Risk of Cancer in Children Conceived by Assisted Reproductive Technology

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abstract

BACKGROUND AND OBJECTIVE: An increasing number of children are born after assisted reproductive technology (ART), and monitoring their long-term health effects is of interest. This study compares cancer risk in children conceived by ART to that in children conceived without.

METHODS: The Medical Birth Registry of Norway contains individual information on all children born in Norway (including information of ART conceptions). All children born between 1984 and 2011 constituted the study cohort, and cancer data were obtained from the Cancer Registry of Norway. Follow-up started at date of birth and ended on the date of the first cancer diagnosis, death, emigration, or December 31, 2011. A Cox proportional hazards model was used to calculate hazard ratios (HR) and 95% confidence intervals (CI) of overall cancer risk between children conceived by ART and those not. Cancer risk was also assessed separately for all childhood cancer types.

RESULTS: The study cohort comprised 1 628 658 children, of which 25 782 were conceived by ART. Of the total 4554 cancers, 51 occurred in ART-conceived children. Risk of overall cancer was not significantly elevated (HR 1.21; 95% CI 0.90–1.63). However, increased risk of leukemia was observed for children conceived by ART compared with those who were not (HR 1.67; 95% CI 1.02–2.73). Elevated risk of Hodgkin's lymphoma was also found for ART-conceived children (HR 3.63; 95% CI 1.12–11.72), although this was based on small numbers.

CONCLUSIONS: This population-based cohort study found elevated risks of leukemia and Hodgkin's lymphoma in children conceived by ART.

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WHAT'S KNOWN ON THIS SUBJECT: Several epidemiologic studies concerning fertility treatment and childhood cancer have found no increase in overall cancer risk. However, some studies report elevated risks for individual cancer types, especially for hematologic cancers.

WHAT THIS STUDY ADDS: The current study found elevated risks of leukemia in assisted reproductive technology (ART)-conceived children. It contributes data to the existing knowledge on cancer risk in ART offspring, by using a large, complete, nationwide cohort of >25 000 children conceived by ART.

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More than 5 million children worldwide have been conceived by assisted reproductive technology (ART),¹ and as these children advance into adulthood, monitoring their long-term health effects is important. Several studies have shown that children conceived by ART have increased risks of perinatal complications,² congenital malformations,^{3–6} and somatic morbidity.⁷

Initial case reports of cancer risk in children born after ART concerned hepatoblastomas,⁸ neuroectodermal tumors,⁹ and malignant lymphomas.¹⁰ It was hypothesized that development of these tumors was influenced by factors related to conception or pregnancy because they are embryonic in type and appear early in life.^{11,12} In addition, children conceived by ART may have an increased incidence of imprinting disorders,^{13,14} some of which also are associated with elevated cancer risks.

Several epidemiologic studies concerning fertility treatment and cancer in the offspring have also been conducted, but only 2 have been nationwide and population-based.^{15,16} A recent meta-analysis, including the first of the 2 studies and several other smaller investigations, found an elevated risk of cancer overall as well as increased risks of several specific cancer types in children conceived by ART,¹⁷ in line with other studies reporting elevated risks of overall cancer.^{15,16} Specifically, some researchers have found increased risks of leukemia,^{16,18,19} central nervous system (CNS) tumors,²⁰ hepatoblastomas,²¹ retinoblastomas,²² and neuroblastomas.²³ On the other hand, many studies fail to detect an association between ART treatment and childhood cancer risk.^{24–27} Because childhood cancer is rare, many of the mentioned studies are restricted by few cancer cases. Furthermore, because the use of

ART is increasing, many studies are limited by short follow-up time because the majority of children conceived by ART have been born in recent years.

The aim of the current study was to compare cancer risk in children conceived by ART to those conceived without ART, by using a cohort comprising all children born in Norway between 1984 and 2011. The study assessed risk of overall cancer and of specific types of childhood cancer as classified by the *International Classification of Childhood Cancer (ICCC)*, including leukemias and myeloproliferative diseases, lymphomas, CNS neoplasms, neuroblastomas, retinoblastomas, renal tumors, hepatic tumors, malignant bone tumors, soft tissue tumors, and germ cell tumors.

