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Twins and Their Risks of Cancer as Children, Teenagers or Young Adults: Updated Meta-Analysis and Retrospective Swedish Cohort Study

Michael F.G. Murphy[1] ⓘ , Jian-Rong He[1] ⓘ , Rema Ramakrishnan[2] ⓘ , Carrie L Williams[3] ⓘ , Bowang Chen[4] and Kari Hemminki[5,6] ⓘ

[1]Nuffield Department of Women's and Reproductive Health, University of Oxford, The Women's Centre, John Radcliffe Hospital, Headington, Oxford, UK, [2]National Perinatal Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Richard Doll Building, Old Road Campus, Oxford, UK, [3]Great Ormond Street Institute of Child Health, University College London, London, UK, [4]NHC Key Laboratory of Clinical Research for Cardiovascular Medications, National Clinical Research Center of Cardiovascular Diseases, State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, National Center for Cardiovascular Diseases, Beijing, China, [5]German Cancer Research Center, Heidelberg, Germany and [6]Biomedical Center, Faculty of Medicine, Charles University, Pilsen, Czech Republic

Abstract

We investigated whether an observed reduction in overall childhood cancer risk (<15 years of age) in twins has been sustained, and how this extends into young adulthood. We searched for English language publications reporting childhood cancer risk in twins, obtained unpublished data directly from some authors, and updated a meta-analysis. We used the Swedish Multigeneration Register to investigate the age to which the reduced overall risk of childhood cancer (observed previously using that Swedish dataset and in this and earlier meta-analyses) persisted into the teenage/young adult years, and which specific tumors accounted for the overall risk reduction beyond childhood. Our meta-analysis of studies of aggregate childhood cancer risk in twins confirmed their approximate 15% reduction in cancer mortality and incidence. Further analysis of Swedish Multigeneration Register data for 1958 to 2002 suggested these reduced risks of cancer (particularly leukaemias and renal tumors) extended from childhood to young adult ages. Reduced risks of these and some other specific tumor types occurring across childhood/teenage/young adult years appeared to account for most of the overall risk reduction. Our results suggest a persistent reduction of overall childhood cancer risk in twins and that this extends into young adulthood. Risk reductions for several specific tumors might account for this and, although there are several potential explanations, intrauterine growth patterns of twins might be a major contributor.

Keywords: Twins; Cancer risk reduction; Children; Teenagers/young adults

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Lifetime cancer incidence in individuals born as twins is similar to that of singletons (Chen et al., 2016; Hemminki & Chen, 2005). However, the risk of breast, testicular and some other adult cancers, and of childhood leukaemia for any member of a twin pair is substantially increased if their co-twin is diagnosed with the same cancer (Couto et al., 2005; Lichtenstein et al., 2000; Swerdlow et al., 1997). Further, twins experience significantly fewer childhood cancers (<15 years of age) compared to singletons though it is not clear why or which specific tumors contribute to this reduced risk (Murphy et al., 2008; Murphy et al., 2001; Puumala et al., 2009).

The cancer burden in childhood is very different from that in adulthood, though there is some evidence of increased overall adult cancer risk in the families of children diagnosed with any childhood cancer (Neale et al., 2013). The tumors occurring at teenage/young adult (TYA) ages show an intermediate pattern, with a mix of those typical of childhood, (though some rise to a peak incidence in young adulthood) with an increasing proportion of those typical of adulthood such as melanomas and carcinomas (Murphy et al., 2013). Because of this transitional tumor profile between childhood and adulthood, we first aimed to clarify the risk of childhood cancer in twins in an updated meta-analysis, and then used the Swedish Multigeneration Register to explore the older ages to which this reduced overall tumor risk persists beyond childhood. We examined the contributions made by specific tumors to the overall cancer risk reduction in the childhood/teenage/young adult (CTYA) age group.

Materials and Methods

Literature Search

We systematically searched Medline and Embase for studies about childhood cancer risk in twins published in English. We conducted a literature search in October 2016 and updated it in March 2020,

with a strategy modified particularly to capture known publications potentially containing data allowing calculation of total cancer risk among the increasing numbers of twins conceived after use of assisted reproductive technology (ART). We conducted further modified searches in 2021 and again, finally in November 2023, exploding the Search terms to capture all studies that we knew to be identified as potentially relevant. The Search strategies are described in the Supplement (which is available on the CUP website). From the principal searches conducted to 2021, we retrieved abstracts of 528 publication, and after deduplication we had 367 records for inspection by two of the authors (MM, RR). In the final 2023 search, we identified no publications containing directly relevant data of which we were previously unaware. All relevant studies already known to us were captured by the searches, apart from one publication which did not directly provide a childhood cancer risk estimate among twins (Pinborg et al., 2004) that we had previously identified.

