# Cancer Risk in Children and Adolescents with Birth Defects: A Population-Based Cohort Study

**Lorenzo D. Botto[1]*, Timothy Flood[2], Julian Little[3], Mark N. Fluchel[4], Sergey Krikov[1], Marcia L. Feldkamp[1], Yuan Wu[5], Rhinda Goedken[5], Soman Puzhankara[5], Paul A. Romitti[5]**

**1** Division of Medical Genetics, Department of Pediatrics, University of Utah, Salt Lake City, Utah, United States of America, **2** Arizona Department of Health Services, Phoenix, Arizona, United States of America, **3** Department of Epidemiology and Community Medicine, University of Ottawa, Ontario, Canada, **4** Division of Pediatric Hematology and Oncology, Department of Pediatrics, University of Utah, Salt Lake City, Utah, United States of America, **5** Department of Epidemiology, College of Public Health, The University of Iowa, Iowa City, Iowa, United States of America

## Abstract

***Objective:*** Birth defects are an increasing health priority worldwide, and the subject of a major 2010 World Health Assembly Resolution. Excess cancer risk may be an added burden in this vulnerable group of children, but studies to date have provided inconsistent findings. This study assessed the risk for cancer in children and young adolescents with major birth defects.

***Methods and Findings:*** This retrospective, statewide, population-based, cohort study was conducted in three US states (Utah, Arizona, Iowa). A cohort of 44,151 children and young adolescents (0 through 14 years of age) with selected major, non-chromosomal birth defects or chromosomal anomalies was compared to a reference cohort of 147,940 children without birth defects randomly sampled from each state's births and frequency matched by year of birth. The primary outcome was rate of cancer prior to age 15 years, by type of cancer and type of birth defect. The incidence of cancer was increased 2.9-fold (95% CI, 2.3 to 3.7) in children with birth defects (123 cases of cancer) compared to the reference cohort; the incidence rates were 33.8 and 11.7 per 100,000 person-years, respectively. However, the excess risk varied markedly by type of birth defect. Increased risks were seen in children with microcephaly, cleft palate, and selected eye, cardiac, and renal defects. Cancer risk was not increased with many common birth defects, including hypospadias, cleft lip with or without cleft palate, or hydrocephalus.

***Conclusion:*** Children with some structural, non-chromosomal birth defects, but not others, have a moderately increased risk for childhood cancer. Information on such selective risk can promote more effective clinical evaluation, counseling, and research.

**Citation:** Botto LD, Flood T, Little J, Fluchel MN, Krikov S, et al. (2013) Cancer Risk in Children and Adolescents with Birth Defects: A Population-Based Cohort Study. PLoS ONE 8(7): e69077. doi:10.1371/journal.pone.0069077

**Editor:** Li-Min Huang, National Taiwan University Hospital, Taiwan

**Received** February 8, 2013; **Accepted** June 5, 2013; **Published** July 17, 2013

**Copyright:** © 2013 Botto et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

**Funding:** Partial support for all datasets within the Utah Population Database was provided by the Huntsman Cancer Institute at the University of Utah. This research was supported by the Utah Cancer Registry, which is funded by Contract #HHSN261201000026C from the National Cancer Institute's SEER Program, with additional support from the Utah Department of Health and the University of Utah. The research was also supported by the Centers for Disease Control and Prevention, National Center on Birth Defects and Developmental Disabilities Grant # MM-1079-09/09. JL holds the Canada Research Chair in Human Genome Epidemiology. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Competing Interests:** The authors have declared that no competing interests exist.

* E-mail: Lorenzo.botto@hsc.utah.edu

## Introduction

An estimated 3% of babies are born with major birth defects [1–3]. In the United States, this translates into at least 120,000 newly affected babies every year, and millions more worldwide. The impact of birth defects is profound and wide-ranging, in affluent as well as, increasingly, in lower income countries. Recognizing such impact, the World Health Organization has recently identified birth defect prevention and care as a global priority [4].

The health burden associated with birth defects is significant; in the United States and many other countries, birth defects are the leading cause of infant death and a major contributor to disability and pediatric hospitalizations [3], [5], [6]. Cancer risk could add to this recognized burden. However, whereas the evidence for increased cancer risk is robust for conditions such as Down syndrome [7–13], it appears less consistent for many structural birth defects, with studies providing varying estimates for different types of birth defects and often only for broad categories with limited clinical specificity [7–19].

Research has uncovered the basis for a few associations between birth defects and cancer, mostly related to genes involved in growth homeostasis [20] and DNA repair/maintenance [20], [21]. However, for most cases in which birth defects and cancer occur together, the underlying causes and mechanisms, whether genetic or environmental, remain unclear. Further clues could be uncovered by better information on patterns and magnitude of cancer risk in children with birth defects. By helping to identify who is, and who is not, at increased cancer risk, such information could translate into better care and long term outcomes.

However, such studies are challenging: they require large population-based samples, longitudinal follow-up, detailed and validated information on clinical phenotype, and appropriate reference populations. In this study, we evaluated a large population-based cohort of U.S. children and young adolescents with birth defects to quantify and qualify their risk of cancer prior to age 15 years.

## Methods

### Study Design, Setting, Subjects (Table 1)

The Institutional Review Board (IRB) in each of the three states (University of Utah, IRB; Utah Department of Health, IRB, Resource for Genetic and Epidemiologic Research Review Board; Arizona Department of Health Service, Human Subjects Review Board; The University of Iowa, Human Subjects Research Office) approved the study. These IRBs waived the requirement to obtain informed consent because the study used existing data collected under public health surveillance statutes as reportable conditions and required no patient contact.

The three states partnered to increase the available study population. This partnership was facilitated by the presence of similar population-based surveillance programs of birth defects and of cancer (Table 1) with access to clinical abstracts for clinical case review. The study compared two population-based cohorts derived from an underlying birth population of 2.7 million singleton liveborn infants of resident mothers in Utah, Arizona, and Iowa (''UTAZIA'' study). The index cohort included all children with selected major, non-chromosomal birth defects and selected chromosomal anomalies identified from these states' population-based birth defect surveillance programs. The reference cohort consisted of children without birth defects, randomly selected from the states' birth certificates and frequency-matched (3:1 ratio) to the index cohort by year of birth. We then linked the reference cohort to the data in the birth defect surveillance programs to exclude children with birth defects.

### Data Sources, Inclusions, Exclusions, Clinical Case Review

The primary data sources were the birth surveillance programs, to select the birth defect cohort, and vital records databases, to select the reference cohort and to obtain death abstracts. These initial cohorts were reviewed (Figure 1) for inclusion and exclusion criteria, leading to the final study cohorts. Briefly, subjects were selected based on the presence of selected major birth defects, as defined by the National Birth Defect Prevention Network [22]. These birth defects account for most clinically significant conditions (found in 1.5 to 2 percent of births overall) while excluding common conditions that are inconsistently identified around the time of birth, may resolve spontaneously, or require minor or no medical procedures (e.g., patent ductus arteriosus in the newborn, bicuspid aortic valve without stenosis, undescended testis, pre-auricular tags, pigmented nevi).

Because of early lethality, we also excluded infants with anencephaly and babies weighing less than 400g at birth or less than 20 weeks of gestational age. Clinical case review by a board-certified clinical geneticist and a pediatric oncologist led to the exclusion of secondary conditions (19 in the birth defect cohort) misclassified as primary birth defects (e.g., ''hydrocephalus'' due to brain tumors obstructing the flow of cerebrospinal fluid [8], hydronephrosis due to mass effect of abdominal tumors, and ''anophthalmia'' due to removal of the eye following a diagnosis of retinoblastoma), and also to the exclusion of all cases of Langerhans cell histiocytosis (two in the reference cohort, one in the birth defect cohort) because of the controversy over whether this condition is a true malignancy [23], [24]. The final study cohorts are summarized in Table 1.