METHODS

Study Subjects

The study included all children born in Norway between January 1, 1984, and December 31, 2011. This time period was chosen because 1984 was the first year a child was born after conception by ART in Norway. Cancer risk during childhood and adolescence in ART-conceived individuals was compared with the risk in those conceived without ART.

Setting

Data on all study subjects were extracted from the Medical Birth Registry of Norway (MBRN). As mandated by Norwegian Legislation, all deliveries in Norway have been registered in the MBRN since 1967, and it comprises information on parental demographics, maternal pregnancy and health, the delivery and postpartum period, and infant perinatal health. As of 1984, all pregnancies initiated by ART have been registered in the MBRN, and by 1988, this registration also became mandatory by Norwegian Legislation.

A unique 11-digit personal identification number (PID) is assigned to all Norwegian inhabitants. The PID provides information on the status (alive at present, dead, emigrated, or missing, as well as the date these events occurred) from the National Registry for all study subjects.

The PID also enabled linkage with the Cancer Registry of Norway (CRN), which was established in 1952 and contains information on all persons diagnosed with cancer since 1953. The reporting of information on all cancer diagnoses of individuals living in Norway is also mandatory by Norwegian Legislation. Cancer data are reported from several independent sources, which ensures high completeness and validity.²⁸

Follow-up

Study subjects were followed from their date of birth to their first cancer, death, emigration, or December 31, 2011, whichever occurred first. When a study subject had ≥ 2 cancers of different types, each cancer case was counted separately, once for each diagnostic group. In the analyses of overall cancer, only the first cancer for each individual was counted.

At the time of linkage of the data, the latest complete update of the cancer data was December 31, 2011.

Exposure

ART is defined as “all treatments or procedures that include the in vitro handling of human oocytes and sperm or embryos for the purpose of establishing a pregnancy.”²⁹ In addition to keeping record of all pregnancies initiated by any ART, the MBRN also contains information on which type of ART was used (conventional in vitro fertilization [IVF], intracytoplasmic sperm injection [ICSI], or other forms of treatment [frozen embryo replacement or ART abroad]).

All individuals registered in the MBRN as having been conceived by ART are classified as ART-conceived children, and all those without a registered ART conception as unexposed to ART.

Outcomes

Cancer data for all study subjects were obtained by linkage to the CRN. Cancer diagnoses were classified according to the third version of the *ICCC*.³⁰ Analyses of cancer risk were made for overall cancer as well as for the 12 main diagnostic groups of the *ICCC*: leukemias and myeloproliferative diseases (I), lymphomas (II), CNS neoplasms (III), neuroblastomas and other peripheral nervous cell tumors (IV), retinoblastoma (V), renal tumors (VI), hepatic tumors (VII), malignant bone tumors (VIII), soft tissue and other extraosseous sarcomas (IX), and germ cell tumors (X); the last 2 diagnostic groups were considered together: other malignant epithelial neoplasms and malignant melanomas (XI) and other and unspecified malignant neoplasms (XII).

For leukemias, lymphomas, and CNS cancers, subanalyses were made for each of the subgroups in the *ICCC* classification; for leukemias: acute lymphoid leukemias (ALL; Ia), acute myeloid leukemias (AML; Ib), and other leukemias (Ic–e); for lymphomas: Hodgkin's lymphoma (IIa), non-Hodgkin's lymphoma (IIb), and Burkitt lymphoma (IIc); for CNS cancer: ependymoma (IIIa), astrocytoma (IIIb), embryonal CNS tumors (IIIc), other gliomas (IIId), and other CNS tumors (IIIe and IIIf).

Statistical Analyses

Cox proportional hazards models were used to compute hazard ratios (HRs) and 95% confidence intervals (CIs) for risk of cancer in children conceived by ART compared with those not conceived by ART. The age of study subjects was used as the time scale. The proportional hazards

assumption was met for all but 2 of 11 analytic groups (neuroblastoma, IV; other cancers, IIIe and IIIf). A nonparametric model was used to assess these 2 cancer types, and results were similar. Therefore, the simplest model was applied where proportionality was assumed throughout.

Stratified analyses by method of ART (IVF, ICSI, or other), gender, and maternal age (>30 years versus <30 years) were made for overall cancer risk, leukemia, lymphoma, and CNS tumors.

