Running title: Confounding radiation exposure from CT scans and cancer risk

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 [248 words, max 250 words]

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 confound the association since 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. Since 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.

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 syndrome, neurofibromatosis type 1 or other CSS do not meaningfully confound. Empirical data on the use of CT scans among CSS patients is 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 tuberous sclerosis complex.

Impact: Future studies should identify TSC patients in order to avoid overestimation of brain tumor risks due to radiation exposure from CT scans.

Keywords (6): bias – syndromes – cancer – computed tomography – leukemia – brain tumors
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 others are underway (6,7). These studies are record-linkage cohort studies on large numbers of patients collected from existing databases (health insurances, 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) (8-13). Confounding by indication occurs if the reason for a CT scan is associated with cancer risk.

With regard to CT studies, primary concern is about two sources of confounding by indication, namely sub-clinical tumors and cancer susceptibility syndromes (CSS). Cancer in a sub-clinical prodromal phase may cause symptoms which 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 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 compared to children without CSS. Since 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, since 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 epidemiological 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: (1) 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 (JM) (14) and (2) a systematic overview of familial cancer syndromes (15). Thirdly, we consulted with physicians specializing in genetic syndromes at three university hospitals (see Acknowledgement) to identify any other rare eligible CSS. Then the pediatric oncologist (JM) 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 to 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

\[
\text{Bias} = \frac{\text{RROBS}}{\text{RR}_{\text{ADJ}}} = \frac{\text{RR}_{\text{CD}} \cdot p_{\text{HI}} + (1-p_{\text{HI}})}{\text{RR}_{\text{CD}} \cdot p_{\text{LO}} + (1-p_{\text{LO}})}
\]

where RROBS is the RR of cancer comparing arbitrarily defined high and low exposure groups without adjustment for CSS, RR_{ADJ} is the corresponding RR adjusted for the CSS, RR_{CD} 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, p_{0} is the CSS prevalence in the general population. Let \( g = p_{\text{HI}} / p_{\text{LO}} \) and \( f = p_{\text{LO}} / p_{0} \), so that the CSS prevalence in the high exposed group is a multiple of the prevalence in the low exposed (reference) group, \( p_{\text{HI}} = g \cdot p_{\text{LO}} \), while the prevalence in the low exposed group is a multiple of that in the general population, \( p_{\text{LO}} = f \cdot p_{0} \), where \( p_{0} \) is the prevalence in the general population (19). If a CSS does not increase cancer risk (RR_{CD}=1), or if CT use is unrelated to CSS occurrence (p_{LO}=p_{HI}), there is no bias (bias=1). An evaluation of potential bias for comparison of children with any CT scans compared to the general population (Standardized Incidence Ratio, SIR) can be carried out by setting \( p_{\text{LO}} = p_{0} \), 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*5*p_0). Since p_0 is small, this is equivalent to CSS patients being 2- and 10-fold more likely to be in the low and high exposed group, 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 since 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 cancer susceptibility syndromes*

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 (DS), 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). DS, Li-Fraumeni syndrome (LFS), NF1, tuberous sclerosis complex (TSC) and von Hippel-Lindau syndrome (VHL) carry the highest risks for leukemia or brain tumors. Childhood mortality from these syndromes is generally low so that they cannot be ruled out as potential confounders based on life expectancy (*Table 1*).
Confounding of leukemia risk due to specific CSS

DS 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 DS is about 50-fold the rate in the general population (21). Ignoring confounding from DS could maximally bias leukemia RRs about 2.0-fold ($p_{HI} = 8p_{LO}$, $p_{LO}/p_0 = 5$, Figure 1a).