Meta-Analysis

Building on earlier meta-analyses (Inskip et al., 1991; Murphy, 1995; Murphy et al., 2001), we identified four more recent studies about childhood cancer risk in twins versus singletons or the general population of births that contributed relevant data (Murphy et al., 2008; Neale et al., 2005; Pinborg et al., 2004; Puumala et al., 2009). Some of the early studies examined cancer mortality as a measure of childhood cancer risk. Our updated meta-analysis was of incidence only, but of the four more recent studies we identified, risks in two (Pinborg et al., 2004; Puumala et al., 2009) could only be estimated by odds ratios (*OR*s) rather than rate/risk ratios (*RR*s). One study (Pinborg et al., 2004) was entirely of births following use of ART, where no cancers were observed among the twins against an expected number of about six ($p = .014$). To include their data in our meta-analysis, we calculated a 'Peto Odds Ratio' rather than using a continuity correction method (Bradburn et al., 2007; Higgins & Green, 2011; Sweeting et al., 2004). In the published data from the other (case-control) study, only *OR*s adjusted for several variables, including birth weight, were presented as the risk estimates (Puumala et al., 2009). We therefore obtained from the authors directly the unpublished, unadjusted (matching factors only) *OR*s. Of the studies identified with relevant data, only one was excluded from our meta-analysis, because of both its size and quality. The published results in this incident case-control study permit calculation of an approximate, all cancer *OR* (95% CI) for being a twin of 1.3 (0.4-4.5) based on only six exposed cases (Savitz & Ananth, 1994). Its inclusion in our analysis makes no difference to our effect estimate. Our meta-analysis was implemented in STATA 13.

Swedish Multigeneration Register and Cancer Incidence Linkage: Cohort Analysis

Statistics Sweden maintains the Multigeneration Register, in which individuals born in Sweden in 1932 and later are registered with their birth parents and organized as families (Hemminki et al., 2001). Information on the database is available at the Nature Genetics website as 'Supplementary information' (Hemminki & Granstrom, 2002). The data on families and cancers have complete coverage, barring some groups of deceased offspring born in the 1930s who died before 1991. Although this small group of offspring with missing links to parents has a negligible effect on risk estimates (Hemminki & Li, 2003), the present report was limited to offspring whose parents were known, to eliminate possibility of

bias. The data were linked using the individually unique national registration number to the Swedish Cancer Registry for the years 1958 to 2002. Cancer registration has been considered to be close to 100% for a long time (Hemminki & Chen, 2005). Twins were defined as children born to the same mother at the same time. Triplets and quadruplets were excluded from the analysis. Use of the data as described here was previously approved by the Ethical Board of the Karolinska Institute.

The Swedish Cancer Registry classifies site of cancer using a 4-digit diagnostic code according to the 7th revision of the International Classification of Diseases (ICD-7; World Health Organization, 1955). This is an imperfect classification system for CTYA cancers. We are therefore mainly constrained to report site-specific cancer risks, rather than categorizing tumors by tissue type. Cancer risks for twins were estimated using standardized incidence ratios (SIRs). The SIR is the ratio of the observed (O) to the expected (E) number of cases. No correction for multiple testing of the SIR measuring different tumor risks was applied. Reference cancer incidence rates for calculating expected numbers were those applying to the much larger number of singletons, using standardization by 5-year age, sex, 10-year period, and area (county) standardized rates. 95% CIs were calculated assuming a Poisson distribution (dos Santos Silva, 1999; Estève et al., 1994). Follow-up was started for each individual at birth or at immigration after January 1, 1958, whichever was the later. Follow-up was terminated on diagnosis of first cancer, death, emigration or the closing date of the study, December 31, 2002. This cohort study was analyzed using SAS 9.2.

Results

Table 1 references the earlier meta-analyses (Inskip et al., 1991; Murphy, 1995; Murphy et al., 2001) and provides some details about each of the 10 studies we identified from 11 publications, from which we were able to extract analysable results about childhood cancer risk in twins versus singletons or the general population of births (Hewitt et al., 1966; Inskip et al., 1991; Jackson et al., 1969; Murphy, 1995; Murphy et al., 2008; Murphy et al., 2001; Neale et al., 2005; Norris & Jackson, 1970; Pinborg et al., 2004; Puumala et al., 2009; Rodvall et al., 1992; Windham et al., 1985). The summary estimate of relative cancer mortality risk in the older publications that examined this outcome (Hewitt et al., 1966; Jackson et al., 1969; Norris & Jackson, 1970; Rodvall et al., 1992) is 0.85 (95% CI [0.74, 0.95]) (Murphy et al., 2001).