Estimates for Burkitt lymphoma, malignant bone tumors, and germ cell tumors were not possible because there were no cases in the ART group, and these were therefore omitted from the analyses. The same was done for estimates for 2 subgroups of CNS tumors: ependymoma (IIIa) and other CNS tumors (IIIe).

P values <.05 were considered statistically significant.

Confounder Adjustment

To establish a priori which covariates were potential confounders and which were to be considered intermediates, a directed acyclic graph was constructed using available literature (Fig 1). Two statistical models were constructed. The first, Model I, included variables that were considered confounders: calendar year at follow-up (categorized as 1983–1992, 1993–2002, 2003–2011) and region of residence (Southeast, Southwest, West, Middle, North, and the capital of Oslo separately) were included because they may influence both cancer incidence as well as likelihood of having been conceived by ART. Maternal age has been demonstrated to influence cancer risk in offspring^{31,32} and is also associated with ART,³³ and so was also classified as a confounder (categorized: <25 years, 25–29 years, 30–35 years, and >35 years). Birth order has

FIGURE 1

A directed acyclic graph showing confounding and mediating factors in the current study associated with ART and childhood cancer. Covariates in red indicate that they have been classified as confounding factors; covariates in blue have been classified as intermediate factors.

been shown to be associated with childhood malignancies (particularly low birth order with leukemias),^{34–36} and children conceived by ART are more likely to be first order, so birth order was included in Model I as a confounder (categorized: 1, 2, 3, and ≥4). Results from Model I are shown in Supplemental Table 4.

Gestational age and birth weight were included in Model II because both have been shown to be associated with risk of childhood cancer, and children conceived by ART are known to have lower gestational age and birth weight than those not conceived by ART.^{37–39} These two were therefore considered intermediate factors and included in the second model, Model II (gestational length categorized as <24, 25–29, 30–34, and ≥35 weeks and birth weight categorized as <2900 g, 2900–4100 g, and >4100 g). Risk of certain cancers is different among males and females, and therefore gender was included as a covariate in Model II.⁴⁰ No literature was found that could support an association between being born as a twin or higher-order multiple birth and childhood cancer, and it was therefore not included in the final model.

FIGURE 2

Description of the establishment of the study cohort. Children conceived by ART are those registered as conceived by ART in the MBRN; children not conceived by ART are those without a registered ART conception in the MBRN.

All analyses were made by using the software package Stata, version 13.0.

The Committee for Medical and Health Research Ethics, South Eastern Health Region of Norway, approved the study.

RESULTS

During the observational period, 1 631 343 children were born in Norway, of which 1 628 658 were eligible for study, with the remaining 2685 excluded because of missing data on either status or status date in the National Registry. In the ART group ($n = 25\,782$), there were 51 cancer cases among 49 study subjects. In the non-ART group ($n = 1\,602\,876$), there were 4503 cancer cases among 4414 study subjects (Fig 2). The total follow-up time was 205 529 person-years for the ART group (median 6.9, range 0–27

years) and 21 807 108 for the non-ART group (median 13.7, range 0–28 years; Table 1).

More than 50% of children conceived by ART were born between 2004 and 2011, whereas the birth dates of children not conceived by ART were evenly distributed over the 3 time periods 1984–1993, 1994–2003, and 2004–2011 (Table 1). Children conceived by ART had lower median birth weight (3220 g) and gestational age (39 weeks) than those who were not conceived by ART (3550 g and 40 weeks; Table 1). Children conceived by ART had older mothers and were more frequently first-order siblings (Table 1). Of the children conceived by ART, 15 170 were a result of conventional IVF, 7798 of ICSI, and 188 of others treatments; 2626 had missing data on ART method. In children with cancer, median age at diagnosis was 3.2 years (range

0–19.2) for children conceived by ART and 8.8 years (range 0–26.4) for those not conceived by ART (Table 1).

ART children made up an increasing proportion of all annual births and use of ICSI increased during the last decade of the study period (Fig 3A). Children conceived by ART were more often multiples (33% ART children and 3% non-ART children; Fig 3B). Differences in gestational weight and age appeared to lessen throughout the study period, although no significant trends were observed (Fig 3 C and D).

