Supplementary Exercise 13.5: *Cancer Risk among Children Born after Assisted Conception*[7]

BACKGROUND: Accurate population-based data are needed on the incidence of cancer in children born after assisted conception.

METHODS: We linked data on all children born in Britain between 1992 and 2008 after assisted conception without donor involvement with data from the United Kingdom National Registry of Childhood Tumours to determine the number of children in whom cancer developed before 15 years of age. Cohort cancer rates were compared with population-based rates in Britain over the same period, with stratification for potential mediating and moderating factors, including sex, age at diagnosis, birth weight, singleton versus multiple birth, parity, parental age, type of assisted conception, and cause of parental infertility.

RESULTS: The cohort consisted of 106,013 children born after assisted conception (700,705 person-years of observation). The average duration of follow-up was 6.6 years. Overall, 108 cancers were identified, as compared with 109.7 expected cancers (standardized incidence ratio, 0.98; 95% confidence interval [CI], 0.81 to 1.19; P=0.87). Assisted conception was not associated with an increased risk of leukemia, neuroblastoma, retinoblastoma, central nervous system tumors, or renal or germ-cell tumors. It was associated with an increased risk of hepatoblastoma (standardized incidence ratio, 3.64; 95% CI, 1.34 to 7.93; P=0.02; absolute excess risk, 6.21 cases per 1 million person-years) and rhabdomyosarcoma (standardized incidence ratio, 2.62; 95% CI, 1.26 to 4.82; P=0.02; absolute excess risk, 8.82 cases per 1 million person-years), with hepatoblastoma developing in 6 children and rhabdo-myosarcoma in 10 children. The excess risk of hepatoblastoma was associated with low birth weight.

CONCLUSIONS: There was no increase in the overall risk of cancer among British children born after assisted conception during the 17-year study period. Increased risks of hepatoblastoma and rhabdomyosarcoma were detected, but the absolute risks were small. (Funded by Cancer Research UK and others.)

STATISTICAL ANALYSIS (in the Methods section): Person-years at risk were calculated from the date of birth until the date of a cancer diagnosis, December 31, 2008, or the child's 15th birthday, whichever came first, and were categorized according to sex, age at diagnosis (0, 1 to 4, 5 to 9, or 10 to 14 years), birth weight, gestational age at birth, singleton or multiple birth, parity, maternal and paternal age, type of assisted conception, fresh or cryopreserved embryos, and cause of parental infertility. To determine the expected number of cancers in the cohort if the risk for cohort members was the same as that for the general population, we used the calculated person-years at risk in conjunction with the NRCT cancer incidence rates for the general population of Britain of the same age during the same period.[29] [8] See Figure S2 in the Supplementary Appendix for details of planned analyses. The number of observed cancers was assumed to follow a Poisson distribution. Standardized incidence ratios, the ratio of observed to expected numbers of cancers, and exact 95% confidence intervals were calculated. P values of less than 0.05, calculated on the basis of the chi-square test,[29] were considered to indicate statistical significance. Analyses were performed with the use of STATA software, version 11.[30]

i. *"Overall, 108 cancers were identified, as compared with 109.7 expected cancers (standardized incidence ratio, 0.98; 95% confidence interval [CI], 0.81 to 1.19; P=0.87)."*

   Compute both the 95% CI and the P-value using (a) the exact distribution of a Poisson random variable; (b) the normal approximation to this random variable; (c) the normal approximation to the log of this random variable; the Poisson distribution in a generalized linear model with (e) identity and (f) log link. For all analyses assume that the 109.7 is a scaled down version of the UK childhood cancer counts, scaled down to match the age-year distribution of the 700,705 child years of observation of the cohort.[9]

ii. *"It was associated with an increased risk of hepatoblastoma (standardized incidence ratio, 3.64; 95% CI, 1.34 to 7.93; P=0.02; absolute excess risk, 6.21 cases per 1 million person-years) and rhabdomyosarcoma (standardized incidence ratio, 2.62; 95% CI, 1.26 to 4.82; P=0.02; absolute excess risk, 8.82 cases per 1 million person-years)"*

   Show how, just from the information in the reported "(standardized incidence ratio, 3.64; 95% CI, 1.34 to 7.93)" and the table of CI's for the mean of a Poisson random variable, back-calculate the number of children in whom hepatoblastomas developed, and how many would have been expected based on the general UK rates. *Hint*: see "3.2 Leukemia Rate Triples near Nuke Plant: Study" in the "Notes for intensity rates:-models".

iii. According to the USA SEER data from 1975-1995 (see below), the % distribution of childhood (to age 15) cancers over the XII major ICCC categories is: 31.5, 10.7, 20.2, 7.8, 3.1, 6.3, 1.3, 4.5, 7, 3.5 , 3.5, 0.5.