**Table 1.** Cohorts, follow-up time, and surveillance programs, UTAZIA study.

| | Arizona | Iowa | Utah | Total |
|---|---|---|---|---|
| Birth years | 1986 to 2004 | 1983 to 2004 | 1994 to 2006 | 1983 to 2006 |
| Follow-up* | 15 years | 15 years | 15 years | 15 years |
| Total liveborn infants | 1,328,053 | 847,258 | 604,126 | 2,779,437 |
| Index cohort (with birth defects) | 19,629 | 16,463 | 8,059 | 44,151 |
| Person Years of follow-up | 165,607 | 151,052 | 46,999 | 363,659 |
| Median follow-up (years) | 10.1 | 11.3 | 6.2 | 9.2 |
| Reference cohort | 66,503 | 53,743 | 27,694 | 147,940 |
| Person Years of follow-up | 646,842 | 551,817 | 181,576 | 1,380,235 |
| Median follow-up (years) | 10.3 | 11.6 | 6.3 | 9.3 |
| Ascertainment basis | Population-based | Population-based | Population-based | |
| Geographic coverage | State-wide | State-wide | State-wide | |
| Case ascertainment | Active | Active | Active | |
| Age cutoff at first diagnosis | 12 months | 12 months | 24 months | |
| Age cutoff for additional defects | Any age | Any age | Any age | |
| Clinical review of cases | Yes (Obstetrician-gynecologist) | Yes (Geneticist) | Yes (Geneticist) | |
| Cancer registry† | NPCR | SEER | SEER | |

UTAZIA: Utah, Arizona, Iowa.
*Follow-up was from birth up to but excluding the 15th birthday.
†NPCR, National Program of Cancer Registries; SEER, Surveillance, Epidemiology and End Results program.
doi:10.1371/journal.pone.0069077.t001

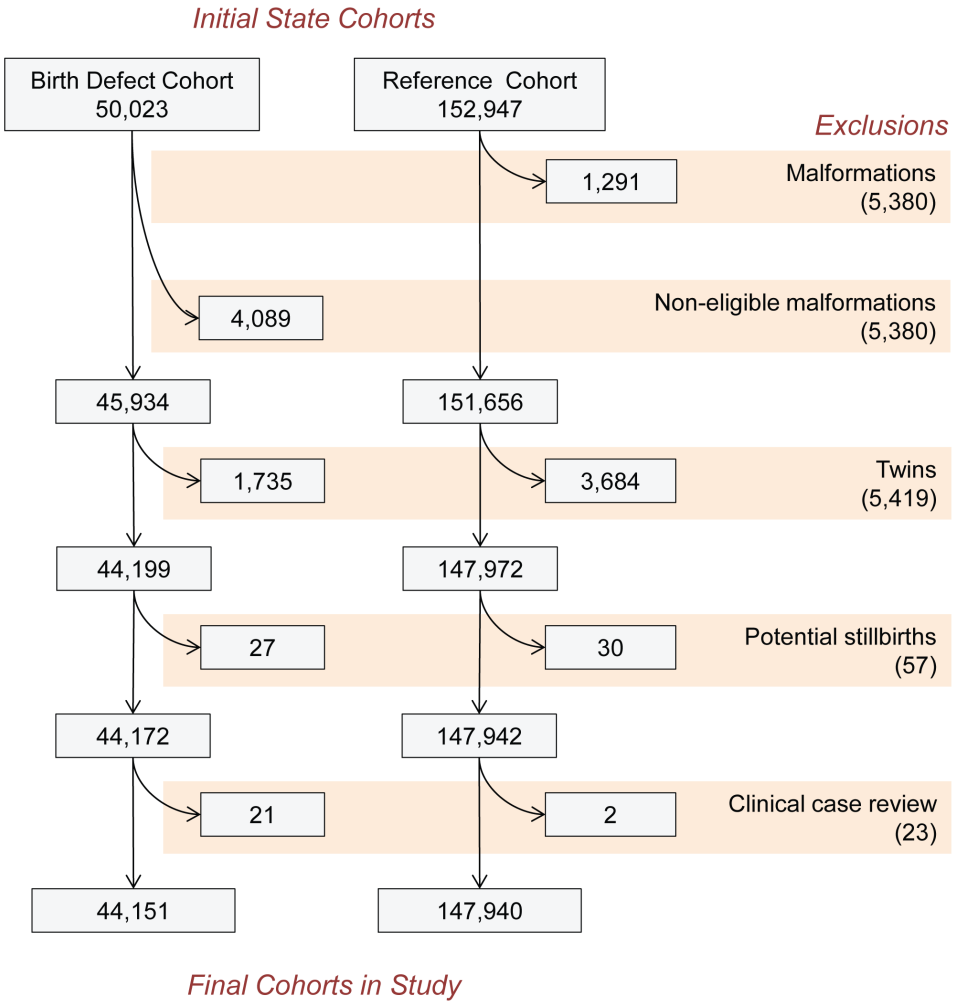


**Figure 1. Inclusions and exclusions leading to final cohorts in the UTAZIA study of birth defects and cancer.**
doi:10.1371/journal.pone.0069077.g001

## Data Classification

We classified structural, non-chromosomal birth defects based on clinical and developmental considerations. For example, we separated limb deficiencies into transverse, preaxial, and postaxial types. We also classified heart defects hierarchically [25]: every child with a heart defect was assigned to a single heart defect group, based on embryologic timing and mechanism [25–27]. Complex heart defects included single ventricle and its variants (e.g., double inlet left ventricle) and laterality defects (e.g., situs ambiguus). When a non-chromosomal birth defect case had two or more unrelated major birth defects, it was counted in each specific birth defect group; for example, a case of spina bifida and hypospadias contributed to the counts for both spina bifida and hypospadias. However, group totals, overall and by organ system (e.g., non-chromosomal birth defects, brain defects) count people with these conditions, not defects.

We included children with trisomy 21 plus Klinefelter syndrome (48 XXY, +21) in the trisomy 21 group. We classified children with other chromosomal anomalies (e.g., deletion 22q11) who had a major birth defect (e.g., a heart defect) in "other chromosomal anomalies." We grouped cancers using the International Classification of Childhood Cancers [28]. One child developed two primary cancers; we considered only the first diagnosed cancer.

## Statistical Methods

We restricted the analysis of individual structural birth defects to non-chromosomal cases. We analyzed chromosomal cases separately, by chromosomal diagnosis. To identify cases of cancer, we linked both cohorts to each state's cancer surveillance program. To identify deaths, we also linked these cohorts by name, birth date, and sex to administrative databases (state vital record, National Death Index, and Social Security Administration). Linkages used a combined probabilistic and deterministic approach, followed by manual review of individual record matches [29]. The follow-up time (Table1) was 363,000 person-years (PY) in the index cohort and 1.38 million PY in the reference cohort.

Using these data we computed person-time as the duration from birth to cancer diagnosis prior to age 15 years, death, or to the end of follow-up period (December 2005 for Arizona and Iowa, and December 2008 for Utah), whichever came first. Age-specific cancer incidence was based on the number of cases per 100,000 PY of follow-up through that age. To appropriately account for censored data, we used the Kaplan-Meier method to estimate cancer-free survival and cumulative cancer incidence. We used Cox proportional hazards models to adjust for potential confounders, including preterm birth, birth weight, sex, and maternal race/ethnicity, age, education, and state. Missing data were not imputed. Due to confidentiality agreements, the number

of cases of cancer is not specified if it is fewer than five. Sample size of the cohort with birth defects was determined based on the largest number available from the three birth defect surveillance programs. Statistical analyses were done with SAS 9.1 (SAS Institute, Cary, NC).

## Results

Baseline characteristics of the cohort with birth defects and the reference cohort are shown in Table 2. The cohort with birth defects had a higher proportion of male births, shorter length of pregnancies, and lower average birth weight. The male excess was driven by the presence of hypospadias, a common male-specific defect. The reference cohort was similar to the total underlying birth population of 2.7 million live births for the same years (data not shown) for all the maternal and child characteristics available in birth certificates. Cancer incidence was 2.9-fold higher in the index cohort (33.8 per 100,000 PY) compared to the reference cohort (11.7 per 100,000 PY), with considerable variation by phenotype (Table 3). Because adjustment for maternal and child characteristics did not appreciably change the estimates, we present the unadjusted estimates and summarize the adjusted estimates in Table S1.

### Non-chromosomal Birth Defects

Compared to the reference cohort, cancer risk was increased two-fold among children with non-chromosomal birth defects. Table 3 summarizes cancer risk by type of birth defect. Among defect groups with at least three cases of cancer, risk was increased in children with eye defects, microcephaly, cleft palate, and some heart and renal defects. Retinoblastoma occurred in a small number of children with cataracts and microphthalmia (data not shown). We also identified a positive association between heart defects as a group and cancer; however, subgroup analysis was limited by the small number of cancer diagnoses by type of heart defect. The types of cancer for which risk was increased included the "embryonal" childhood cancers, such as neuroblastoma, retinoblastoma, and hepatoblastoma (Table 4). In contrast, for many common defects, including hypospadias, pyloric stenosis, cleft lip with or without cleft palate, and hydrocephalus, cancer risk was not increased compared to the reference cohort.