The most common cancers were leukemias (33% of all cancers in the ART group and 23% in the non-ART group) and CNS cancers (24% and 23%, respectively; Table 2). Soft tissue tumors were the third most frequent cancer in children conceived by ART (10%), out of which 3 were rhabdomyosarcomas (data not shown). Seven percent (308) of the cancers in the non-ART group were soft tissue tumors (92 rhabdomyosarcomas). Lymphomas were the fourth most common cancer in the ART group, comprising 8% of the total tumors, and the third most common cancer in the non-ART group (10%; Table 2).

No significant difference in overall cancer risk was found between children conceived by ART and those not conceived by ART (HR 1.21; 95% CI 0.90–1.63; Table 3).

Analyses by cancer type revealed an elevated risk of leukemia in children conceived by ART compared with children not conceived by ART (HR 1.67; 95% CI 1.02–2.73), when applying the fully adjusted model (Table 3). Subgroup analyses by type of leukemia showed that the risk was increased for AML (HR 2.63; 95% CI 1.04–6.64) and other leukemias (HR 5.13; 95% CI 1.50–7.60), with no increase noted for ALL (HR 1.16; 95% CI 0.60–2.27). The HR of lymphoma in children

TABLE 1 Baseline Characteristics of the Study Population

Characteristics	ART Children	Non-ART Children	Total
Total number of persons	25 782	1 602 876	1 628 658
Persons with cancer, <i>n</i>	49	4414	4463
Age at cancer diagnosis, median (IQR)	3.2 (1.9–7.7)	8.8 (3.1–17.4)	8.7 (3.0–17.3)
Follow-up time, ^a median (IQR)	6.9 (3.1–12.0)	13.7 (6.5–20.5)	13.5 (6.5–20.5)
Total follow-up time, person-years	205 529	21 807 108	22 012 552
Birth year, <i>n</i> (%)			
1984–1993	2097 (8)	562 833 (35)	564 930 (35)
1994–2003	9313 (36)	577 093 (36)	586 406 (36)
2004–2011	14 372 (56)	462 950 (29)	477 322 (29)
Total	25 782 (100)	1 602 876 (100)	1 628 658 (100)
Gender, <i>n</i> (%)			
Male	12 594 (49)	823 300 (51)	835 894 (51)
Female	13 188 (51)	779 576 (49)	792 764 (49)
Total	25 782 (100)	1 602 876 (100)	1 628 658 (100)
Multiple or singleton birth, <i>n</i> (%)			
Multiple birth	8432 (33)	41 199 (3)	49 631 (3)
Singleton	17 350 (67)	1 561 677 (97)	1 579 027 (97)
Total	25 782 (100)	1 602 876 (100)	1 628 658 (100)
Birth weight, g, median (IQR)	3220 (2670–3670)	3550 (3200–3900)	3550 (3196–3900)
<2900, <i>n</i> (%)	8739 (34)	185 896 (12)	194 635 (12)
2900–4100, <i>n</i> (%)	14 849 (58)	1 177 308 (73)	1 192 157 (73)
≥4100, <i>n</i> (%)	2167 (8)	238 188 (15)	240 355 (15)
Missing, <i>n</i> (%)	27 (0)	1484 (0)	1511 (0)
Total, <i>n</i> (%)	25 782 (100)	1 602 876 (100)	1 628 658 (100)
Gestational length, wk, median (IQR)	39 (37–40)	40 (39–41)	40 (39–41)
<24, <i>n</i> (%)	74 (0)	642 (0)	716 (0)
24–30, <i>n</i> (%)	516 (2)	7055 (0)	7571 (0)
30–35, <i>n</i> (%)	2110 (8)	31 540 (2)	33 650 (2)
36–42, <i>n</i> (%)	19 903 (77)	1 323 206 (83)	1 343 109 (82)
Over 42, <i>n</i> (%)	1095 (4)	158 513 (10)	159 608 (10)
Missing	2084 (8)	81 920 (5)	84 004 (5)
Total	25 782 (100)	1 602 876 (100)	1 628 658 (100)
Method of ART, <i>n</i> (%)			
Classic IVF	15 170 (59)	—	—
ICSI	7798 (30)	—	—
Other	188 (1)	—	—
Missing	2626 (10)	—	—
Total	25 782 (100)	—	—
Maternal age at delivery, median (IQR)	33.0 (30.0–36.0)	28.0 (25.0–32.0)	28.0 (25.0–32.0)
<25, <i>n</i> (%)	409 (2)	369 653 (23)	370 062 (23)
25–29, <i>n</i> (%)	4823 (19)	563 005 (35)	567 828 (35)
30–35, <i>n</i> (%)	11 397 (44)	457 485 (29)	468 882 (29)
>35, <i>n</i> (%)	9152 (35)	212 711 (13)	221 863 (14)
Missing, <i>n</i> (%)	1 (0)	22 (0)	23 (0)
Total, <i>n</i> (%)	25 782 (100)	1 602 876 (100)	1 628 658 (102)
Birth order, <i>n</i> (%)			
1	16 792 (65)	663 704 (41)	680 496 (42)
2	7371 (29)	569 706 (36)	577 077 (35)
3	1254 (5)	265 000 (17)	266 254 (16)
4	276 (1)	72 999 (5)	73 275 (4)
≥5	89 (0)	31 466 (2)	31 555 (2)
Missing	0 (0)	1 (0)	1 (0)
Total	25 782 (100)	1 602 876 (100)	1 628 658 (100)
Age at cancer diagnosis, <i>y</i> , <i>n</i> (%)			
<5	29 (64)	1637 (36)	1666 (37)
5–10	12 (26)	719 (16)	731 (16)
10–15	4 (8)	598 (13)	602 (13)
15–20	4 (8)	724 (16)	728 (16)
>20	0 (0)	736 (16)	736 (16)
Total	49 (106)	4414 (97)	4463 (100)
Birthplace (Health Region of Norway), <i>n</i> (%)			
Southeast	8493 (33)	543 113 (34)	551 606 (34)