Figure 1 displays the results of each of the seven non-overlapping studies of childhood cancer incidence shown in Table 1. One study (Rodvall et al., 1992) presented results about both Swedish cancer mortality and cancer incidence. Their incidence data were excluded because they were entirely contained within another Swedish study we did include (Murphy et al., 2008). For one study (Pinborg et al., 2004), we calculated a 'Peto Odds Ratio' *OR* 0.19 (95% CI [0.05, 0.72]). The continuity corrected estimate based on the same data was *OR* 0.08 (95% CI [0.004, 1.37]). There is little heterogeneity between the seven studies and the summary risk estimate from a random effects analysis was *OR* 0.83 (95% CI [0.72, 0.94]). Excluding the extreme *OR* we calculated for the Danish ART study (Pinborg et al., 2004) made little difference to the random effects risk estimate *OR* 0.86 (95% CI [0.79, 0.94]).The risk estimate from a fixed effects analysis of the seven studies was also very similar *OR* 0.86 (95% CI [0.78, 0.93]).

Although not shown in Figure 1, an additional estimate of risk in a cohort of twins conceived with ART has become available. By

Table 1. Cancer occurrence in twins versus single births or the general population of children (modified from Inskip et al., 1991; Murphy, 1995; Murphy et al., 2001)

Studies	Outcomes	Year of birth	Cancer risks as O/E underlying the SIRs depicted in Figure 1, and/or as ORs with 95% CI		
			Total cancer	Leukaemia	All other cancers
UK (Hewitt et al., 1966)	Mortality	1943−63	121/152[a]	−	−
USA California (Jackson et al., 1969; Norris & Jackson, 1970)	Mortality	1940−64	100/111	48/52	52/59.3
Norway (Windham et al., 1985)	Incidence	1967−79	14/15.6[b]	4/5.7[b]	10/9.9[b]
USA Connecticut (Inskip et al., 1991)	Incidence	1930−69	31/46.4	13/15.6	18/30.8
Sweden (Rodvall et al., 1992)	Incidence	1952−67	59/61.7	17/18.1	42/43.6
	Mortality		41/45.6	19/21.6	22/24
UK ORLS (Murphy et al., 2001)	Incidence	1963−89	15/18.9	3/6.4	12/12.5
USA Utah (Neale et al., 2005)	Incidence	1934−2000	33/40.2[c]	16/14	17/26.2
Sweden (Murphy et al., 2008)	Incidence	1932−2002	166/204.9[d]	55/65.5	111/139.4
Denmark (Pinborg et al., 2004)	Incidence	1995−2000	0/6 and OR = 0.19 (0.05-0.72)[e]		
USA (5 states) (Puumala et al., 2009)	Incidence	1970−2004	0.93 (0.82, 1.05)[f]	0.95 (0.49, 1.86)	0.93 (0.82, 1.05)

Note: O, observed; E, expected; SIRs, standardized incidence ratios; ORL, Oxford Record Linkage Study.
[a]Expected number of cancers adjusted upward to account for twins' greater frequency of exposure to prenatal X-rays in Hewitt et al. (1966);
[b]Expected number of cancers estimated from relative risk and observed number of cancers for Windham et al. (1985);
[c]Expected numbers of cancers estimated from adjusted relative risk and observed number of cancers for Neale et al. (2005; leukemia = hematopoietic);
[d]Expected number of cancers estimated from adjusted SIR and observed number of cancers for Murphy et al. (2008);
[e]Expected number of cancers estimated for twins from the cancer rate for singletons assuming same average follow-up time from birth in this pure IVF/ICSI cohort. OR calculated by 'Peto Method for rare events';
[f]Population-based record-linkage case-control study. Unpublished, unadjusted (matching factors only) ORs with twinning as exposure in babies weighing < or = 4000 g at birth obtained from the authors.
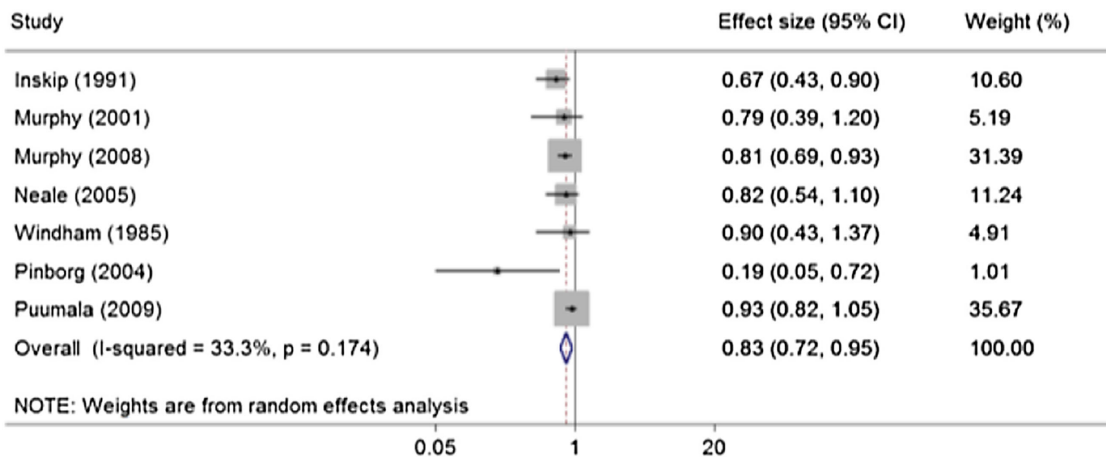

Figure 1. Meta-analysis of seven studies of childhood cancer incidence in twins.

comparison with national childhood cancer rates, an SIR (95% CI) of 0.95 (0.68, 1.30) was published for this cohort of ART births studied across Great Britain (Williams et al., 2013). Its inclusion in the meta-analysis makes little difference to the result, with the random effects estimate becoming 0.84 (0.75, 0.95).