### Chromosomal Anomalies

No case of cancer was reported among 615 children with trisomy 13 or 18 (Table 3). Among children with Down syndrome, cancer incidence was 14-fold higher than in the reference cohort. Children with Down syndrome represented 7% of the index cohort (3202/44151) but contributed 35% of the cancer diagnoses (43/123). The distribution of common vs. variant forms of Down syndrome (e.g., Robertsonian (21;21) translocation, partial duplication of chromosome 21, or trisomy 21 with Klinefelter syndrome) were similar in children with Down syndrome who did vs. did not develop cancer. The excess cancer risk in children with Down syndrome was driven mainly by leukemias (Table 5), with the highest incidence rate ratio (IRR) observed for acute myeloid leukemia (IRR, 224.0). As a group, cancers other than leukemias and lymphomas (Table 5, bottom row) occurred at a frequency comparable to the reference cohort (IRR, 1.0), although within this group the rates of individual types of cancer varied considerably, with increased rates noted for myelodysplastic disorders, osteosarcoma, and teratoma (Table 5).

The "other chromosomal anomalies" group had a 7-fold increased risk compared to the reference cohort. The recorded cancers included lymphocytic lymphoma, nephroblastoma, and pilocytic astrocytoma, in children with Wolf-Hirschhorn/4p- syndrome, Cri-du-chat/5p- syndrome, and Turner syndrome.

### Effect of Clinical Case Review and Classification

Because of earlier reports of increased cancer risk in children with hydrocephalus or heart defects, we evaluated these associations before and after clinical case review. Before clinical case review we had identified 15 cancer diagnoses in children with hydrocephalus, suggesting a 10-fold increased cancer risk (IRR, 10.7). However, with clinical case review, all but one of the hydrocephalus diagnoses were found to be secondary to a brain tumor obstructing cerebrospinal flow or to intraventricular hemorrhage in a preterm baby (1 case). After excluding these cases, the excess cancer risk disappeared (IRR 0.9, Table 3). Similarly, after the hierarchical classification of heart defects, many of the previously significant increased risks (tricuspid atresia/stenosis and atrioventricular septal defects) were reduced to levels comparable to the reference cohort, although a modestly elevated cancer risk remained for some septal defects (Table 3).

### Time Course of Cancer Risk

The cancer-free survival curves of the index and reference cohorts diverged significantly ($p<0.001$) soon after birth, markedly in the group with chromosomal anomalies (Figure 2, top panel), and less so in the group with non-chromosomal birth defects (Figure 2, middle panel). The hazard for cancer was highest in the first 3 to 5 years (Figure 1, lower panel), after which it was similar to the reference cohort (see Table S2 for additional data). A similar pattern was also seen among children with Down syndrome (data not shown). The corresponding cumulative incidence of cancer over time is shown in Figure 3.

## Discussion

### Key Results

In this population-based study, children and young adolescents with major non-chromosomal birth defects had a two-fold increased risk for cancer prior to age 15 years. However, cancer risk varied markedly by type of birth defect. In particular, we found increased cancer risks in children with microphthalmia, genitourinary defects (renal hypoplasia and obstructive renal defects), microcephaly, and cleft palate (Table 3). These associations could be clues to underlying cancer-predisposing conditions, which could be pursued in further studies. Conversely, and reassuringly, for many common defects the risk for cancer was low and similar to that observed in the reference population of children without birth defects.

With regard to cancer type, the excess cancer risk in children with non-chromosomal birth defects appeared to be driven mainly by tumors other than leukemias and lymphomas; such "embryonal" tumors, which include neuroblastoma, hepatoblastoma, and nephroblastoma, were temporally restricted to childhood and exceedingly rare later in life. Biologically, these tumors could represent the endpoint of mis-programmed organ development rather than the result of early exposure to carcinogens, and unlike typical cancers of the adult, may share pathophysiologic features with birth defects. To date, evidence of causal or mechanistic commonalities between birth defects and cancer has been scarce. Aside from a few Mendelian conditions (e.g. Fanconi syndrome [21]) and genomic disorders (e.g., Beckwith Wiedemann syndrome [20]), few genetic factors are known be associated both with major structural birth defects and childhood cancer. Some morphologic factors, such as low birth weight, are associated with birth defects and possibly with hepatoblastoma [30]; however, the causal role of

**Table 2.** Maternal and child characteristics in index and reference cohorts, UTAZIA study.

| | Index Cohort (with birth defects) | | Reference Cohort (without birth defects) | |
|---|---|---|---|---|
| | **No.** | **%** | **No.** | **%** |
| **Cohort size** | 44,151 | | 147,940 | |
| **Maternal age (years)** | | | | |
| less than 20 years | 5,000 | 11.3 | 15,971 | 10.8 |
| 20 to 24 | 11,752 | 26.6 | 39,815 | 26.9 |
| 25 to 29 | 11,947 | 27.1 | 42,740 | 28.9 |
| 30 to 34 | 8,052 | 18.2 | 27,816 | 18.8 |
| 35 and over | 5,006 | 11.3 | 13,264 | 9.0 |
| Missing | 2,394 | 5.4 | 8,334 | 5.6 |
| **Maternal race/ethnicity** | | | | |
| Non-Hispanic White | 32,655 | 74.0 | 107,061 | 72.4 |
| Non-Hispanic Black | 993 | 2.2 | 3,806 | 2.6 |
| Hispanic | 6,532 | 14.8 | 23,610 | 16.0 |
| Native American | 1,922 | 4.4 | 6,020 | 4.1 |
| Asian/Pacific Islander | 1,441 | 3.3 | 5,913 | 4.0 |
| Other | 132 | 0.3 | 549 | 0.4 |
| Missing | 476 | 1.1 | 981 | 0.7 |
| **Maternal education** | | | | |
| High School or less | 24,308 | 55.1 | 78,880 | 53.3 |
| More than High School | 19,466 | 44.1 | 68,015 | 46.0 |
| Missing | 377 | 0.9 | 1,045 | 0.7 |
| **Child Sex** | | | | |
| Male | 28,692 | 65.0 | 75,318 | 50.9 |
| Female | 15,436 | 35.0 | 72,622 | 49.1 |
| Ambiguous/missing | 23 | 0.0 | 0 | 0.0 |
| **Child birth weight** | | | | |
| Less than 2500 g | 7,756 | 17.6 | 7,141 | 4.8 |
| 2500–3999 g | 32,625 | 73.9 | 125,326 | 84.7 |
| 4000 and more g | 3,595 | 8.1 | 15,345 | 10.4 |
| Missing | 175 | 0.4 | 128 | 0.1 |
| **Child gestational age** | | | | |
| Less than 37 weeks | 7,998 | 18.1 | 10,014 | 6.8 |
| 37 or more weeks | 31,458 | 71.3 | 116,712 | 78.9 |
| Missing | 4,695 | 10.6 | 21,214 | 14.3 |

UTAZIA: Utah, Arizona, Iowa.
Note: percentages may not add up to 100 due to rounding.
doi:10.1371/journal.pone.0069077.t002

low birth weight is unclear, as it could also represent an associated outcome or a marker of exposure (for example to parental smoking). Even less is known for environmental factors. For example, parental smoking is an established risk factor for orofacial clefts [31], but its link with most types of childhood cancers remains uncertain [32–34]. Finally, we found a 14-fold increased cancer risk among children with Down syndrome mainly due to lymphoid and myeloid leukemia. Although such relative risk is high, the absolute risk was fairly low. For example, for childhood leukemia, the absolute risk was in the order of 1 event in 600 person-years. Of note, in Down syndrome the risk for other types of cancers (e.g., the "embryonal" tumors) was not decreased, unlike what has been reported for cancers occurring later in the life of people with Down syndrome [35].

Cancer risk was also time-dependent. The cancer-free time curves of the reference cohort and the affected cohorts (Figure 2) diverge early in life. Interestingly, the curves continue to diverge for the children with chromosomal anomalies but seem to stabilize in early childhood for children with non-chromosomal birth defects. This is reflected in rising cumulative incidence curves in the main study cohorts (Figure 3), and is confirmed by the age-specific hazard rates (Figure 2, bottom panel) indicating an excess risk clustered in the first 3 to 5 years of life. The clinical implication is that clinical surveillance can be focused in time as well as by defect type.

Several high-quality studies, some recent, have examined aspects of the relation between birth defects and cancer; the findings, however, are variable and inconsistent [7–19], [36–48].