TABLE 1 Continued

Characteristics	ART Children	Non-ART Children	Total
Oslo	3677 (14)	217 945 (14)	221 622 (14)
Southwest	4744 (18)	244 687 (15)	249 431 (15)
West	4243 (16)	288 305 (18)	292 548 (18)
Middle	2700 (10)	140 730 (9)	143 430 (9)
North	1917 (7)	167 037 (10)	168 954 (10)
Missing	8 (0)	1059 (0)	1067 (0)
Total	25 782 (100)	1 602 876 (100)	1 628 658 (100)

ART children are those registered as conceived by ART in the MBRN; non-ART children are those registered as not conceived by ART. IQR, interquartile range.

^a This is equal to the age of study subjects at end of follow-up or censoring.

conceived by ART compared with non-ART children was 1.79 (95% CI 0.66–4.90). Separate analyses by subgroups of lymphoma revealed a significant increase in risk of Hodgkin's lymphoma in the ART group (HR 3.63; 95% CI 1.12–11.72), based on only 3 cases in the ART group (Table 3).

The risk of CNS cancer was the same for both comparison groups (HR 0.92; 95% CI 0.47–1.79; Table 3). No difference was seen when stratifying on type of CNS tumor (Table 3).

For other cancers, no difference was found between children who were conceived by ART and those who were not (Table 3).

In analyses stratified by ART method, gender, and maternal age, no significant differences between the groups were detected (data not shown).

DISCUSSION

In this population-based study, we have examined cancer risk during childhood and adolescence in individuals conceived by ART compared with those not conceived by ART. Risk of overall cancer was not elevated, but a significantly increased risk of leukemia was seen in children conceived by ART. Furthermore, subgroup analyses indicated significantly elevated risks of AML and Hodgkin's lymphoma.