Results for DS indicate that the potential for confounding depends on the excess frequency of CT scans among DS patients. Based on a recent review (22), imaging modalities other than CT were adequate for DS patients in most clinical situations (Supplementary Table S1). In the absence of quantitative data from the literature, we interviewed a DS expert (MEW, 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 DS 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 DS 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 (24) or Hirschsprung’s disease) are usually evaluated by X-ray. Experts stated that trauma does not seem to occur more often among children with DS compared with other children and that the fraction of DS 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 DS 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 DS patients per year attributable to DS 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 DS patients than among other children, leading to less than 20% bias of the SIR (\(p_{\text{LO}}=p_0\) and \(p_{\text{HI}}=4*p_{\text{LO}}\)) and no appreciable bias of the RR because the prevalence of DS is not increasing further with exposure level since several CT scans due to DS are very unlikely (Figure 1a).

For Noonan syndrome and leukemia, the unadjusted RR overestimated the adjusted RR by maximally 30% (Figure 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 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 (SEGAs), which develop in 9-14% of patients and almost always occur before 20-25 years of age (27), are a major feature specific for TSC (15). Bias can be up to 4-fold (Figure 2a). In the past, screening for SEGAs was recommended among children with TSC using CT or magnetic resonance imaging (MRI) of the head every 1-3 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 to children in the general population. Therefore, the potential bias of the SIR is about two-fold \((p_{LO}=p_0\) and \(p_{HI}=7.6*p_{LO}\)) and bias of the RR could be more severe since a non-negligible fraction of TSC patients might have received a considerable number of head CTs (Figure 2a).

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), 60-90% of patients with VHL develop hemangioblastomas of the cerebellum or the brain stem (31). VHL biased brain tumor risk by up to 6-fold (Figure 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 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. CT also has no important role in the screening for other VHL-related morbidity (personal communication: Prof. Peter Vandertop, VU University Medical Center Amsterdam and
Academic Medical Center Amsterdam; Dr. Netteke Schouten-van Meeteren, Emma Children’s Hospital, 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 patients are included in an epidemiologic study on CT scanning and most of those would not have received several head CTs during childhood.

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 Figure 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 DS/VHL (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 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 DS, 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. Since 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 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 was defined as the outcome of interest (5). ERRs for leukemia or brain tumors were not or only mildly attenuated after adjustment for Down or NF, 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 over-representation 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 1980-2010 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 non-significantly 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 5-7% 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 50-70% 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, XP, LFS) (15). For those CSS, we might have underestimated bias since 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 since results are likely similar.
both across Western countries with 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
socio-economic status (SES), 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 all 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
(CVID) has a prevalence of approximately one 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.
Acknowledgments

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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 teleangiectasia</td>
<td>AT</td>
<td>1-3/100,000 (15)</td>
<td>20-49 yr (44)</td>
<td>Case series of 78 AT patients (45), case report of 1 patient (46), 1 patient (47)</td>
<td>1x T-CLL/ 1x T-PLL/ 5x-ALL</td>
<td>1 Astrocytoma 1 Medulloblastoma</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>1-19 yr (49)</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>
</tr>
<tr>
<td>Bloom syndrome</td>
<td>BS</td>
<td>&lt;1/100,000 (50)</td>
<td>20-49 yr (50)</td>
<td>Blooms syndrome Registry with 129 BS patients and 205 neoplasms (50)</td>
<td>12 ALL / 25 AML neoplasms</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), 1 patient (58), 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 yr (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>20-49 yr (63)</td>
<td>Retrospective cohort with 2841 patients (21)</td>
<td>all leukemia 0-4yr SIR 56.4 15-19 yr SIR 9.88 all ages SIR 17.6 ALL 0-4 yr SIR 40.7 15-19 yr SIR 12.4 all ages SIR 24.4 AML 0-4 yr SIR 153.9 15-19 yr SIR 10.3 all ages SIR 20.3</td>
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<td>Table 1: continued</td>
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<tr>
<td>Synonym</td>
<td>Prevalence</td>
<td>Life Expectancy</td>
<td>Study design and population</td>
<td>Leukemia</td>
<td>Brain Tumors</td>
<td>Credibility/ Validity</td>
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<tr>
<td><strong>Dubowitz syndrome</strong></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>
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<tr>
<td><strong>Fanconi Anemia</strong></td>
<td>FA</td>
<td>&lt;1/100,000 (66)</td>
<td>20-49 yr (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 (2nd primary after NHL)</td>
</tr>
<tr>
<td><strong>Fetal alcohol syndrome</strong></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><strong>Gardner’s syndrome</strong></td>
<td>Familial Colorectal Polyposis</td>
<td>6/100,000 (76)</td>
<td>50-69 yr (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>
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<tr>
<td><strong>Gorlin syndrome</strong></td>
<td>Nevoid Basal cell carcinoma syndrome (NBCCS)</td>
<td>&lt;1-100,000 (76)</td>
<td>&gt;70 yr (79)</td>
<td>Case series of 173 patients (80), case reports with 1 patient (81-85)</td>
<td>3% of the 173 patients had Medulloblastoma, Case reports reported 5 Medulloblastoma and 1 Meningioma</td>
<td></td>
</tr>
<tr>
<td><strong>Incontinentia Pigmentia</strong></td>
<td>Bloch-Sulzenberger syndrome</td>
<td>&lt;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 granulocytic leukemia</td>
<td></td>
</tr>
</tbody>
</table>
Table 1: continued