Table 2 shows the all-cancer SIR (95% CI) for all twins, all like-sex pairs (male-male [MM] or female-female [FF]) and all unlike-sex pairs (male-female [MF]), together with the numbers of affected twins on which the SIRs are based, for the nested age groups to attained age 34 years. SIR was low among all twins until about 30 years attained age, with both like- and unlike-sex pairs contributing to the reduction. Age-band specific risks for all twins from age 15−19 to age 30−34 are not included in the

table but were estimated by subtracting the O and the E between the nested age groups shown, which for all twins showed a steady increase in all-cancer SIRs in the four age-groups (0.85; 0.94; 1.04; 1.09) across the age range, but none were significantly raised or lowered.

The aggregate reduced risk to age 30 years is based on nearly 3 times the number of observed cancers compared to the childhood risk at age 0–14 years. Concordance increased from four pairs in childhood (affected by hematopoietic tumors only) to seven pairs by age 30 years (five haematopoietic, one central nervous system, one breast) together with a further pair of testicular cancer cases where one concordant twin pair member was diagnosed above age 30 years.

Table 2. Total cancer risk in Swedish twins by age group

Age group (years)	All twins			Like-sex (MM/FF) pairs			Unlike-sex (MF) pairs		
	n	SIR	95% CI	n	SIR	95% CI	n	SIR	95% CI
0−14	166	0.81	(0.69, 0.94)	111	0.77	(0.64, 0.93)	55	0.90	(0.67, 1.73)
0−19	228	0.82	(0.72, 0.94)	156	0.81	(0.69, 0.94)	72	0.86	(0.67, 1.08)
0−24	316	0.85	(0.76, 0.94)	223	0.87	(0.76, 0.99)	93	0.80	(0.65, 0.98)
0−29	457	0.90	(0.82, 0.98)	313	0.90	(0.81, 1.01)	144	0.88	(0.74, 1.04)
0−34	659	0.95	(0.88, 1.03)	445	0.96	(0.87, 1.05)	214	0.94	(0.81, 1.07)

Table 3 indicates for the age group 0–29 years (beyond which attained age the all-twin SIR rapidly approaches 1 and becomes non-significant) greater detail of the contribution made to the reduced overall cancer incidence by the range of specific sites/types provided by the Swedish Cancer Registry, and by sex combination of twin pairs. A variety of sites/types contribute, notably with a marginally significant risk reduction for leukemias in all twins (significantly so in all like-sex twins, particularly MM) and a significant reduction for renal tumors (five Wilms, one other renal) in all twins, particularly among all like-sex twins. A reduced risk for connective tissue tumors, in all twins and again particularly in all like-sex twins, is also observed.

Discussion

Our updated meta-analysis of childhood cancer in twins confirms both their aggregate cancer mortality and incidence risk reduction of about 15% compared to singletons. It extends to young adult ages more detailed analyses of the Swedish Multigeneration Register/Cancer Registry data, using which we have previously demonstrated a reduced childhood cancer risk that was included in our updated meta-analysis (Murphy et al., 2008). The lifetime risk of cancer in twins has been found to be otherwise unremarkable compared to singletons in the same dataset (Chen et al., 2016; Hemminki & Chen, 2005). Our results demonstrate a reduced aggregate cancer risk to ~30 years of age, contributed by several specific cancer sites. Some of these tumor types contributed to the significant reduction in aggregate childhood cancer risk seen previously. The numbers observed in childhood sometimes constitute the majority of those observed at age 0–29; for example, renal tumors. Nevertheless, the reduced risk is extended in the 0–29 age grouping to tumor types (e.g., connective tissue tumors) similar to those for which significant protection was not observed when considering childhood risks alone, albeit based on very small numbers in childhood and much more substantial numbers by age 30 years.

How far the reduced childhood cancer risk observed in twins extends into the TYA age group has not previously been examined. There are 3 times as many observed cancers on which to base risk estimates to age 30 years, compared to childhood occurrence only, which can lead to narrower confidence intervals around risk estimates. Some tumors occur frequently in both childhood and young adulthood and some do not, with increasing numbers of carcinomas represented in the older age groups. Testicular cancer risk in Swedish twins was (non-significantly) raised in childhood (Murphy et al., 2008), and is barely so here though two overlapping previous Swedish studies of testicular cancer (Braun et al., 1995; Hemminki & Chen, 2006) found it to be raised, one significantly so. These studies included cases to older ages than TYA.