**Table 3.** Risk for cancer by type of chromosomal anomaly and major birth defect, UTAZIA study.

| Diagnosis | Cohort size | Person Years follow-up | Cases of cancer | Incidence rate* | Incidence rate ratio | | 95% CI |
|---|---|---|---|---|---|---|---|
| **Cohort without Birth Defects (Reference)** | 147,940 | 1,380,235 | 161 | 11.7 | 1.0 | | Reference |
| **Cohort with Birth Defects** | 44,151 | 363,659 | 123 | 33.8 | 2.9 | † | 2.3–3.7 |
| **Birth Defects, non-chromosomal** | 39,726 | 333,782 | 77 | 23.1 | 2.0 | † | 1.5–2.6 |
| Brain defects | 4,311 | 34,813 | 9 | 25.9 | 2.2 | † | 1.1–4.3 |
| Neural tube defects, all | 1,334 | 11,056 | <5 | 27.1 | 2.3 | | 0.7–7.3 |
| Spina bifida w/out anencephalus | 1,108 | 9,588 | <5 | 31.3 | 2.7 | | 0.9–8.4 |
| Encephalocele | 226 | 1,468 | 0 | 0.0 | 0.0 | | |
| Microcephaly | 1,801 | 14,611 | 5 | 34.2 | 2.9 | † | 1.2–7.1 |
| Holoprosencephaly | 63 | 349 | <5 | 286.3 | 24.5 | † | 3.4–175.3 |
| Hydrocephalus (no spina bifida) | 1,271 | 9,780 | <5 | 10.2 | 0.9 | | 0.1–6.3 |
| Eye defects | 928 | 7,305 | 8 | 109.5 | 9.4 | † | 4.6–19.1 |
| Anophthalmia/microphthalmia | 432 | 3,064 | <5 | 97.9 | 8.4 | † | 2.7–26.3 |
| Congenital cataract | 530 | 4,453 | 6 | 134.8 | 11.6 | † | 5.1–26.1 |
| Aniridia | 31 | 278 | <5 | 359.2 | 30.8 | † | 4.3–219.9 |
| Ear defects (anotia/microtia) | 626 | 5,162 | <5 | 19.4 | 1.7 | | 0.2–11.9 |
| Craniosynostosis | 422 | 2,509 | <5 | 39.9 | 3.4 | | 0.5–24.4 |
| Heart defects | 11,211 | 82,890 | 28 | 33.8 | 2.9 | † | 1.9–4.3 |
| Complex heart defects | 465 | 2,390 | <5 | 41.8 | 3.6 | | 0.5–25.6 |
| Common truncus | 172 | 656 | <5 | 152.3 | 13.1 | † | 1.8–93.3 |
| Transposition of great arteries | 687 | 4,627 | <5 | 43.2 | 3.7 | | 0.9–14.9 |
| Tetralogy of Fallot | 759 | 5,359 | <5 | 18.7 | 1.6 | | 0.2–11.4 |
| Atrioventricular septal defect (AV canal) | 350 | 1,890 | <5 | 105.8 | 9.1 | † | 2.2–36.6 |
| Total anomalous pulmonary venous return | 64 | 418 | <5 | 239.1 | 20.5 | † | 2.9–146.4 |
| Pulmonary valve atresia | 182 | 985 | 0 | 0.0 | 0.0 | | |
| Tricuspid valve atresia and stenosis | 153 | 1,200 | 0 | 0.0 | 0.0 | | |
| Ebstein anomaly | 141 | 967 | 0 | 0.0 | 0.0 | | |
| Hypoplastic left heart syndrome | 509 | 872 | 0 | 0.0 | 0.0 | | |
| Coarctation of the aorta | 1,024 | 8,032 | <5 | 12.5 | 1.1 | | 0.1–7.6 |
| Aortic valve stenosis | 540 | 3,821 | <5 | 52.3 | 4.5 | † | 1.1–18.1 |
| Other major congenital heart defects | 203 | 1,638 | 0 | 0.0 | 0.0 | | |
| Pulmonary valve stenosis | 1,037 | 7,760 | <5 | 25.8 | 2.2 | | 0.5–8.9 |
| Ventricular septal defect, membranous | 2,330 | 17,492 | 5 | 28.6 | 2.5 | † | 1.0–6.0 |
| Ventricular septal defect, NOS | 1,276 | 15,257 | <5 | 26.2 | 2.2 | | 0.8–6.1 |
| Atrial septal defect | 1,404 | 10,157 | 6 | 59.1 | 5.1 | † | 2.2–11.4 |
| Orofacial clefts | 4,756 | 41,001 | 6 | 14.6 | 1.3 | | 0.6–2.8 |
| Cleft palate, without cleft lip | 1,656 | 13,273 | 5 | 37.7 | 3.2 | † | 1.3–7.9 |
| Cleft lip with or without cleft palate | 3,100 | 27,728 | <5 | 3.6 | 0.3 | | 0–2.2 |
| Choanal atresia | 387 | 3,121 | 0 | 0.0 | 0.0 | | |
| Gastrointestinal (GI) defects | 7,207 | 65,278 | 13 | 19.9 | 1.7 | † | 1.0–3.0 |
| GI atresias, all | 1,367 | 10,649 | <5 | 28.2 | 2.4 | | 0.8–7.6 |
| Esophageal atresia/ TE Fistula | 562 | 4,364 | <5 | 22.9 | 2.0 | | 0.3–14 |
| Duodenal atresia | 67 | 410 | 0 | 0.0 | 0.0 | | |
| Jejunal/Ileal atresia | 79 | 508 | 0 | 0.0 | 0.0 | | |
| Small Intestinal atresia | 9 | 72 | 0 | 0.0 | 0.0 | | |
| Rectal/intestinal atresia/stenosis | 1,025 | 8,020 | <5 | 37.4 | 3.2 | † | 1.0–10 |
| Pyloric stenosis | 5,071 | 48,431 | 6 | 12.4 | 1.1 | | 0.5–2.4 |
| Hirschsprung disease | 377 | 3,317 | <5 | 60.3 | 5.2 | † | 1.3–20.8 |
| Biliary atresia | 163 | 1,128 | <5 | 177.3 | 15.2 | † | 3.8–61.3 |
| Abdominal wall defects and variants | 1,479 | 11,258 | <5 | 26.6 | 2.3 | | 0.7–7.2 |

**Table 3.** Cont.

| Diagnosis | Cohort size | Person Years follow-up | Cases of cancer | Incidence rate* | Incidence rate ratio | | 95% CI |
|---|---|---|---|---|---|---|---|
| Omphalocele | 368 | 2,681 | <5 | 37.3 | 3.2 | | 0.4–22.8 |
| Gastroschisis | 972 | 7,442 | <5 | 26.9 | 2.3 | | 0.6–9.3 |
| Cloacal exstrophy | 17 | 102 | 0 | 0.0 | 0.0 | | |
| Bladder exstrophy | 66 | 475 | 0 | 0.0 | 0.0 | | |
| Epispadias | 131 | 1,155 | 0 | 0.0 | 0.0 | | |
| Diaphragmatic hernia | 605 | 3,220 | <5 | 62.1 | 5.3 | † | 1.3–21.5 |
| Genitourinary (GU) defects | 10,887 | 92,735 | 20 | 21.6 | 1.8 | † | 1.2–2.9 |
| Renal, all | 4,349 | 31,308 | 12 | 38.3 | 3.3 | † | 1.8–5.9 |
| Renal agenesis/hypoplasia | 977 | 5,168 | 5 | 96.7 | 8.3 | † | 3.4–20.2 |
| Obstructive GU defect | 3,561 | 27,226 | 8 | 29.4 | 2.5 | † | 1.2–5.1 |
| Hypospadias (includes 1st degree) | 6,691 | 62,574 | 8 | 12.8 | 1.1 | | 0.5–2.2 |
| Limb deficiencies | 1,019 | 8,987 | <5 | 22.3 | 1.9 | | 0.5–7.7 |
| Transverse | 663 | 5,669 | <5 | 35.3 | 3.0 | | 0.7–12.2 |
| Preaxial | 299 | 2,169 | <5 | 46.1 | 4.0 | | 0.6–28.2 |
| Postaxial | 332 | 2,770 | 0 | 0.0 | 0.0 | | |
| Limb deficiency, NEC/NOS | 439 | 4,038 | 0 | 0.0 | 0.0 | | |
| Amniotic bands | 218 | 1,740 | 0 | 0.0 | 0.0 | | |
| **Chromosomal anomalies** | 4,425 | 29,877 | 46 | 154.0 | 13.2 | † | 9.5–18.3 |
| Trisomy 21 (Down syndrome) | 3,202 | 25,876 | 43 | 166.2 | 14.2 | † | 10.2–19.9 |
| Trisomy 18 | 378 | 237 | 0 | 0.0 | 0.0 | | |
| Trisomy 13 | 237 | 178 | 0 | 0.0 | 0.0 | | |
| Other chromosomal conditions | 608 | 3,587 | <5 | 83.6 | 7.2 | † | 2.3–22.5 |

UTAZIA: Utah, Arizona, Iowa.
*Rates are per 100,000 Person Years.
†$P < 0.05$ for incidence rate ratios (vs. reference cohort).
NOS, not otherwise specified; NEC, not elsewhere classified; TE fistula, tracheosophageal fistula.
doi:10.1371/journal.pone.0069077.t003

Among genitourinary defects, we confirmed an increased cancer risk in children with renal hypoplasia and obstructive renal defects [7], [8], even after careful case review to exclude hydronephrosis due to a mass effect of an abdominal tumor, but found no increased risk in children with hypospadias. Among children in the reference cohort, the incidence of cancer was higher in younger children, as has been seen repeatedly in large population surveys [7], [49], [50], and was very similar (11.7 vs. 11.6 per 100,000 PY) to that reported in a recent comparable Canadian study in the same age group [7].