<table>
<thead>
<tr>
<th>Synonym</th>
<th>Prevalence</th>
<th>Life Expectancy</th>
<th>Risk of cancer</th>
</tr>
</thead>
<tbody>
<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>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 Leukemia OR = 6.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>32 Brain tumors OR = 35 (19-60)</td>
</tr>
<tr>
<td>Neurofibromatosis type 1</td>
<td>39/100,000 (77)</td>
<td>70+ yr (77)</td>
<td>Clinicopathologic study of 100 patients (95), longitudinal study of 176 patients (96), retrospective study 104 patients (97), population based study on 2,700 deaths of people (98), multicentre collaboration of 2108 patients (99), population base study of 135 patients (100), case reports (101,102)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>15-20% of children with NF1 develop OPG 1 glioblastoma 1 medulloblastoma</td>
</tr>
<tr>
<td>Neurofibromatosis type 2</td>
<td>2/100,000 (77)</td>
<td>50-69 yr (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>
</tr>
<tr>
<td></td>
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<td></td>
<td>Bilateral vestibular schwannomas 90-95% Other cranial nerve schwannomas 24-51%</td>
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<td></td>
<td>Intracranial meningeomas 45-58%</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>
</tr>
<tr>
<td></td>
<td></td>
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<td>3 T-cell precursor ALL 1 AML 1 T-cell prolymphocytic Leukemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 Medulloblastoma</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>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10% Myeloproliferative disorder, 3 precursor B-ALL,4 Juvenile myelomonocytic leukemia,3 ALL , 2 CMML</td>
</tr>
<tr>
<td>Synonym</td>
<td>Prevalence</td>
<td>Life Expectancy</td>
<td>Risk of cancer</td>
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<tr>
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</tr>
<tr>
<td><strong>Rubinstein–Taybi syndrome</strong></td>
<td>&lt;1-1/100,000 (121)</td>
<td>Normal (122)</td>
<td>Case reports (123,124)</td>
</tr>
<tr>
<td><strong>Severe congenital neutropenia</strong></td>
<td>&lt;1/100,000 (87)</td>
<td>NM</td>
<td>Registry with 82 patients (125)</td>
</tr>
<tr>
<td><strong>Silver-Russel syndrome</strong></td>
<td>1/100,000 (126)</td>
<td>Normal (127)</td>
<td>Case reports (128,129)</td>
</tr>
<tr>
<td><strong>Sotos syndrome</strong></td>
<td>1/14,000 (87)</td>
<td>Normal</td>
<td>Case series with 224 patients (130) and 27 patients (131)</td>
</tr>
<tr>
<td><strong>Sturge-Weber Syndrome</strong></td>
<td>2-5/100,000 (132)</td>
<td>Normal (133)</td>
<td>Retrospective study with 55 patients (134, 135)</td>
</tr>
<tr>
<td><strong>Trisomy 8 mosaicism</strong></td>
<td>1/100,000 (136)</td>
<td>Normal</td>
<td>15-20% develop leukemia, syndrome often detected at leukemia diagnosis</td>
</tr>
<tr>
<td><strong>Trisomy 13</strong></td>
<td>4/100,000 (137)</td>
<td>&lt;1 yr (138)</td>
<td>1 Pilocytic Astrocytoma</td>
</tr>
<tr>
<td><strong>Tuberous sclerosis</strong></td>
<td>8/100,000 (140)</td>
<td>shortened (141)</td>
<td>Review (87), (141), retrospective cross-sectional study with 285 patients (27)</td>
</tr>
<tr>
<td><strong>Turet syndrome</strong></td>
<td>10/100,000 (87)</td>
<td>Unknown</td>
<td>Registry with 14 families (142)</td>
</tr>
</tbody>
</table>