A meta-analysis also suggests risk of testicular cancer in twins is truly raised across the entire age range in which males are potentially affected (Neale et al., 2008). This might incriminate the hormonal influences found in a twin pregnancy. Risks of different types of testicular cancer have been related to both extremes of birth weight (high and low) and individual members of twin pairs are generally of lower average birthweight than singletons (Michos et al., 2007), so it is uncertain how intrauterine growth relates to risk of testicular tumors.

Early explanations to account for the childhood cancer deficit in twins, despite a greater frequency of exposure to X-rays in utero, included the low birth weight distribution of twins and/or selective early mortality of twin fetuses or infants who would otherwise have developed a clinical cancer (Inskip et al.; 1991; Wakeford & Bithell, 2021). The prenatal environment of twins and singletons does clearly differ. The proportion of twin pregnancies arising from subfertility treatment in the parents is much greater than for singletons (Monden et al., 2021). Twin pregnancies are also more likely to be complicated by conditions such as pre-eclampsia, gestational diabetes, and hyperemesis. But none of these factors are yet convincingly related to childhood cancer risk, though they may all exert effects on in utero growth patterns.

Like-sex (particularly MM) twin pairs are generally under-represented among childhood cancer cases, which might result from selective elimination in utero, infancy or childhood of (one or both) cancer prone twins (Inskip et al., 1991). A recent study has provided some indirect support for this hypothesis (Bruckner et al., 2021). The starting point for considering selective loss in pregnancy is the primary (conception) sex ratio. Some have reported the number of males and females is usually equal at this time, but others disagree, and it is uncertain whether intrauterine loss is always greater for one than the other throughout the trimesters of pregnancy (James & Grech, 2020; Orzack et al., 2015). However, the secondary (birth) sex ratio almost always favors males in both singletons and twins. Although many twin pairs 'vanish' in utero, in natural as well as ART conceptions (at least in MM and FF pairs), the sex ratio at birth is lower than for singletons but still favors males (Chen et al., 2017; James & Grech, 2020; Orzack et al., 2015). Although stillbirth rates have been falling for a long time and contribute little numerically to the overall sex ratio at birth, there remains a male excess at stillbirth registration, which has been even higher in the past than now (Shaw, 1989). Thus, considering birth registration data for England and Wales, among nearly 180,000 twin pairs born over the period 1993–2011, 4450 twin pairs included at least one stillbirth. Their average livebirth sex ratio was about 1.01 and the stillbirth ratio about 1.1. In about 3% of MM pairs there was at least one stillbirth, in FF about 2.7%, but among unlike-sex pairs stillbirth occurrence was about 1% for both males and females. Over the same 19-year period, among