Cancer risk was reassuringly low and comparable to the reference cohort for many common defects such as hypospadias, cleft lip (with or without cleft palate), pyloric stenosis, and hydrocephalus. This is at variance with some prior findings [8–10], [14], [15], [48]. The incorporation of clinical record review in our study could explain some of the discrepancies. For example, some studies reported an association between brain tumors and brain malformations such as hydrocephalus [8], [13], [14]. Concern has been raised [8] that in registry-based studies a diagnosis of hydrocephalus could be assigned to cases in which the hydrocephalus was secondary to a brain tumor obstructing the flow of cerebrospinal fluid, generating a spurious association. Because of this concern, we compared the association between brain cancer and hydrocephalus before and after clinical case review, and found that what appeared initially to be a strong association disappeared completely once cases of secondary hydrocephalus were identified and excluded.

For Down syndrome, prior studies [7–10], [12], [13], [17], [51–53] reported similar risk patterns, with some variation in the magnitude of the estimates. Children with trisomy 13 or 18 had a different risk profile. Previous case reports have documented the occurrence of Wilms tumor and hepatoblastoma in a few children with trisomy 18 [45], [54–56]. In our population-based cohort study we found no reported cases of cancer in this group, suggesting that an excess risk for cancer in children with trisomy 13 or 18, if present, is probably low and has a limited population impact; this limited impact is also due to the high mortality (and therefore short time at risk for cancer) in this group of children. This is consistent with an estimate suggesting that the absolute risk is in the order of 1% or less [56].

Compared to the studies reported to date, the current study adds information on specific birth defect groups that are clinically relevant and more precise than groupings based exclusively on the ICD coding conventions [7], [8]. Whereas the specific grouping may in some cases lead to relatively small sample sizes, it provides a level of detail that can be helpful to clinicians and researchers, and facilitates future meta-analyses.

## Limitations

In studies of birth defects, ascertainment is a significant challenge. In this study, which is based on liveborn infants

**Table 4.** Risk for specific types of cancer in children with structural birth defects, UTAZIA study. Chromosomal conditions were excluded.

| Cancer Type | Cohort without Birth Defects (Reference) | | Cohort with Birth Defects | | | | |
|---|---|---|---|---|---|---|---|
| | N = 147,940 | | N = 44,151 | | | | |
| | No. with Cancer | Rate* | No. with Cancer | Rate* | Incidence Rate Ratio | | 95% CI |
| Leukemia | 45 | 3.3 | 13 | 3.9 | 1.19 | | 0.6–2.2 |
| Acute lymphoid leukemia | 36 | 2.6 | 12 | 3.6 | 1.38 | | 0.7–2.6 |
| Acute myeloid leukemia | 5 | 0.4 | <5 | 0.3 | 0.83 | | 0.1–7.1 |
| Other/unspecified leukemia | <5 | 0.3 | 0 | 0.0 | 0.00 | | |
| Myelodysplastic/ myeloproliferative disease | <5 | 0.1 | <5 | 0.9 | 12.41 | ‡ | 1.3–119.3 |
| Lymphoma | 10 | 0.7 | <5 | 1.2 | 1.65 | | 0.5–5.3 |
| Non-Hodgkin lymphoma | 6 | 0.4 | <5 | 0.3 | 0.69 | | 0.1–5.7 |
| Hodgkin lymphoma | <5 | 0.3 | <5 | 0.3 | 1.03 | | 0.1–9.2 |
| Lymphoma, not specified | 0 | 0.0 | <5 | 0.6 | – | | |
| Brain tumor | 38 | 2.8 | 16 | 4.8 | 1.74 | | 1.0–3.1 |
| Astrocytoma | 17 | 1.2 | 5 | 1.5 | 1.22 | | 0.4–3.3 |
| Medulloblastoma | 13 | 0.9 | <5 | 1.2 | 1.27 | | 0.4–3.9 |
| Other brain tumor | 8 | 0.6 | 7 | 2.1 | 3.62 | † | 1.3–10.0 |
| Neuroblastoma spectrum | 17 | 1.2 | 11 | 3.3 | 2.68 | † | 1.3–5.7 |
| Neuroblastoma | 15 | 1.1 | 8 | 2.4 | 2.21 | | 0.9–5.2 |
| Other peripheral nervous system tumor | <5 | 0.1 | <5 | 0.9 | 6.20 | † | 1–37.1 |
| Retinoblastoma | 7 | 0.5 | 6 | 1.8 | 3.54 | † | 1.2–10.5 |
| Kidney tumor | 16 | 1.2 | <5 | 1.2 | 1.03 | | 0.3–3.1 |
| Wilms tumor | 15 | 1.1 | <5 | 1.2 | 1.10 | | 0.4–3.3 |
| Other kidney tumor | <5 | 0.1 | 0 | 0.0 | 0.00 | | |
| Liver tumor | <5 | 0.1 | 8 | 2.4 | 16.54 | § | 3.5–77.9 |
| Hepatoblastoma | <5 | 0.1 | 7 | 2.1 | 14.47 | § | 3.0–69.7 |
| Other liver tumors | 0 | 0.0 | <5 | 0.3 | – | | |
| Sarcoma | 16 | 1.2 | 6 | 1.8 | 1.55 | | 0.6–4.0 |
| Rhabdomyosarcoma | 5 | 0.4 | <5 | 1.2 | 3.31 | | 0.9–12.3 |
| Osteosarcoma | <5 | 0.1 | 0 | 0.0 | 0.00 | | |
| Ewing sarcoma | <5 | 0.1 | <5 | 0.3 | 2.07 | | 0.2–22.8 |
| Fibrosarcoma | <5 | 0.3 | 0 | 0.0 | 0.00 | | |
| Other soft tissue sarcoma | <5 | 0.2 | <5 | 0.3 | 1.38 | | 0.1–13.8 |
| Germ cell, trophoblastic, and gonadal tumor | 6 | 0.4 | 6 | 1.8 | 4.14 | † | 1.3–12.8 |
| Teratoma | <5 | 0.2 | <5 | 1.2 | 5.51 | † | 1.2–24.6 |
| Other germ cell tumor | <5 | 0.2 | <5 | 0.6 | 2.76 | | 0.5–16.5 |
| Miscellaneous tumors | <5 | 0.2 | 0 | 0.0 | 0.00 | | |
| **Total** | **161** | **11.7** | **77** | **23.1** | **1.98** | § | **1.5–2.6** |
| Tumors other than leukemias and lymphomas | 105 | 7.6 | 57 | 17.1 | 2.2 | § | 1.6–3.1 |

UTAZIA: Utah, Arizona, Iowa.
*Rates are per 100,000 Person Years.
†$P < 0.05$;
‡$P < 0.01$;
§$P < 0.001$ for incidence rate ratios vs. reference cohort.
doi:10.1371/journal.pone.0069077.t004

followed over time, the rates of individual birth defects were consistent with prevalence rates in livebirths reported in high quality surveillance programs in the United States [22] and internationally [57]. Clinical case review was completed through review of medical records abstracted into birth defect and cancer surveillance reports, rather than direct clinical examination; thus, some diagnoses and clinical syndromes may have been missed.

An ascertainment bias of cancer in children with birth defects is unlikely, for several reasons. Children with birth defects are not monitored more closely for cancer than other children, and