### Study design and population
- **Rubinstein–Taybi syndrome**: Case reports (123,124)
- **Severe congenital neutropenia**: Registry with 82 patients (125)
- **Silver-Russel syndrome**: Case reports (128,129)
- **Sotos syndrome**: Case series with 224 patients (130) and 27 patients (131)
- **Sturge-Weber Syndrome**: Retrospective study with 55 patients (134, 135)
- **Trisomy 8 mosaicism**: 15-20% develop leukemia, syndrome often detected at leukemia diagnosis
- **Trisomy 13**: Case report (139)
- **Tuberous sclerosis**: Review (87), (141), retrospective cross-sectional study with 285 patients (27)
- **Turet syndrome**: Registry with 14 families (142)

### Leukemia
- **Rubinstein–Taybi syndrome**: 1 ALL
- **Severe congenital neutropenia**: NM
- **Silver-Russel syndrome**: MDS and AML
- **Sotos syndrome**: 3 ALL
- **Sturge-Weber Syndrome**: 3 Ipsilateral leptomeningeal angioma
- **Trisomy 8 mosaicism**: 1 Pilocytic Astrocytoma
- **Trisomy 13**: 1 Pilocytic Astrocytoma
- **Tuberous sclerosis**: SEGA: prevalence estimate: 0.11, 95%CI: 0.09-0.14
- **Turet syndrome**: Increased CNS: RR all ages=7, RR 0-29 yr=23
Table 1: (continued)

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Synonym</th>
<th>Prevalence</th>
<th>Life Expectancy</th>
<th>Risk of cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Study design and population</td>
<td>Leukemia</td>
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<td></td>
<td>Cohort study with 3425 patients (143), case report (144)</td>
<td>1 Leukemia</td>
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<td></td>
<td>Follow-up study of 225 patients with VHL-related CNS hemangioblastoma (31)</td>
<td>CNS (hemangioblastoma) 60-90% penetrance</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Literature review with 189 patients from case reports (145)</td>
<td>Leukemia and pre-leukemia</td>
</tr>
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<td></td>
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<td></td>
<td>Case report of 4 patients (149), case reports of 132 patients (150), systematic study of 830 cases (148)</td>
<td>1 Glioblastoma 3 Brain sarcoma 1 Medulloblastoma</td>
</tr>
</tbody>
</table>

Abbreviations: AL, acute leukemia; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; CML, chronic myeloid leukemia; CNS, central nervous system; 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; SEGA, Subependymal giant cell tumors; SIR, standardized incidence ratio; yr, year.

*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’.