Overall Cancer

The present finding of no increase in risk of overall cancer in children

conceived by ART is in line with recent studies, including a Danish study assessing the association between fertility hormones and childhood cancer,¹⁸ a large British study,⁴¹ a Nordic collaborative study,²⁰ and a study using data from the Danish infertility cohort.²⁵ Earlier, smaller cohort studies also demonstrated no elevated risk of overall cancer.^{24,27,42–45} On the other hand, 1 large population-based study from Sweden comprising 26 692 children born after ART found a 42% risk increase for overall cancer in children conceived by ART.¹⁵ Although most studies report no risk increase, a recent meta-analysis from 2014 (based on 10 studies) concluded that there was an association between risk of overall cancer and fertility treatment.¹⁷

Hematological Cancers

We discovered an elevated risk of leukemia in children conceived by ART compared with those conceived without ART. The finding is consistent with the mentioned meta-analysis,¹⁷ as well as the 2 largest cohort studies to date, from Sweden¹⁵ and Denmark.¹⁸ The Swedish study reported increased numbers of hematologic cancers in a cohort of 26 692 children born after ART (18 observed vs 12.3 expected cases), and the Danish study demonstrated an elevated risk of leukemia (HR 4.96) in children whose mothers were treated with progesterone. Furthermore, 3 case-control studies^{4,19,46} reported an elevated risk of hematologic cancers among

children conceived by ART. On the other hand, several studies report no increased risk of leukemia in children conceived by ART.^{20,25,26,41} We discovered an elevated risk of AML, although this estimate was based on few cancer cases and must therefore be interpreted with caution. Other researchers have found elevated risks of ALL, a much more common tumor histology in young children.^{4,19}

Studies have assessed the possibility of an association between ART treatment and lymphoma, but no risk increase in children conceived by ART has been found,^{15,18,20,25,41} in line with our findings. Our observed increased risk of Hodgkin's lymphoma should be interpreted with caution because it was based on few cases and has not been described previously.

CNS Cancer

No elevated risk of CNS cancer was found in our study, in line with a large British study based on a cohort of 106 013 ART-conceived children in the United Kingdom.⁴¹ In line with this, a recent meta-analysis that reported an elevated risk of CNS/neural tumors after medically assisted reproduction found no risk increase once CNS tumors were assessed separately from neural tumors.¹⁷ However, a Nordic study found an increase in risk of CNS tumors after ART (HR 1.44, 95% CI 1.01–2.05), based on 42 cases in the ART group.²⁰ The current study (with only 12 cases of CNS tumors in the ART group) is underpowered to rule out such an increased risk.

Other Cancers

In contrast to 4 case-control studies,^{22,47–49} we found no increase in risk of retinoblastoma in children conceived by ART. There was only 1 retinoblastoma case in the ART group, but this is consistent with an incidence rate of 0.9 and 0 per 100 000 person-years in the age groups 0 to 4 and 5 to 9 years, respectively.⁵⁰ Contrary to previous studies,^{21,41,51,52} we did not find any evidence of increased risks of hepatoblastomas or rhabdomyosarcomas.

Etiology of Childhood Cancers

Few known risk factors exist regarding childhood cancer, although there is some evidence that risks may increase after exposure to ionizing radiation^{53–55} or diethylstilbestrol.⁵⁶ Some demographic factors (race, parental occupation, and socioeconomic status)⁵⁷ and certain parental risk factors (such as advanced parental age) have also been implicated, especially for cancers that arise early in childhood.^{31,58} A case-control study from the Netherlands found that mothers of children with leukemia were more likely to report “problems with fertility.”⁵⁹ Hargreave et al found elevated cancer risk in children born to mothers who were infertile and also found an increase in risk associated with progesterone use for infertility.¹⁸ Thus, it is difficult to disentangle whether it is the ART treatment, parental infertility, or both that are contributing to observed associations, as also discussed by Hargreave and colleagues.

Strengths and Limitations

The study has a number of strengths, including the fact that we were able to use an entire population of individuals born in 1 country to compare risks between those conceived by ART and those who were not. This, in addition to including all children conceived by

TABLE 2 Distribution of Cancers by Diagnostic Groups in Children Conceived by ART and Children Conceived Without ART, Norway, 1984–2011