**Table 5.** Risk for specific types of cancer in children with Down syndrome (trisomy 21), UTAZIA study.

| Cancer Type | Cohort without Birth Defects (Reference) | | Cohort with Down Syndrome | | | | |
|---|---|---|---|---|---|---|---|
| | N = 147,940 | | N = 3,202 | | | | |
| | No. with Cancer | Rate* | No. with Cancer | Rate* | Incidence Rate Ratio | | 95% CI |
| Leukemia | 45 | 3.3 | 38 | 146.9 | 45.0 | § | 29.2–69.4 |
| ALL (Acute lymphoid leukemia) | 36 | 2.6 | 16 | 61.8 | 23.7 | § | 13.2–42.7 |
| AML (Acute myeloid leukemia) | 5 | 0.4 | 21 | 81.2 | 224.0 | § | 84.5–594.1 |
| Other/unspecified leukemia | <5 | 0.3 | <5 | 3.9 | 13.3 | ‡ | 1.5–119.3 |
| Myelodysplastic/ myeloproliferative disease | <5 | 0.1 | <5 | 7.7 | 106.7 | § | 9.7–1,176.6 |
| Lymphoma | 10 | 0.7 | <5 | 3.9 | 5.3 | | 0.7–41.7 |
| Non-Hodgkin lymphoma | 6 | 0.4 | 0 | 0.0 | 0.0 | | |
| Hodgkin lymphoma | <5 | 0.3 | 0 | 0.0 | 0.0 | | |
| Lymphoma, not specified | 0 | 0.0 | <5 | 3.9 | | | |
| Brain tumor | 38 | 2.8 | 0 | 0.0 | 0.0 | | |
| Astrocytoma | 17 | 1.2 | 0 | 0.0 | 0.0 | | |
| Medulloblastoma | 13 | 0.9 | 0 | 0.0 | 0.0 | | |
| Other brain tumor | 8 | 0.6 | 0 | 0.0 | 0.0 | | |
| Neuroblastoma spectrum | 17 | 1.2 | 0 | 0.0 | 0.0 | | |
| Neuroblastoma | 15 | 1.1 | 0 | 0.0 | 0.0 | | |
| Other peripheral nervous system tumor | <5 | 0.1 | 0 | 0.0 | 0.0 | | |
| Retinoblastoma | 7 | 0.5 | 0 | 0.0 | 0.0 | | |
| Kidney tumor | 16 | 1.2 | 0 | 0.0 | 0.0 | | |
| Wilms tumor | 15 | 1.1 | 0 | 0.0 | 0.0 | | |
| Other kidney tumor | <5 | 0.1 | 0 | 0.0 | 0.0 | | |
| Liver tumor | <5 | 0.1 | 0 | 0.0 | 0.0 | | |
| Hepatoblastoma | <5 | 0.1 | 0 | 0.0 | 0.0 | | |
| Other liver tumors | 0 | 0.0 | 0 | 0.0 | 0.0 | | |
| Sarcoma | 16 | 1.2 | <5 | 3.9 | 3.3 | | 0.4–25.1 |
| Rhabdomyosarcoma | 5 | 0.4 | 0 | 0.0 | 0.0 | | |
| Osteosarcoma | <5 | 0.1 | <5 | 3.9 | 26.7 | § | 2.4–294.1 |
| Ewing sarcoma | <5 | 0.1 | 0 | 0.0 | 0.0 | | |
| Fibrosarcoma | <5 | 0.3 | 0 | 0.0 | 0.0 | | |
| Other soft tissue sarcoma | <5 | 0.2 | 0 | 0.0 | 0.0 | | |
| Germ cell, trophoblastic, and gonadal tumor | 6 | 0.4 | <5 | 3.9 | 8.9 | † | 1.1–73.8 |
| Teratoma | <5 | 0.2 | <5 | 3.9 | 17.8 | § | 1.8–170.9 |
| Other germ cell tumor | <5 | 0.2 | 0 | 0.0 | 0.0 | | |
| Miscellaneous tumors | <5 | 0.2 | 0 | 0.0 | 0.0 | | |
| **Total** | **161** | **11.7** | **43** | **166.2** | **14.2** | § | **10.2–19.9** |
| Tumors other than leukemias and lymphomas | 105 | 7.6 | <5 | 7.9 | 1.0 | | 0.2–3.9 |

UTAZIA: Utah, Arizona, Iowa.
*Rates are per 100,000 Person Years.
†$P < 0.05$;
‡$P < 0.01$;
§$P < 0.001$ for incidence rate ratios vs. reference cohort.
doi:10.1371/journal.pone.0069077.t005

because cancer often develops years after a diagnosis of a major birth defect is made, the diagnostic evaluation for birth defects would not uncover cases of cancer. The converse, however, is probably a greater concern; finding previously undiagnosed birth defects during the diagnostic evaluation of a child with cancer. Factors that we think make such bias unlikely in this study include the focus on major birth defects, rather than minor anomalies that are more likely to have been missed early in life, and the clinical case review that examined the timing of diagnosis (to ensure that the birth defect diagnosis preceded that of the cancer). The case review also specifically mitigated another potential bias, that is, the miscoding as a birth defect of a structural finding that was a

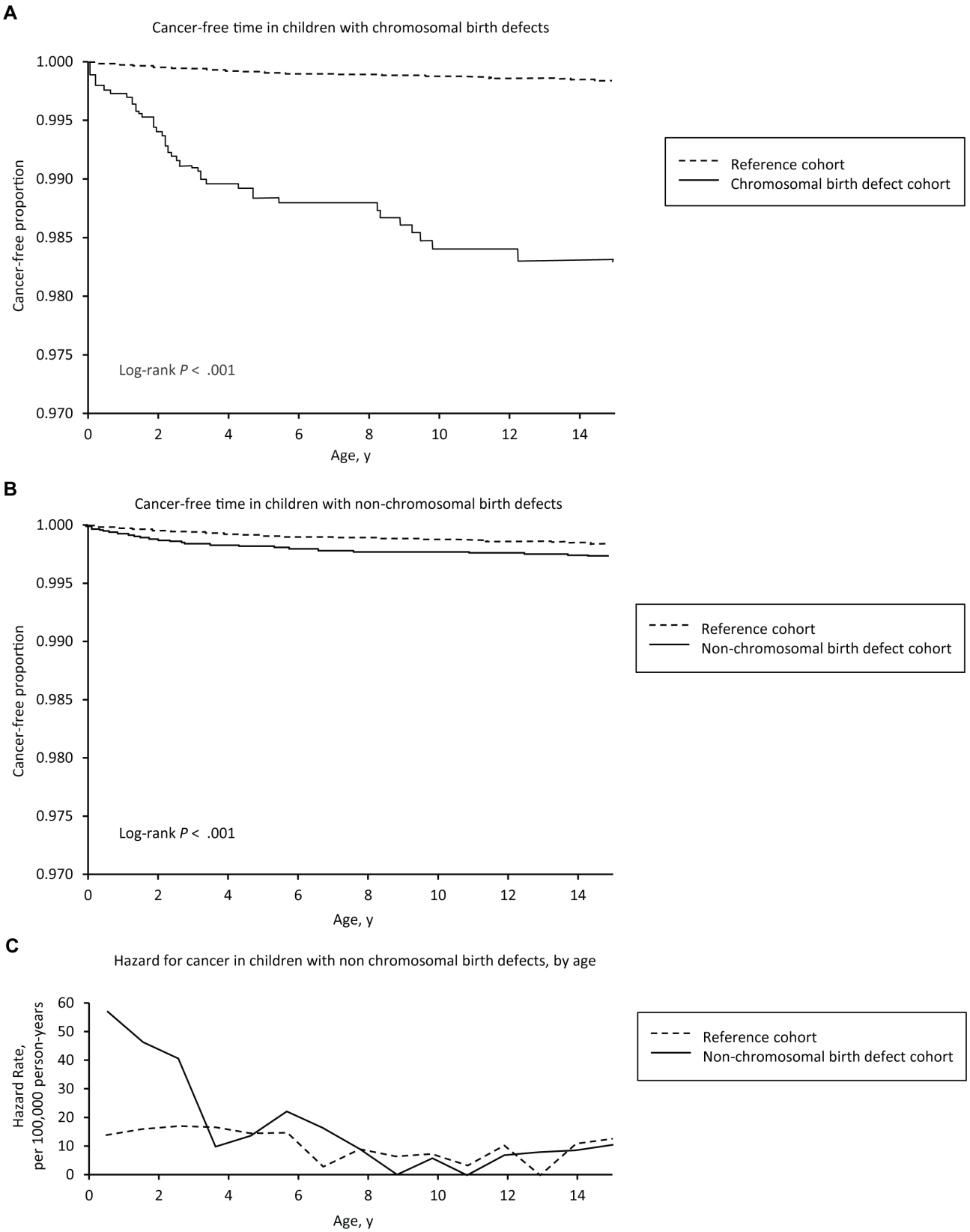


**Figure 2. Cancer-free time curves of reference cohort vs. children with chromosomal anomalies (top panel) and children with non-chromosomal birth defects (middle panel), together with hazard rate for cancer by age in reference cohort vs. children with non-chromosomal birth defects (lower panel).**
doi:10.1371/journal.pone.0069077.g002