Table 3. Cancer occurrence in Swedish twins aged 0–29 years

Site	All twins				All like-sex twins				MM twin pairs				FF twin pairs			
	E	O	SIR	95% CI	E	O	SIR	95% CI	E	O	SIR	95% CI	E	O	SIR	95% CI
Upper aero-digestive tract	4.8	6	1.25	0.45, 2.74	3.2	3	0.93	0.17, 2.75	1.8	3	1.69	0.32, 5	1.5	0		
Salivary gland	2.9	1	0.35	0, 2	1.9	1	0.53	0, 3.04	0.7	0			1.1	1	0.88	0, 5.03
Stomach	1.4	2	1.47	0.14, 5.42	0.9	1	1.1	0, 6.28	0.4	0			0.5	1	1.9	0, 10.87
Colorectum	16.9	18	1.06	0.63, 1.68	11.3	11	0.98	0.49, 1.75	4.4	5	1.14	0.36, 2.68	6.9	6	0.87	0.31, 1.91
Liver	4.2	3	0.71	0.13, 2.11	3	3	1.01	0.19, 3	1.6	1	0.61	0, 3.52	1.3	2	1.5	0.14, 5.52
Nose	0.6	2	3.2	0.3, 11.77	0.4	1	2.37	0, 13.59	0.3	0			0.1	1	8.53	0, 48.91
Lung	2.7	2	0.74	0.07, 2.74	1.8	2	1.1	0.1, 4.04	0.9	0			0.9	2	2.26	0.21, 8.32
Breast	9.1	14	1.54	0.84, 2.59	6	9	1.51	0.68, 2.88	0	0			5.9	9	1.52	0.69, 2.9
Cervix	19	22	1.16	0.72, 1.75	12.3	12	0.97	0.5, 1.71	0	0			12.3	12	0.97	0.5, 1.71
Other uterus	1.4	2	1.43	0.14, 5.27	0.9	2	2.22	0.21, 8.18	0	0			0.9	2	2.22	0.21, 8.18
Ovary	13.8	8	0.58	0.25, 1.15	9	3	**0.33**	**0.06, 0.98**	0	0			9	3	**0.33**	**0.06, 0.98**
Testis	35.7	39	1.09	0.78, 1.5	23.8	26	1.09	0.71, 1.6	23.8	26	1.09	0.71, 1.6	0	0		
Kidney	14.2	6	**0.42**	**0.15, 0.92**	9.8	3	**0.31**	**0.06, 0.91**	4.6	1	0.22	0, 1.25	5.2	2	0.39	0.04, 1.42
Urinary bladder	4.2	8	1.91	0.82, 3.78	2.7	5	1.82	0.57, 4.28	1.8	2	1.09	0.1, 4.02	0.9	3	3.26	0.61, 9.64
Melanoma	37.7	38	1.01	0.71, 1.39	24.9	23	0.92	0.58, 1.39	8.7	8	0.92	0.39, 1.82	16.2	15	0.92	0.52, 1.53
Skin	4.5	4	0.88	0.23, 2.28	3	3	0.99	0.19, 2.93	1.8	1	0.57	0, 3.25	1.3	2	1.58	0.15, 5.81
Eye	10	8	0.8	0.34, 1.58	6.8	5	0.73	0.23, 1.72	3.4	2	0.59	0.06, 2.18	3.5	3	0.87	0.16, 2.56
Nervous system	103	105	1.02	0.83, 1.23	71.2	83	1.17	0.93, 1.45	38.5	43	1.12	0.81, 1.5	32.7	40	1.22	0.87, 1.67
Thyroid gland	17.9	10	0.56	0.27, 1.03	11.7	7	0.6	0.24, 1.24	2.6	4	1.55	0.4, 4.01	9.1	3	**0.33**	**0.06, 0.97**
Endocrine glands (other)	17.5	18	1.03	0.61, 1.63	11.7	16	1.37	0.78, 2.23	5	6	1.2	0.43, 2.62	6.7	10	1.5	0.72, 2.77
Bone	20.3	17	0.84	0.49, 1.35	14	9	0.64	0.29, 1.23	8.3	8	0.96	0.41, 1.91	5.7	1	0.18	0, 1.01
Connective tissue	16.5	8	**0.49**	**0.21, 0.96**	11.3	4	**0.35**	**0.09, 0.92**	5.5	1	0.18	0, 1.03	5.7	3	0.52	0.1, 1.55
Non-Hodgkin lymphoma	28.5	21	0.74	0.46, 1.13	19.7	18	0.91	0.54, 1.44	13.5	15	1.11	0.62, 1.84	6.2	3	0.48	0.09, 1.42
Hodgkin lymphoma	32.3	26	0.8	0.52, 1.18	21.7	21	0.97	0.6, 1.48	11.8	13	1.1	0.58, 1.89	9.9	8	0.81	0.35, 1.6
Leukemia	86.7	69	0.8	0.62, 1.01	61.1	42	**0.69**	**0.5, 0.93**	34.6	20	**0.6**	**0.35, 0.9**	26.5	22	0.83	0.52, 1.26
All tumors	510	457	**0.9**	**0.82, 0.98**	347	313	0.9	0.81, 1.01	175	159	0.91	0.77, 1.06	172	154	0.9	0.76, 1.05

Site	All unlike-sex (MF) twin pairs				Males in MF twin pairs				Females in MF twin pairs			
	E	O	SIR	95% CI	E	O	SIR	95% CI	E	O	SIR	95% CI
Upper aero-digestive tract	1.6	3	1.93	0.36, 5.71	0.9	2	2.34	0.22, 8.61	0.7	1	1.43	0, 8.17
Salivary gland	1	0			0.4	0			0.6	0		
Stomach	0.4	1	2.25	0, 12.92	0.2	0			0.3	1	3.76	0, 21.58
Colorectum	5.7	7	1.23	0.49, 2.55	2.2	4	1.83	0.48, 4.73	3.5	3	0.86	0.16, 2.53