Major Diagnostic Group	ICCC Site Group ^a	ART	Non-ART	Total Tumors
		<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)
Overall cancer		49	4414	4463
Leukemia ^b	I	17 (33)	1021 (23)	1038 (23)
ALL	1a	9 (18)	768 (17)	777 (17)
AML	1b	5 (10)	175 (4)	180 (4)
Other leukemias	1c–e	3 (6)	79 (2)	81 (2)
Lymphoma (all) ^b	II	4 (8)	457 (10)	461 (10)
Hodgkin's	IIa	3 (6)	258 (6)	261 (6)
Non-Hodgkin's	IIb	1 (2)	147 (3)	148 (3)
Burkitt	IIc	0 (0)	52 (1)	52 (1)
CNS ^b	III	12 (24)	1020 (23)	1032 (23)
Ependymoma	IIIa	0 (0)	92 (2)	92 (2)
Astrocytoma	IIIb	5 (12)	362 (8)	368 (8)
Embryonal CNS	IIIc	4 (8)	175 (4)	179 (4)
Other gliomas	IIId	1 (2)	104 (2)	105 (2)
Other CNS tumors	IIIe	0 (0)	146 (3)	146 (3)
Unspecified CNS tumors	IIIf	1 (2)	132 (3)	133 (3)
Neuroblastoma	IV	4 (8)	185 (4)	189 (4)
Retinoblastoma	V	1 (2)	102 (2)	103 (2)
Renal	VI	3 (6)	252 (6)	255 (6)
Hepatic	VII	2 (4)	109 (2)	111 (2)
Bone	VIII	0 (0)	169 (4)	169 (4)
Soft tissue	IX	5 (10)	308 (7)	313 (7)
Germ cell	X	0 (0)	387 (9)	387 (8)
Others	XI–XII	3 (6)	493 (11)	496 (11)
Total ^c		51 (100)	4503 (100)	4554 (100)

^a Cancers are classified according to the third version of the *ICCC*.

^b In summing up the total number of cancers, each case of leukemia, lymphoma, and CNS cancer is counted only once.

^c A total of 4554 cancers were diagnosed among the 4473 children with cancer because some children experienced >1 cancer, in different diagnostic groups. Therefore, the total number of cancers by diagnostic group differs from the number of individuals with cancer.

ART since the first ART infant was born in Norway, means that the study is larger than most studies previously performed on this topic. The CRN has a high ascertainment of cancers, which enabled complete cancer data and negligible losses to follow-up. The use of a registry-based design allowed for unbiased collection of data about exposure, reducing the possibility of recall bias. Through the MBRN, we were able to obtain data on maternal age and could adjust for this, which is important given that advanced maternal age has been associated

with the development of childhood cancers.³¹ The method of ART used is indicative of the kind of infertility the couple suffers; when male factor infertility is identified, a couple is often selected for ICSI. We were able to look at risk in children conceived by conventional IVF as well as those conceived by IVF with ICSI, which was a strength of our study, although no differences between these 2 groups were detected.

Imprinting disorders have been associated with both ART^{13,60} and certain cancers (such as

hepatoblastoma and kidney tumors in Beckwith-Wiedemann patients)⁶¹ and may in the current study be mediating some of the observed effects, which unfortunately could not be measured. Indeed, a study using data from Norway and Sweden found elevated risk of cancer in children with congenital malformations, and the authors suggested that “cancer may be a complication of some birth defects.”⁶² If parental genetics leads to a couple's infertility or congenital disorders in the offspring, then maternal and/or paternal genetics would represent a possible confounder that we were unable to account for in our study. Furthermore, although we were able to adjust for maternal age, we could not adjust for the paternal age. As discussed, the current study does not allow for distinction of whether an elevated cancer risk in ART offspring is associated with parental infertility or the processes involved in ART. The

FIGURE 3 Continued

Characteristics of ART offspring compared with non-ART offspring in Norway, changes over 28 years (1984–2011). A, Number of children born after being conceived by ART, by method, each year in Norway, 1984–2011. B, Number of children born as being part of a multiple birth (percent of all pregnancies), by mode of conception in Norway, 1984–2011. C, Birth weight of children born in Norway 1984–2011, by mode of conception and birth year. D, Gestational age of children born in Norway, 1984–2011, by mode of conception and birth year. In panels C and D, the length of the colored intervals indicates the values that lie between the 25th and 75th percentiles. The length of the black lines indicates the range.