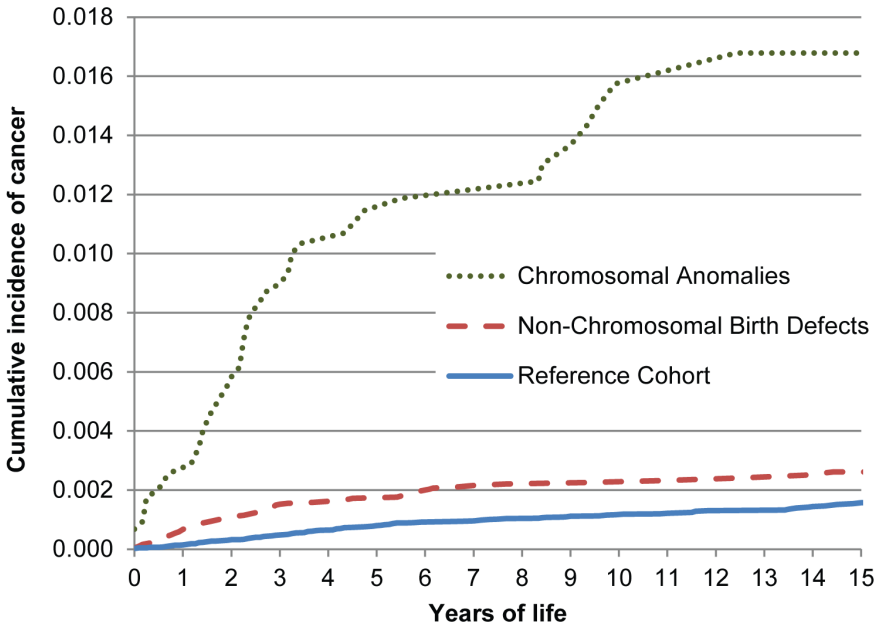


**Figure 3. Cumulative incidence of cancer prior to age 15 years in children with non-chromosomal birth defects and with chromosomal anomalies, UTAZIA study.** Cumulative incidence is expressed as a proportion (0.01 = 1 percent).
doi:10.1371/journal.pone.0069077.g003

consequence of the cancer: one example of such miscoding is "hydrocephalus" secondary to a brain tumor impeding the circulation of cerebrospinal fluid.

We used population-based cohorts and population-based cancer and death registries to minimize selection and follow-up biases. Because no single cancer registry exists country wide, people who moved from the state of birth to another state and there developed cancer would not have been identified in the study. If this occurred differentially in the two cohorts, bias could have arisen. If similar in the different cohorts, such inaccuracies would tend to dilute the estimates of cancer risk towards the null. This study also had limited power to detect weak cancer risks associated with rare defects, a limitation common to many cohort studies. A meta-analysis of similar studies could strengthen the quantification of risk associated with rare defects. Several birth defect subgroups were small with few cancer events (Table 3) and the associated risk estimates are inherently unstable: the addition of a single or a few cases of cancer would change the risk estimates considerably. Nevertheless, the primary results–cancer risk among non-chromosomal birth defects and selected chromosomal anomalies–as well as the secondary analyses of the larger birth defect groups, were considerably more stable (Table 3), due to the comparatively large cohort size. Because of the many groups analyzed (<150 in Tables 3, 4, 5), chance may have played a role in some of the findings beyond the primary analyses. Correcting for multiple testing is controversial in epidemiologic studies; highly regarded epidemiologists disagree not only on methods but also on its intrinsic value [58–60]. Corrections are often applied in studies with a massive number of tests. Thousands of 'tests' are commonly done in genome-wide association studies or in nutrient studies with hundreds of compounds and multiple outcomes. In this study, however, the number of tests is still relatively low and the full scope of the analysis is provided, allowing for a direct evaluation of the potential role of chance. In addition, the analysis of the main groups (e.g., overall risk for cancer, with or without chromosomal anomalies) was hypothesis-driven and based on previous reports. Ultimately, however, as for all studies, associations will be confirmed or dismissed based on replication, and specifically, the joint findings of high quality studies.

Finally, the study focused on childhood cancer, defined as cancer occurring prior to age 15 years. Whether children with birth defects are at increased risk for cancer at a later age is an important question that can be answered with longer follow-up.

### Interpretation and Conclusions

We found a modest but significant increased risk for cancer for specific non-chromosomal birth defects, including microcephaly, congenital cataract, microphthalmia, cleft palate, renal hypoplasia, obstructive renal defects, and selected heart defects. Conversely, for many common birth defects, the risk was not significantly increased. In a clinical setting, focusing on overall risk estimates would be inaccurate and potentially misleading, and may produce unnecessary concern in many families with affected children while potentially failing to properly consider cancer risk in children with specific clinical phenotypes. In some of these clinical presentations associated with increased cancer risk, in-depth genetic consultation could be indicated, with the goal of identifying recognized cancer-predisposing conditions. Furthermore, with the increasing power of molecular evaluation, such clinical research could lead to discovering new conditions that could shed further light on the origin and development of cancers among children and adolescents.

## Supporting Information

**Table S1 Adjusted Relative Risk for cancer by major class of birth defects, UTAZIA study.**
(DOCX)

**Table S2 Hazard rate with 95% confidence interval (95%CI) for cancer, by age, in children with non-chromosomal birth defects and in reference cohort of children without birth defects, UTAZIA study.** Hazard rate is by 100,000 person-years.
(DOCX)

## Acknowledgments

We thank Dr Sonja Rasmussen, MD, MS, and Dr Jun Li, MD. PhD, Centers for Disease Control and Prevention, for technical advice. No compensation was received for their contribution.

We thank the Utah Resource for Genetic and Epidemiologic Research (RGE) for access to the Utah Population Database.

Julian Little holds a Tier 1 Canada Research Chair in Human Genome Epidemiology.

**Data access and responsibility**

The principal investigator (LDB) had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

## Author Contributions

Analyzed the data: LDB TF JL M. Fluchel SK M. Feldkamp RG SP YW PAR. Wrote the paper: LDB TF JL M. Fluchel SK M. Feldkamp RG SP YW PAR. Conception and design: LDB TF JL M. Fluchel SK M. Feldkamp RG SP PR. Acquisition of data: LDB TF SK M. Fluchel RG SP PR.