   Conditional on the sum $y = y_1 + y_2$ of $y_1 \sim$ Poisson$[\mu_1]$ and $y_2 \sim$ Poisson$[\mu_2]$ random variables, the distribution of the $\{y_1, y_2\}$ split is binomial with parameter $\pi = \mu_1/(\mu_1 + \mu_2),\ 1 - \pi = \mu_2/(\mu_1 + \mu_2)$.

   Likewise, the (sum-conditional) distribution of the split of several (e..g. XII) Poisson counts, is multinomial with $\pi_j = \mu_j/(\mu_1 + \cdots + \mu_{XII})$.

   Using the 12 above percentages as multinomial relative frequencies, and e.g., `rmultinom` in `R`, simulate how likely it would be, in 108 such cancers, to obtain a statistically significant excess in *at least one* ICCC category.

[7] N Engl J Med 2013;369:1819-27.

[8] The reference is to 29. Breslow NE, Day NE. Statistical methods in cancer research. Vol. 2. The design and analyses of cohort studies. Lyon, France: International Agency for Research on Cancer, 1987. (IARC scientific publications no. 82.) See also the textbook by Armitage and Berry, or JH's Notes for the intensity parameter of the Poisson distribution.

[9] From UK Office of National Statistics & USA SEER: The numbers of births in England and Wales went steadily down from 690K to 590K from 1992 to 2001 and then steadily up to 708K in 2008. "The estimated populations of the four constituent countries of the UK in mid-2012 are 53.5 million people in England, 5.3 million in Scotland, 3.1 million in Wales and 1.8 million in Northern Ireland." SEER covers $\approx$ 14% of USA population]

Table 1: Percent distribution of childhood cancers by ICCC category and age group, all races, both sexes, SEER, 1975-95

	Age					
	<5	5-9	10-14	15-19	<15	<20
All Sites - Number of cases	9,402	5,024	5,419	9,814	19,845	29,659
	%	%	%	%	%	%
All Sites	100.0	100.0	100.0	100.0	100.0	100.0
I(total) - Leukemia	36.1	33.4	21.8	12.4	31.5	25.2
Ia - Lymphoid Leukemia	29.2	27.2	14.7	6.5	24.7	18.7
Ia - excl. Acute Lymphoid	0.2	0.3	0.2	0.1	0.2	0.2
Acute Lymphoid	29.0	27.0	14.5	6.4	24.5	18.5
Ib - Acute Leukemia	4.6	4.1	5.4	4.1	4.7	4.5
Ib - excl. Acute Myeloid	1.9	0.9	1.6	0.9	1.5	1.3
Acute Myeloid	2.8	3.2	3.8	3.2	3.2	3.2
Ic - Chronic myeloid leukemia	0.6	0.7	0.9	1.2	0.7	0.9
Id - Other specified leukemias	0.2	0.2	0.1	0.1	0.2	0.2
Ie - Unspecified leukemias	1.4	1.2	0.8	0.5	1.2	1.0
II(total) - Lymphomas and reticuloendothelial neoplasms	3.9	12.9	20.6	25.1	10.7	15.5
IIa - Hodgkins' disease	0.4	4.5	11.4	17.7	4.4	8.8
IIb - Non-Hodgkins' Lymphoma	2.0	5.2	6.1	6.0	4.0	4.6
IIc - Burkitt's lymphoma	0.8	2.4	1.9	0.6	1.5	1.2
IId - Miscellaneous lymphoreticular neoplasms	0.4	0.2	0.3	0.2	0.3	0.3
IIe - Unspecified lymphomas	0.3	0.7	0.9	0.7	0.6	0.6
III(total) - CNS and miscellaneous intracranial and intraspinal neoplasms	16.6	27.7	19.6	9.5	20.2	16.7
IIIa - Ependymoma	2.6	1.3	1.1	0.5	1.9	1.4
IIIb - Astrocytoma	6.7	14.2	11.8	6.0	10.0	8.7
IIIc - Primitive neuroectodermal tumors	4.3	6.3	3.1	1.0	4.5	3.3
IIId - Other gliomas	2.2	5.0	2.9	1.5	3.1	2.6
IIIe - Miscellaneous intracranial and intraspinal neoplasms	0.2	0.3	0.3	0.3	0.3	0.3
IIIf - Unspecified intracranial and intraspinal neoplasms	0.5	0.6	0.4	0.2	0.5	0.4
IV(total) - Sympathetic nervous system	14.3	2.7	1.2	0.5	7.8	5.4
IVa - Neuroblastoma and ganglioneuroblastoma	14.0	2.6	0.8	0.3	7.5	5.1
IVb - Other sympathetic nervous system tumors	0.3	0.1	0.3	0.1	0.3	0.2
V(total) - Retinoblastoma	6.3	0.5	0.1	0.0	3.1	2.1
VI(total) - Renal tumours	9.7	5.4	1.1	0.6	6.3	4.4
VIa - Wilms' tumor, rhabdoid and clear cell sarcoma	9.7	5.2	0.7	0.2	6.1	4.2
VIb - Renal carcinoma	0.1	0.1	0.4	0.4	0.2	0.2
VIc - Unspecified malignant renal tumors	0.0	0.0	0.0	0.0	0.0	0.0