Site	E	O	SIR	95% CI	E	O	SIR	95% CI	E	O	SIR	95% CI
Liver	1.3	0			0.7	0			0.6	0		
Nose	0.2	1	4.92	0, 28.22	0.1	0			0.1	1	18.7	0.01, 107.02
Lung	0.9	0			0.4	0			0.4	0		
Breast	3.1	5	1.6	0.5, 3.76	0	0			3.1	5	1.61	0.51, 3.79
Cervix	6.7	10	1.5	0.71, 2.76	0	0			6.7	10	1.5	0.71, 2.76
Other uterus	0.5	0			0	0			0.5	0		
Ovary	4.8	5	1.05	0.33, 2.47	0	0			4.8	5	1.05	0.33, 2.47
Testis	11.9	13	1.1	0.58, 1.88	12	13	1.1	0.58, 1.88	0	0		
Kidney	4.5	3	0.67	0.13, 1.99	2	2	0.98	0.09, 3.61	2.4	1	0.41	0, 2.37
Urinary bladder	1.4	3	2.09	0.39, 6.18	1	2	2.09	0.2, 7.67	0.5	1	2.09	0, 11.99
Melanoma	12.8	15	1.18	0.66, 1.94	4.3	4	0.92	0.24, 2.39	8.4	11	1.3	0.65, 2.34
Skin	1.5	1	0.67	0, 3.81	0.9	1	1.17	0, 6.72	0.7	0		
Eye	3.2	3	0.94	0.18, 2.78	1.5	2	1.3	0.12, 4.77	1.7	1	0.6	0, 3.46
Nervous system	32.2	22	0.68	0.43, 1.04	17	13	0.76	0.41, 1.31	15	9	0.59	0.27, 1.13
Thyroid gland	6.2	3	0.48	0.09, 1.44	1.3	3	2.25	0.42, 6.65	4.9	0		
Endocrine glands (other)	5.9	2	0.34	0.03, 1.26	2.4	1	0.41	0, 2.37	3.4	1	0.29	0, 1.67
Bone	6.3	8	1.27	0.54, 2.51	3.7	4	1.09	0.28, 2.81	2.6	4	1.52	0.4, 3.94
Connective tissue	5.2	4	0.77	0.2, 1.98	2.5	1	0.4	0, 2.31	2.7	3	1.1	0.21, 3.25
Non-Hodgkin lymphoma	8.8	3	0.34	0.06, 1.01	5.9	1	**0.17**	**0, 0.97**	2.9	2	0.7	0.07, 2.56
Hodgkin lymphoma	10.6	5	0.47	0.15, 1.11	5.7	0			4.9	5	1.02	0.32, 2.41
Leukemia	25.6	27	1.06	0.69, 1.54	14	13	0.93	0.49, 1.59	12	14	1.21	0.66, 2.04
All tumors	163	144	0.88	0.74, 1.04	80	66	0.83	0.64, 1.06	84	78	0.93	0.74, 1.16

Note: O, observed; E, expected, SIR, standardized incidence ratio; MM, male-male; FF, female-female; MF, male-female. Results are not shown for nine sites (esophagus, small intestine, anus, pancreas, endometrium, other female genitals, prostate, other male genitals, and myeloma) because the observed number of cases was zero in each case. SIRs whose 95% CI does not include 1 are highlighted by bold font.

nearly 12.5 million livebirths there were nearly 75,000 deaths before age 18 years. Low birth weight, being male and a member of a multiple birth were among the factors separately influencing death rates (Watkins et al., 2016). So the potential for selective loss of males throughout the period from birth is clear. It has been suggested that one way to begin to unpick the influence of selective elimination of cancer-prone individuals as a contributor to the reduced cancer risk in twins versus singletons, is to conduct a competing-risks analysis. We believe such a study would need to involve a large historical cohort followed to adulthood, encompassing all births and vital events of interest probably through nationwide record-linkage with causes of stillbirth/death recorded, but also information on a number of potential confounding factors such as subfertility (treatment) and other baby/parental characteristics. Such an analysis is beyond the scope of the present study.

Selective elimination as a potential contributing explanation may also be compatible with the other main hypothesis to explain childhood cancer risk reduction, namely the in utero growth pattern of twins. Males on average weigh more than females at all gestational ages, whether born as singletons or (probably) as members of a like- or unlike-sex twin pair (McKeown & Record, 1952). Although this is generally considered to be due to the effects of androgens on in utero growth, in twins this is complicated by effects of sex-combination of the pair, zygosity, and chorionicity, which may all affect growth velocity and birth weight (discordance) of the pair (Derom et al., 2005; González-Quintero et al., 2003; Jelenkovic et al., 2018; Luke et al., 2005). All twins normally have restricted in utero growth (velocity) compared to singletons from about 30 weeks gestation, and consequently a lower average birthweight per baby of 1000 grams compared to singletons (McKeown & Record., 1952). The in utero growth of twins, and any restriction thereof, may be conditioned by a different balance of factors from those operating in singleton pregnancies (Hall, 2003), but the genetic (if not epigenetic) control of in utero growth in twins and singletons is similar (Beck et al., 2021; van Dongen et al., 2021).

Many studies have demonstrated an association of intrauterine growth and higher birth weight with increased risks of many childhood cancers, and often have included twin birth weights in their analyses (O'Neill et al., 2015), though some studies have been restricted to singleton births (Paltiel et al., 2019; Paltiel et al., 2015). One of the largest international studies of birth weight and childhood cancer risks included twins and demonstrated a 15% change in the aggregate cancer risk for each 1000 g change in birth weight, very comparable to the reduction in childhood cancer risk observed here in our meta-analysis of twins (O'Neill et al., 2015). One USA study (Puumala et al., 2009), which also examined higher multiples, did not find evidence that birth weight accounted for the reduced risk of aggregate childhood cancer seen in twins. Nevertheless, childhood leukemia, renal tumors, and soft tissue sarcomas were among the tumors most strongly related to birth weight in the large international study mentioned above (O'Neill et al., 2015). Although the tumor classification systems used in that study and used here are not identical, similar tumor types appear to be among those for which low birth weight is associated with reduced cancer risk in childhood, and for which a CTYA risk reduction is most evident here in twins, supporting the idea that intrauterine growth-related mechanisms underpin the risk reduction observed.