## References

1. Hoyert DL, Mathews TJ, Menacker F, Strobino DM, Guyer B (2006) Annual summary of vital statistics: 2004. Pediatrics 117: 168–183.
2. Centers for Disease Control and Prevention (2008) Update on Overall Prevalence of Major Birth Defects –- Atlanta, Georgia, 1978–2005. Morb Mortal Wkly Rep (MMWR) 57: 1–5.
3. Christianson A, Howson CP, Modell B (2006) March of Dimes global report on birth defects: the hidden toll of dying and disabled children. White Plains, New York: March of Dimes Birth Defects Foundation.
4. (2010) Resolutions of the 63rd World Assembly. World Health Organization.
5. Rosano A, Botto LD, Botting B, Mastroiacovo P (2000) Infant mortality and congenital anomalies from 1950 to 1994: an international perspective. J Epidemiol Community Health 54: 660–666.
6. Yoon PW, Olney RS, Khoury MJ, Sappenfield WM, Chavez GF, et al. (1997) Contribution of birth defects and genetic diseases to pediatric hospitalizations. A population-based study. Arch Pediatr Adolesc Med 151: 1096–1103.
7. Agha MM, Williams JI, Marrett L, To T, Zipursky A, et al. (2005) Congenital abnormalities and childhood cancer. Cancer 103: 1939–1948.
8. Bjorge T, Cnattingius S, Lie RT, Tretli S, Engeland A (2008) Cancer risk in children with birth defects and in their families: a population based cohort study of 5.2 million children from Norway and Sweden. Cancer Epidemiol Biomarkers Prev 17: 500–506.
9. Mili F, Khoury MJ, Flanders WD, Greenberg RS (1993) Risk of childhood cancer for infants with birth defects. I. A record-linkage study, Atlanta, Georgia, 1968–1988. Am J Epidemiol 137: 629–638.
10. Mili F, Lynch CF, Khoury MJ, Flanders WD, Edmonds LD (1993) Risk of childhood cancer for infants with birth defects. II. A record-linkage study, Iowa, 1983–1989. Am J Epidemiol 137: 639–644.
11. Narod SA, Hawkins MM, Robertson CM, Stiller CA (1997) Congenital anomalies and childhood cancer in Great Britain. Am J Hum Genet 60: 474–485.
12. Rankin J, Silf KA, Pearce MS, Parker L, Ward Platt M (2008) Congenital anomaly and childhood cancer: A population-based, record linkage study. Pediatr Blood Cancer 51: 608–612.
13. Windham GC, Bjerkedal T, Langmark F (1985) A population-based study of cancer incidence in twins and in children with congenital malformations or low birth weight, Norway, 1967–1980. Am J Epidemiol 121: 49–56.
14. Altmann AE, Halliday JL, Giles GG (1998) Associations between congenital malformations and childhood cancer. A register-based case-control study. Br J Cancer 78: 1244–1249.
15. Bille C, Winther JF, Bautz A, Murray JC, Olsen J, et al. (2005) Cancer risk in persons with oral cleft–a population-based study of 8,093 cases. Am J Epidemiol 161: 1047–1055.
16. Infante-Rivard C, Amre DK (2001) Congenital anomalies in children with acute lymphoblastic leukaemia and in their family. Int J Epidemiol 30: 350–352.
17. Linabery AM, Blair CK, Gamis AS, Olshan AF, Heerema NA, et al. (2008) Congenital abnormalities and acute leukemia among children with Down syndrome: a Children's Oncology Group study. Cancer Epidemiol Biomarkers Prev 17: 2572–2577.
18. Mertens AC, Wen W, Davies SM, Steinbuch M, Buckley JD, et al. (1998) Congenital abnormalities in children with acute leukemia: a report from the Children's Cancer Group. J Pediatr 133: 617–623.
19. Carozza SE, Langlois PH, Miller EA, Canfield M (2012) Are children with birth defects at higher risk of childhood cancers? Am J Epidemiol 175: 1217–1224.
20. Weksberg R, Shuman C, Beckwith JB (2010) Beckwith-Wiedemann syndrome. Eur J Hum Genet 18: 8–14.
21. Auerbach AD (2009) Fanconi anemia and its diagnosis. Mutat Res 668: 4–10.
22. National Birth Defects Prevention Network (2011) Selected Birth Defects Data from Population-based Birth Defects Surveillance Programs in the United States, 2004–2008 Birth Defects Res A Clin Mol Teratol 91: 1028–1149.
23. Abla O, Egeler RM, Weitzman S (2010) Langerhans cell histiocytosis: Current concepts and treatments. Cancer Treat Rev 36: 354–359.
24. Egeler RM, van Halteren AG, Hogendoorn PC, Laman JD, Leenen PJ (2010) Langerhans cell histiocytosis: fascinating dynamics of the dendritic cell-macrophage lineage. Immunol Rev 234: 213–232.
25. Botto LD, Lin AE, Riehle-Colarusso T, Malik S, Correa A (2007) Seeking causes: Classifying and evaluating congenital heart defects in etiologic studies. Birth Defects Res A Clin Mol Teratol 79: 714–727.
26. Clark EB (1996) Pathogenetic mechanisms of congenital cardiovascular malformations revisited. Semin Perinatol 20: 465–472.
27. Clark EB (2001) Etiology of Congenital Cardiovascular Malformations: Epidemiology and Genetics. In: Allen HD, Gutgesell HP, Clark EB, Driscoll DJ, editors. Moss and Adams' Heart Disease in Infants, Children, and Adolescents. Sixth ed. Philadelphia: Lippincott Williams & Wilkins. 64–79.
28. Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P (2005) International Classification of Childhood Cancer, third edition. Cancer 103: 1457–1467.
29. Romitti PA, Watanabe-Galloway S, Budelier WT, Lynch CF, Puzhankara S, et al. (2010) Identification of Iowa live births in the Agricultural Health Study. Arch Environ Occup Health 65: 154–162.
30. Spector LG, Birch J (2012) The epidemiology of hepatoblastoma. Pediatr Blood Cancer 59: 776–779.
31. Little J, Cardy A, Munger RG (2004) Tobacco smoking and oral clefts: a meta-analysis. Bull World Health Organ 82: 213–218.
32. Antonopoulos CN, Sergentanis TN, Papadopoulou C, Andrie E, Dessypris N, et al. (2011) Maternal smoking during pregnancy and childhood lymphoma: a meta-analysis. Int J Cancer 129: 2694–2703.
33. Klimentopoulou A, Antonopoulos CN, Papadopoulou C, Kanavidis P, Tourvas AD, et al. (2012) Maternal smoking during pregnancy and risk for childhood leukemia: a nationwide case-control study in Greece and meta-analysis. Pediatr Blood Cancer 58: 344–351.
34. Milne E, Greenop KR, Scott RJ, Ashton LJ, Cohn RJ, et al. (2013) Parental smoking and risk of childhood brain tumors. Int J Cancer 133: 253–259.
35. Yang Q, Rasmussen SA, Friedman JM (2002) Mortality associated with Down's syndrome in the USA from 1983 to 1997: a population-based study. Lancet 359: 1019–1025.
36. Citak FE, Citak EC, Akkaya E, Kosan B, Ezer U, et al. (2011) Minor anomalies in children with hematological malignancies. Pediatr Blood Cancer 56: 258–261.
37. Durmaz A, Durmaz B, Kadioglu B, Aksoylar S, Karapinar D, et al. (2011) The Association of minor congenital anomalies and childhood cancer. Pediatr Blood Cancer 56: 1098–1102.
38. Green DM, Fiorello A, Zevon MA, Hall B, Seigelstein N (1997) Birth defects and childhood cancer in offspring of survivors of childhood cancer. Arch Pediatr Adolesc Med 151: 379–383.
39. Hartley AL, Birch JM, Blair V, Kelsey AM (1994) Malformations in children with soft tissue sarcoma and in their parents and siblings. Paediatr Perinat Epidemiol 8: 423–432.
40. Johnson KJ, Roesler MA, Linabery AM, Hilden JM, Davies SM, et al. (2010) Infant leukemia and congenital abnormalities: a Children's Oncology Group study. Pediatr Blood Cancer 55: 95–99.
41. Mallol-Mesnard N, Menegaux F, Lacour B, Hartmann O, Frappaz D, et al. (2008) Birth characteristics and childhood malignant central nervous sytem tumors: the ESCALE study (French Society for Childhood Cancer). Cancer Detect Prev 32: 79–86.
42. Mehes K, Kajtar P, Sandor G, Scheel-Walter M, Niethammer D (1998) Excess of mild errors of morphogenesis in childhood lymphoblastic leukemia. Am J Med Genet 75: 22–27.
43. Merks JH, Ozgen HM, Koster J, Zwinderman AH, Caron HN, et al. (2008) Prevalence and patterns of morphological abnormalities in patients with childhood cancer. JAMA 299: 61–69.
44. Nishi M, Miyake H, Takeda T, Hatae Y (2000) Congenital malformations and childhood cancer. Med Pediatr Oncol 34: 250–254.
45. Olson JM, Hamilton A, Breslow NE (1995) Non-11p constitutional chromosome abnormalities in Wilms' tumor patients. Med Pediatr Oncol 24: 305–309.
46. Powell JE, Kelly AM, Parkes SE, Cole TR, Mann JR (1995) Cancer and congenital abnormalities in Asian children: a population-based study from the West Midlands. Br J Cancer 72: 1563–1569.
47. Little J (1999) Epidemiology of childhood cancer. IARC Scientific Publications 149: 306–317. Lyon (France): International Agency for Research on Cancer.
48. Fisher PG, Reynolds P, Von Behren J, Carmichael SL, Rasmussen SA, et al. (2012) Cancer in Children with Nonchromosomal Birth Defects. J Pediatr.
49. Linet MS, Ries LA, Smith MA, Tarone RE, Devesa SS (1999) Cancer surveillance series: recent trends in childhood cancer incidence and mortality in the United States. J Natl Cancer Inst 91: 1051–1058.
50. Parkin DM, Stiller CA, Draper GJ, Bieber CA (1988) The international incidence of childhood cancer. Int J Cancer 42: 511–520.

51. Patja K, Pukkala E, Sund R, Iivanainen M, Kaski M (2006) Cancer incidence of persons with Down syndrome in Finland: a population-based study. Int J Cancer 118: 1769–1772.
52. Sullivan SG, Hussain R, Glasson EJ, Bittles AH (2007) The profile and incidence of cancer in Down syndrome. J Intellect Disabil Res 51: 228–231.
53. Tabares-Seisdedos R, Dumont N, Baudot A, Valderas JM, Climent J, et al. (2011) No paradox, no progress: inverse cancer comorbidity in people with other complex diseases. Lancet Oncol 12: 604–608.
54. Anderson CE, Punnett HH, Huff V, de Chadarevian JP (2003) Characterization of a Wilms tumor in a 9-year-old girl with trisomy 18. Am J Med Genet A 121A: 52–55.
55. Faucette KJ, Carey JC, Lemons RL, Toledano S (1991) Trisomy 18 and Wilms tumor: is there an association? Clin Res: 96A.
56. Carey JC (2010) Trisomy 18 and trisomy 13 syndrome. In: Cassidy SB, Allanson JE, editors. Management of Genetic Syndromes. 3rd ed. Hoboken, New Jersey: Wiley-Blackwell. 807–823.
57. International Clearinghouse for Birth Defects Surveillance and Research (2010) Annual Report 2010. In: Mastroiacovo P, editor. Rome Italy. Available: www.icbdsr.org. Accessed 2013 June 17.
58. Greenland S (2008) Multiple comparisons and association selection in general epidemiology. Int J Epidemiol 37: 430–434.
59. Rothman KJ (1990) No adjustments are needed for multiple comparisons. Epidemiology 1: 43–46.
60. Thompson JR (1998) Invited commentary: Re: "Multiple comparisons and related issues in the interpretation of epidemiologic data". Am J Epidemiol 147: 801–806.