Table 1 (cont'd): Percent distribution of childhood cancers by ICCC category and age group, all races, both sexes, SEER, 1975-95

	Age					
	<5	5-9	10-14	15-19	<15	<20
All Sites - Number of cases	9,402	5,024	5,419	9,814	19,845	29,659
	%	%	%	%	%	%
VII(total) - Hepatic tumors	2.2	0.4	0.6	0.6	1.3	1.1
VIIa - Hepatoblastoma	2.1	0.2	0.1	0.0	1.0	0.7
VIIb - Hepatic carcinoma	0.1	0.3	0.5	0.5	0.3	0.3
VIIc - Unspecified malignant hepatic tumors	0.0	0.0	0.0	0.0	0.0	0.0
VIII(total) - Malignant bone tumors	0.6	4.6	11.3	7.7	4.5	5.6
VIIIa - Osteosarcoma	0.2	2.2	6.6	4.4	2.4	3.1
VIIIb - Chondrosarcoma	0.0	0.1	0.6	0.6	0.2	0.3
VIIIc - Ewing's sarcoma	0.3	2.1	3.7	2.3	1.7	1.9
VIIId - Other specified malignant bone tumors	0.1	0.1	0.3	0.3	0.2	0.2
VIIIe - Unspecified malignant bone tumors	0.0	0.1	0.1	0.1	0.1	0.1
IX(total) - Soft-tissue sarcomas	5.6	7.5	9.1	8.0	7.0	7.4
IXa - Rhabdomyosarcoma and embryonal sarcoma	3.4	4.2	2.8	1.9	3.4	2.9
IXb - Fibrosarcoma, neurofibrosarcoma and other fibromatous neoplasms	1.0	1.4	3.1	3.1	1.7	2.1
IXc - Kaposi's sarcoma	0.0	0.1	0.0	0.1	0.0	0.1
IXd - Other specifed soft-tissue sarcomas	0.7	1.2	2.2	2.1	1.3	1.5
IXe - Unspecifed soft-tissue sarcomas	0.4	0.7	1.0	0.9	0.6	0.7
X(total) - Germ-cell, trophoblastic and other gonadal tumors	3.3	2.0	5.3	13.9	3.5	7.0
Xa - Intracranial and intraspinal germ-cell tumors	0.2	0.8	1.3	0.9	0.7	0.7
Xb - Other and unspecified non-gonadal germ-cell tumors	1.7	0.1	0.5	1.4	1.0	1.1
Xc - Gonadal germ-cell tumors	1.4	1.1	3.0	9.4	1.7	4.2
Xd - Gonadal carcinomas	0.0	0.0	0.4	1.9	0.1	0.7
Xe - Other and unspecified malignant gonadal tumors	0.0	0.1	0.1	0.3	0.1	0.1
XI(total) - Carcinomas and other malignant epithelial neoplasms	0.9	2.5	8.9	20.9	3.5	9.2
XIa - Adrenocortical carcinoma	0.2	0.1	0.1	0.1	0.1	0.1
XIb - Thyroid carcinoma	0.1	1.0	3.5	7.4	1.2	3.3
XIc - Nasopharyngeal carcinoma	0.0	0.1	0.7	0.8	0.2	0.4
XId - Malignant melanoma	0.4	0.7	2.0	6.8	0.9	2.9
XIe - Skin carcinoma	0.0	0.0	0.1	0.1	0.0	0.0
XIf - Other and unspecified carcinomas	0.2	0.7	2.5	5.7	1.0	2.5
XII(total) - Other and unspecified malignant neoplasms	0.5	0.3	0.6	0.8	0.5	0.6
XIIa - Other specified malignant tumors	0.1	0.1	0.1	0.3	0.1	0.1
XIIb - Other unspecified malignant tumors	0.4	0.3	0.5	0.5	0.4	0.4

ORIGINAL ARTICLE

Cancer Risk among Children Born after Assisted Conception

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ABSTRACT

BACKGROUND

Accurate population-based data are needed on the incidence of cancer in children born after assisted conception.