There has been a steadily increasing number of twins born worldwide following treatment for subfertility, particularly with use of ART since the 1980s (Monden et al., 2021). Most of the new information we acquire from now on about CTYA cancer risks in twins and higher multiple births will derive from deliveries following ART. Medical conditions underlying the use of ART for subfertility, and the various forms of ART may affect the birthweight of the offspring differently, at least in singletons (Purkayastha et al., 2021), but subfertility treatments, including different types of ART, are not clearly associated in meta-analyses with increased CTYA cancer risk among singletons or multiple births (Zhang et al., 2020). In fact, the limited published evidence available suggests twins conceived using ART may experience the same kind of childhood cancer risk reduction compared to singletons as natural conceptions (Pinborg et al., 2004). CTYA cancer risk was not importantly altered after maternal ART in the reports from three major studies, though with predominantly childhood cancer outcomes measured (Spector et al., 2019; Sundh et al., 2014; Williams et al., 2018; Williams et al., 2013). These three studies (in four Nordic countries, the UK and the US) included 622 childhood cancer cases among nearly 280,000 singleton babies and 210,000 born as part of a multiple birth following IVF/ART, but did not report the twin/singleton risk contrast directly. Three other ART studies around the same time (Hargreave et al., 2019; Reigstad et al., 2016; Spaan et al., 2019) reported similarly, though the Dutch study (Spaan et al., 2019) included a simple, age-adjusted relative hazard (of 0.99) among children and teenagers combined, for all multiples versus singletons, in its Supplementary tables. An updated report from that group allows calculation of an unadjusted, all cancer risk ratio (95% CI) among all multiples versus singletons up to age 18 years of 0.85 (0.66, 1.08; Spaan et al., 2023). Similarly, a recent study from the US (Luke et al., 2022), related to the earlier cited study (Spector et al., 2019), did report a heavily adjusted (not crude) childhood cancer risk for twins versus singletons (of 0.97), though the adjusted model did not include birth weight/gestation. Although a recent Taiwanese study (Weng et al., 2022) examined intrauterine growth as a confounder for the increased childhood cancer risks they observed following ART conception, the multiple/singleton risk contrast was not presented, nor was it in a further Nordic ART study of CTYA cancer (Sargisian et al., 2022). Added to the large numbers contained in the earlier ART reports, these more recent studies combined could contribute data about CTYA cancer cases among about a further 100,000 multiple births, which might allow meaningful stratification of risk between twins and higher multiples separately and help to clarify causal pathways. Additional historical and contemporary data could also come from the NORCAN twin/cancer record-linkage studies (Skytthe et al., 2019), whose results already corroborate studies using Swedish data alone about the lifetime cancer risks in twins (Chen et al., 2016; Hemminki & Chen, 2005), but which have not yet reported the twin/singleton risk contrast for CTYA cancers separately. In one of these (Skytthe et al., 2019) significant risk reductions for a few cancer sites including kidney were noted, and in another study there was also a tendency towards the same reduction (Chen et al., 2016). This corresponds with what we observed at much younger ages, though the nature of the kidney cancers incriminated may not be the same.

Our study has both strengths and some limitations. We believe our iterative literature searches captured every study with relevant published data and our updated meta-analysis includes information from all those studies. However, the mortality studies (from a time when childhood cancer mortality approximated incidence), although coherent, are very old, and there have been no new publications containing extractable twin childhood cancer incidence risks since 2013. Nevertheless, the summary mortality and

incidence estimates agree very closely and the more numerous incidence data are not heterogeneous. Both random and fixed effects summary incidence estimates agree closely and sensitivity analyses suggest the results are robust. There are almost no recent published studies of the risk of childhood cancer in twins versus singletons conceived following subfertility treatment. Whether the findings from Denmark from a pure ART cohort (Pinborg et al., 2004) will be sustained is uncertain, but is under investigation. Although no recent study has ever reported an increased risk of childhood cancer in twins versus singletons, we must consider our findings about the extension of risk reduction from childhood to young adulthood, the particular tumors that contribute to this aggregate risk reduction, and any possible influence of subfertility treatment on this risk as provisional.

In conclusion, we believe our analyses of both overall and specific cancer risks in twins contribute to understanding the important overlaps between childhood and TYA tumor risk factors. They point towards the importance of prenatal factors in the determination of risk for both age groups. Further work on both childhood and TYA cancers is needed to understand these risk factors.

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