+nontransplanted CF patients or before transplantation for transplanted patients

+slightly increased number of SEGAS for recent years due to screening

+Pre-leukemia: Myelofibrosis, myelodysplasia, Refractory anemia with excess blasts

CREDIBILITY/VALIDITY
- High (++): large cohort studies (>1000 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 (<1000 population)
- Low (-): case series, case reports; physician surveys; reviews of case series/case reports
Table 2: Selected cancer susceptibility syndromes (CSS) by general population prevalence and relative risk of leukemia and brain tumors.

<table>
<thead>
<tr>
<th>General population prevalence of CSS (per 100,000)</th>
<th>&lt;1</th>
<th>1-&lt;5</th>
<th>5-&lt;25</th>
<th>25-&lt;50</th>
<th>50-160</th>
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<tbody>
<tr>
<td>RR(CSS–Cancer)**</td>
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<tr>
<td>Low</td>
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<tr>
<td>AT&lt;sup&gt;l&lt;/sup&gt;</td>
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<tr>
<td>Trisomy 8&lt;sup&gt;l&lt;/sup&gt;</td>
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<tr>
<td>Gorlin&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Sotos&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>CF&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Medium</td>
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<tr>
<td>Biallelic Lynch&lt;sup&gt;bl&lt;/sup&gt;</td>
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<td>NF type 2&lt;sup&gt;n&lt;/sup&gt;</td>
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<tr>
<td>Turcot&lt;sup&gt;bl&lt;/sup&gt;</td>
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<tr>
<td>Gardner's&lt;sup&gt;bn&lt;/sup&gt;</td>
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<td>Turner&lt;sup&gt;n&lt;/sup&gt;</td>
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<td>Noonan&lt;sup&gt;n&lt;/sup&gt;</td>
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<td>High</td>
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<tr>
<td>Li-Fraumeni&lt;sup&gt;n&lt;/sup&gt;</td>
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<tr>
<td>NF type 1&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Down&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>Very high</td>
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<tr>
<td>VHL&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>TSC&lt;sup&gt;n&lt;/sup&gt;</td>
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</tbody>
</table>

Abbreviations: AT, ataxia telangiectasia; NF, neurofibromatosis; CF, cystic fibrosis; TSC, tuberous sclerosis complex; VHL, von Hippel-Lindau syndrome

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

** RR=1-2, medium: RR=2-15, high: RR=15-50, very high: RR > 50 with a maximum RR of 28,000.

<sup>l</sup> Risk of leukemia

<sup>n</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 compared with others is about 20.
Figure 1a: Estimated potential bias of the relative risk of leukemia among high versus low exposed subjects by failure to adjust for Down syndrome*.

*Bias=RR_{OBS}/RR_{ADJ}=[RR_{CD}*p_{HI} + (1-p_{HI})]/[RR_{CD}*p_{LO} + (1-p_{LO})], where RR_{OBS} is the RR of leukemia comparing arbitrarily defined high and low (reference) exposure groups without adjustment for Down syndrome, RR_{ADJ} is the corresponding RR adjusted for Down syndrome, RR_{CD} is the RR of leukemia due to Down syndrome in the reference population, and p_{HI}, p_{LO}, and p_{0} are the prevalences of Down syndrome in the high exposed, low exposed and general population, respectively (19).

Example: Under the assumption that the prevalence of Down syndrome among low exposed subjects is 5 times the general population prevalence (p_{LO}/p_{0}=5), and among the high exposed subjects is twice that in the low exposed group (p_{HI}=2*p_{LO}=2*5p_{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%.
Figure 1b: Estimated potential bias of the relative risk leukemia among high versus low exposed subjects by failure to adjust for Noonan syndrome*.