METHODS

We linked data on all children born in Britain between 1992 and 2008 after assisted conception without donor involvement with data from the United Kingdom National Registry of Childhood Tumours to determine the number of children in whom cancer developed before 15 years of age. Cohort cancer rates were compared with population-based rates in Britain over the same period, with stratification for potential mediating and moderating factors, including sex, age at diagnosis, birth weight, singleton versus multiple birth, parity, parental age, type of assisted conception, and cause of parental infertility.

RESULTS

The cohort consisted of 106,013 children born after assisted conception (700,705 person-years of observation). The average duration of follow-up was 6.6 years. Overall, 108 cancers were identified, as compared with 109.7 expected cancers (standardized incidence ratio, 0.98; 95% confidence interval [CI], 0.81 to 1.19; P=0.87). Assisted conception was not associated with an increased risk of leukemia, neuroblastoma, retinoblastoma, central nervous system tumors, or renal or germ-cell tumors. It was associated with an increased risk of hepatoblastoma (standardized incidence ratio, 3.64; 95% CI, 1.34 to 7.93; P=0.02; absolute excess risk, 6.21 cases per 1 million person-years) and rhabdomyosarcoma (standardized incidence ratio, 2.62; 95% CI, 1.26 to 4.82; P=0.02; absolute excess risk, 8.82 cases per 1 million person-years), with hepatoblastoma developing in 6 children and rhabdomyosarcoma in 10 children. The excess risk of hepatoblastoma was associated with low birth weight.

CONCLUSIONS

There was no increase in the overall risk of cancer among British children born after assisted conception during the 17-year study period. Increased risks of hepatoblastoma and rhabdomyosarcoma were detected, but the absolute risks were small. (Funded by Cancer Research UK and others.)

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Since the introduction of in vitro fertilization (IVF) in 1978, the number and proportion of children born after assisted conception have increased annually, and currently there are more than 5 million such persons worldwide.[1] Well-recognized perinatal complications in this population include low birth weight, prematurity, and congenital malformations.[2-4] However, there remains a dearth of population-based studies investigating important but rare health outcomes.

The possibility of an increased risk of cancer in this population has been suggested previously.[5-9] This concern is supported by the discovery of altered epigenetic patterns in human embryos,[10,11] cord blood,[12] and placentas[12,13] after assisted conception. Epigenetic defects were also found to be responsible for rare imprinting disorders in unexpectedly large numbers of children born after assisted conception.[14-19] Epigenetic mechanisms have been shown to play an important role in human carcinogenesis, both as part of and independently of imprinting disorders.[20,21]

A large population-based study investigated this potential risk in a cohort of 26,692 children born after assisted conception in Sweden between 1982 and 2005.[7] A total of 47 cancers (excluding histiocytosis) were observed in this cohort, which had a higher risk of childhood cancer than did children conceived without assisted conception during the same period (odds ratio after the exclusion of infants with histiocytosis, 1.34; 95% confidence interval [CI], 1.02 to 1.76). Although this study was population-based and used registry data collected on a mandatory basis, exploration of individual cancers was limited. Other, albeit smaller, studies have shown similar nonsignificant increases in the overall risk of childhood cancer.[22-24]

We conducted a large population-based linkage study, aiming to provide robust risk estimates for childhood cancer overall and for specific diagnostic subgroups in children born after assisted conception.

METHODS

STUDY POPULATION AND OVERSIGHT

Records relating to children born between January 1, 1992, and December 31, 2008, in Britain (England, Wales, and Scotland) after non–donor-assisted reproduction were identified by the United Kingdom Human Fertilisation and Embryology Authority (HFEA). Non–donor-assisted reproduction was defined as "all treatments or procedures that include the in vitro handling of both human oocytes and sperm, or embryos, for the purpose of establishing a pregnancy," excluding treatments that use donor oocytes, sperm, or embryos.[25] U.K. law mandates the reporting of all assisted conception cycles to the HFEA, including details of the outcome. Thus, the data set can be considered complete.[26] Records relating to 12,930 children conceived after donor cycles in the same time period were not considered, because HFEA statutes prevent the viewing of identifiable data relating to these children by any third party. See Figure S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org, for an overview of inclusions and exclusions.

