
<td>Review (87, 141), retrospective cross-sectional study with 285 patients (27)</td>
<td>SEGA: prevalence estimate: 0.11; 95% CI, 0.09-0.14&lt;sup&gt;b&lt;/sup&gt;</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Turcot syndrome</td>
<td>10/100,000 (87)</td>
<td>Unknown</td>
<td>Registry with 14 families (142)</td>
<td>Increased</td>
<td>CNS: RR all ages = 7: RR 0-29 y = 23</td>
<td>–</td>
</tr>
<tr>
<td>Turner syndrome</td>
<td>50/100,000 females (143)</td>
<td>NM</td>
<td>Cohort study with 3,425 patients (143), case report (144)</td>
<td>1 Leukemia</td>
<td>7 Meningioma; RR = 12.0 (4.8-24.8)</td>
<td>+</td>
</tr>
<tr>
<td>von Hippel-Lindau disease</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 (31)</td>
<td>CNS (hemangioblastoma)</td>
<td>5 Other brain tumors; RR = 2.5 (0.8-5.8)</td>
<td>+</td>
</tr>
<tr>
<td>Werner syndrome</td>
<td>&lt;1/100,000 (145)</td>
<td>Short but depends on type</td>
<td>Literature review with 189 patients from case reports (145)</td>
<td>Leukemia and preleukemia&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Meningioma</td>
<td>–</td>
</tr>
<tr>
<td>Xeroderma pigmentosum</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>1 Glioblastoma</td>
<td>3 Brain sarcoma</td>
<td>1 Medulloblastoma</td>
</tr>
</tbody>
</table>

<sup>a</sup>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 life-span was available, we reported “shortened.”

<sup>b</sup>Non-transplanted CF patients or before transplantation for transplanted patients.

<sup>c</sup>Slightly increased number of SEGAS for recent years due to screening.

<sup>d</sup>Preleukemia: Myelofibrosis, myelodysplasia, refractory anemia with excess blasts.

**Abbreviations:** AL, acute leukemia; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; CNS, central nervous system; 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; ONS, 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 life-span was available, we reported “shortened.”*
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 the general population (21). Ignoring confounding from Down syndrome is about 50-fold higher than that in mild-to-moderate intellectual disability. Leukemia risk among patients with Down syndrome is about 50-fold higher than that in the general population. Therefore, the potential bias of the SIR (pLO = pL and pHI = 4*pLO) 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).

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. Weijsman, pediatrician and head of the Down Center Netherlands), a pediatrician (Dr. Joost Frenkel, University Medical Center Utrecht), and an experienced primary care physician (Dr. Bart Meijman, Amsterdam). 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 evaluated by X-ray. Experts stated that trauma does not seem to occur more often among children with Down syndrome compared with other children and that the fraction of Down syndrome children with several CT scans due to the 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 (say, under 10 years of age) compared with other children, this would represent 20 CT scans per 1,000 Down syndrome patients per year attributable to Down syndrome in addition to the approximately 7 CT scans per 1,000 children per year in the general Dutch population (25). There would then be about (20 + 7)/7 ≈ 4-times as many CT scans among Down syndrome patients than among other children, leading to less than 20% bias of the SIR (pL = pL and pHI = 4*pL) 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).

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 compared with others is about 50.

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 Zonnenberg and Floor Janssen, University Medical Center Utrecht; Dr. Marie Claire de Wit, Erasmus Medical Center Rotterdam). A scenario consistent with these expert opinions assumes that 10% of the TSC patients in a CT study cohort were born before 1990 and received, on average, 3 head CTs during an average of 25 years follow-up per patient, with corresponding numbers of 30%, 1 head CT, and 15 years follow-up, as well as 60%, no head CT, and 10 years of follow-up for those born in 1990–2000 and after 2000, respectively. In this case, 46 head CTs per 1,000 TSC patients per year would be indicated by TSC alone, which results in (46 + 7)/7 = 7.6 times as many head CTs among TSC patients compared with others or, equivalently, a 7.6-fold higher prevalence of TSC among children with at least one CT scan compared with children in the general population. Therefore, the potential bias of the SIR is about 2-fold (pL = pL and pHI = 7.6*pL) and bias of the RR could be more severe because a nonnegligible fraction of TSC patients might have received a considerable number of head CTs (Fig. 2A).

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>
<th>&lt;1</th>
<th>1–5</th>
<th>5–25</th>
<th>25–50</th>
<th>50–160</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>AT* Trisomy 8* Gorlin*</td>
<td>Sotos*</td>
<td>CF*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td>Biallelic Lynch* NF type 2*</td>
<td>Turcot* Gardiner’s* Turner* Noonan*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>VHL*</td>
<td>Li-Fraumeni* NF type 1* Down*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

*Low, RR = 1–2; medium, RR = 2–15; high, RR = 15–50; very high, RR > 50 with a maximum RR of 28,000.

*Risk of leukemia.

*Risk of brain tumors.
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).

Because VHL-associated hemangioblastomas of the cerebellum and the brain stem occur rarely during childhood, screening is recommended to commence in the mid-teens and MRI is uniformly the modality of choice, although CT was mentioned in earlier versions of some guidelines (32–34). Accordingly, imaging of the head for screening purposes among young children with VHL disease was not commonly done in the Netherlands. When performed, CT might have been used before 1990–1995, while MRI is the modality of choice since then.

Confounding Radiation Exposure from CT Scans and Cancer Risk

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 = RROBS/RRADJ = [RRCD×pH/(1−pH)/RRCD×pL/(1−pL)], where RRCD is the RR of leukemia due to Down syndrome in the reference population, and pH, pL, and p0 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 (pL/p0 = 5), and among the high exposed subjects is twice that in the low exposed group (pH = 2×pL = 2×5×p0, 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 RR 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 (5). 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 results are likely similar both across Western countries with a comparable number of pediatric CTs and for countries with higher levels of pediatric CT scanning, as long as CT scanning is more common across all indications. However, it should be noted that our results are only generalizable to countries with a roughly similar prevalence of a CSS. Fourth, confounding by other risk factors such as socioeconomic status, birth weight, and parental smoking is beyond the scope of these analyses (39, 40). Finally, although we thoroughly reviewed the literature, we were not able to find prevalence estimates for some CSS and those we found for others are very heterogeneous with regard to precision. Nevertheless, we believe that the CSS we identified cover all relevant 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

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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.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J.M. Meulepas, C.M. Ronckers, M. Hauptmann
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References


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