*Bias=RR_{OBS}/RR_{ADJ}=[RR_{CD}*p_{HI} + (1-p_{HI})]/[RR_{CD}*p_{LO} + (1-p_{LO})], where RR_{OBS} is the RR of leukemia comparing arbitrarily defined high and low (reference) exposure groups without adjustment for Noonan syndrome, RR_{ADJ} is the corresponding RR adjusted for Noonan syndrome, RR_{CD} is the RR of leukemia due to Noonan syndrome in the reference population, and p_{HI}, p_{LO}, and p_0 are the prevalences of Noonan syndrome in the high exposed, low exposed and general population, respectively (19).
Figure 2a: Estimated potential bias of the relative risk for a brain tumor among high versus low exposed subjects by failure to adjust for tuberous sclerosis complex*. 

*Bias=RR_{OBS}/RR_{ADJ}=[RR_{CD}*p_{HI} + (1-p_{HI})]/[RR_{CD}*p_{LO} + (1-p_{LO})], where RR_{OBS} is the RR of brain tumors comparing arbitrarily defined high and low (reference) exposure groups without adjustment for tuberous sclerosis complex, RR_{ADJ} is the corresponding RR adjusted for tuberous sclerosis complex, RR_{CD} is the RR of brain tumors due to tuberous sclerosis complex in the reference population, and p_{HI}, p_{LO}, and p_{0} are the prevalences of tuberous sclerosis complex in the high exposed, low exposed and general population, respectively (19).
Figure 2b: Estimated potential bias of the relative risk for a brain tumor among high versus low exposed subjects by failure to adjust for von Hippel-Lindau syndrome.*

*Bias = \( \frac{RR_{OBS}}{RR_{ADJ}} = \frac{RR_{CD}p_{HI} + (1-p_{HI})}{RR_{CD}p_{LO} + (1-p_{LO})} \), where \( RR_{OBS} \) is the RR of brain tumors comparing arbitrarily defined high and low (reference) exposure groups without adjustment for VHL, \( RR_{ADJ} \) is the corresponding RR adjusted for VHL, \( RR_{CD} \) is the RR of brain tumors due to VHL in the reference population, and \( p_{HI}, p_{LO}, \) and \( p_0 \) are the prevalences of VHL in the high exposed, low exposed and general population, respectively (19).
Estimated bias of CT-related RR

Figure 1a
Figure 1b

Estimated bias of CT-related RR

- $p_{HI} = 8p_{LO}$
- $p_{HI} = 7p_{LO}$
- $p_{HI} = 6p_{LO}$
- $p_{HI} = 5p_{LO}$
- $p_{HI} = 4p_{LO}$
- $p_{HI} = 3p_{LO}$
- $p_{HI} = 2p_{LO}$

$p_{LO}/p_0$ versus Estimated bias of CT-related RR

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Figure 2a

Estimated bias of CT-related RR

$\text{Estimated bias of CT-related RR}$

$p_{HI} = 8p_{LO}$

$p_{HI} = 7p_{LO}$

$p_{HI} = 6p_{LO}$

$p_{HI} = 5p_{LO}$

$p_{HI} = 4p_{LO}$

$p_{HI} = 3p_{LO}$

$p_{HI} = 2p_{LO}$
Figure 2b

Estimated bias of CT-related RR

$p_{hi}/p_{lo}$

$p_{hi}=8p_{lo}$

$p_{hi}=7p_{lo}$

$p_{hi}=6p_{lo}$

$p_{hi}=5p_{lo}$

$p_{hi}=4p_{lo}$

$p_{hi}=3p_{lo}$

$p_{hi}=2p_{lo}$
Cancer Epidemiology, Biomarkers & Prevention

Confounding of the association between radiation exposure from CT scans and risk of leukemia and brain tumors by cancer susceptibility syndromes

Johanna M Meulepas, Cecile M. Ronckers, Johannes Merks, et al.

Cancer Epidemiol Biomarkers Prev  Published OnlineFirst November 23, 2015.

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Supplementary Material  Access the most recent supplemental material at: http://cebp.aacrjournals.org/content/suppl/2015/11/21/1055-9965.EPI-15-0636.DC1

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