TABLE 3 Risk of Cancer in Children Conceived by ART Compared With Children Conceived Without ART, Norway, 1984–2011

Cancer Site	ICCC Site Group	Total Number of Tumors			Crude		Model II ^a	
		ART	Non-ART	Total	HR	95% CI	HR	95% CI
Leukemia ^b	I	17	1012	1029	1.52	0.94–2.45	1.67*	1.02–2.73
ALL	1a	9	768	777	1.03	0.53–1.98	1.16	0.60–2.27
AML	1b	5	173	178	2.65*	1.09–6.46	2.63*	1.04–6.64
Other leukemias	1c–e	3	71	74	4.91*	1.53–15.7	5.13*	1.50–7.60
Lymphoma ^c	II	4	456	460	1.52	0.57–4.08	1.79	0.66–4.90
Hodgkin's	IIa	3	258	261	2.62	0.84–8.21	3.63*	1.12–11.72
Non-Hodgkin's	IIb	1	147	148	0.93	0.13–6.69	0.99	0.14–7.28
CNS ^c	III	12	1007	1019	1.25	0.71–2.21	0.92	0.47–1.79
Astrocytomas	IIIb	5	362	368	1.71	0.76–3.83	1.45	0.63–3.29
Embryonal CNS tumors	IIIc	3	175	179	2.13	0.79–5.74	1.70	0.62–4.69
Other gliomas	IIId	1	104	105	1.17	0.16–8.40	1.19	0.16–8.80
Other CNS tumors	IIIf	1	132	133	0.43	0.60–3.06	0.50	0.07–3.59
Neuroblastoma	IV	4	184	188	1.52	0.56–4.08	1.79	0.64–4.99
Retinoblastoma	V	1	90	91	0.75	0.10–5.38	—	—
Renal	VI	3	251	254	1.37	0.44–4.28	1.40	0.44–4.48
Hepatic	VII	2	108	110	2.22	0.54–9.07	1.76	0.41–7.46
Soft tissue	IX	5	307	312	1.69	0.70–4.09	1.33	0.54–3.30
Others	XI–XII	3	488	491	1.10	0.35–3.44	1.21	0.38–3.82
All		49	4414	4463	1.27	0.90–1.63	1.21	0.90–1.63

Cancers are classified by the third version of the *ICCC*. The proportional hazards assumption was tested with the Schoenfeld residuals.

^a Adjusted for birth year, birth order, maternal age at delivery, place of birth, gender, birth weight, and gestational age.

^b In summing up the total number of cancers, each case of lymphoma and leukemia is counted only once.

^c Analyses for sites with no cancer cases in the ART group were not performed and are therefore omitted from Table 3.

* Significant HRs.

use of registry-based data poses a risk of misclassification bias because some children may have been conceived by ART but not registered as ART children in the MBRN. This limitation must be kept in mind because such misclassification is likely nondifferential concerning cancer outcome and may bias the estimates toward the null. Because the ART group is still young, the study may be underpowered to evaluate the risk of cancers arising later in childhood and adolescence. Children conceived by ART in the current study are younger and have shorter follow-up time than the children not conceived by ART, and because leukemia is more common in younger children, it is consequently the most frequent cancer in the ART group. Therefore, as children conceived by ART successively grow older, attention should also be paid to cancers with peak ages above the first few years of life.

CONCLUSIONS

The findings in this study, although reassuring for overall cancer, are indicative of an elevated risk of hematologic cancers in children conceived by ART. We observed not only an increased risk of leukemia, but also of Hodgkin's lymphoma.

These findings are in line with most previous studies showing no elevated risk of overall cancer among ART-conceived children but possible increases for certain cancer types. The most frequently noted increases have been hematologic cancers, although other cancers have been highlighted. Keeping in mind that the absolute risk of childhood cancer is low, it must be noted that the 60% increase found in this investigation is a significant increase. Because the children conceived by ART in this cohort are still young, continued observation should be pursued.

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ABBREVIATIONS

ALL: acute lymphoid leukemia
 AML: acute myeloid leukemia
 ART: assisted reproductive technology
 CI: confidence interval
 CNS: central nervous system
 CRN: Cancer Registry of Norway
 HR: hazard ratio
ICCC: *International Classification of Childhood Cancer*
 ICSI: intracytoplasmic sperm injection
 IVF: in vitro fertilization
 MBRN: Medical Birth Registry of Norway
 PID: personal identification number

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