Approval of the study and a waiver of the requirement for individual written informed consent were obtained from the National Information Governance Board for Health and Social Care and the London Research Ethics Committee. Families can withdraw consent for their HFEA data to be used for research, and 0.3% of families had done so by the time of our study. Their data were not included. All authors assume responsibility for the accuracy and completeness of the data linkage and analysis. The HFEA and the National Registry of Childhood Tumours (NRCT) vouch for the accuracy and completeness of their respective registry data.

OUTCOME DATA

The incidence of cancer was the primary outcome. Clinical details were obtained from the NRCT. A large national population-based childhood cancer registry, the NRCT ascertains validated information from multiple sources regarding children in the United Kingdom who receive a diagnosis of cancer before 15 years of age and is considered almost complete.[27]

More than 90% of NRCT records include birth-registration details, which are required for successful data linkage. Records lacking birth-registration information are likely to be for children born outside Britain or adopted children and are therefore extremely unlikely to relate to cohort members. Cancers were classified according to the International Classification of Childhood Cancer, third edition (ICCC-3).[28] Coexisting conditions known at the time of the child's

cancer diagnosis are reported to the NRCT by the registering pediatric oncology center. Such information is considered reasonably complete for major congenital anomalies.

DATA LINKAGE

To maximize the sensitivity and specificity of the data linkage, a protocol was developed on the basis of metadata of identified cohort variables (see Table S1 in the Supplementary Appendix). Initially, deterministic linkage was applied to all 106,381 HFEA records of eligible children born after assisted conception and to all 14,896 records of eligible children documented by the NRCT as having been born between 1992 and 2008, with birth-registration details available, and as having received a diagnosis of cancer before January 1, 2009.

Deterministic linkage, with the use of SQL software, involved 19 separate linkages of multiple combinations of the following variables: birth weight, date of birth, maternal date of birth, and paternal date of birth. Probabilistic linkage, with the use of Jaro–Winkler software, was applied to the resulting 4,677,887 potential matches with the use of the father's forename and surname, the mother's forename, and any maternal surnames recorded. Two of the authors applied accuracy criteria independently, with confirmation by a third author, and then manually and independently validated 3949 of the most likely matches. Potential matches were excluded when additional information was in conflict, including sex, twin status, date of embryo transfer, treatment center, the mother's forename and surname at birth, the mother's and father's dates of birth, and the mother's and father's places of birth. When the status of the potential match could not be agreed on or when any doubt existed regarding the validity of the match, the third reviewer made the final decision. Additional details of the record-linkage methods are provided in Table S2 in the Supplementary Appendix.

STATISTICAL ANALYSIS

Person-years at risk were calculated from the date of birth until the date of a cancer diagnosis, December 31, 2008, or the child's 15th birthday, whichever came first, and were categorized according to sex, age at diagnosis (0, 1 to 4, 5 to 9, or 10 to 14 years), birth weight, gestational age at birth, singleton or multiple birth, parity, maternal and paternal age, type of assisted conception, fresh or cryopreserved embryos, and cause of parental infertility. To determine the expected number of cancers in the cohort if the risk for cohort members was the same as that for the general population, we used the calculated person-years at risk in conjunction with the NRCT cancer incidence rates for the general population of Britain of the same age during the same period.[29] See Figure S2 in the Supplementary Appendix for details of planned analyses. The number of observed cancers was assumed to follow a Poisson distribution. Standardized incidence ratios, the ratio of observed to expected numbers of cancers, and exact 95% confidence intervals were calculated. P values of less than 0.05, calculated on the basis of the chi-square test,[29] were considered to indicate statistical significance. Analyses were performed with the use of STATA software, version 11.[30]

RESULTS

CHARACTERISTICS OF THE STUDY PARTICIPANTS

A total of 106,381 children from 83,697 pregnancies, who were conceived by non–donor-assisted conception and born in Britain between 1992 and 2008, were identified from HFEA records. Records for all were included in the data linkage. The year of birth was not available for 368 children, who were therefore excluded from the cohort; the remaining 106,013 children were included in the analysis. Table S3 and Figure S3 in the Supplementary Appendix show the cohort size according to the year of birth and the proportion that each birth year contributed to the total person-years of follow-up. The average duration of follow-up was 6.6 years. A total of 108 children were linked to NRCT records and identified as having received a diagnosis of cancer. Baseline demographic characteristics were similar for cohort members in whom cancer developed and those in whom it did not develop (Table 1). The mean (±SD) age at diagnosis was 4.2±3.3 years. No child in the cohort had more than one recorded diagnosis of cancer.

OVERALL CANCER RISK

On the basis of a total number of expected cancers of 109.7, the standardized incidence ratio in the study cohort was 0.98 (95% CI, 0.81 to 1.19; P=0.87). Similar results were obtained with

Table 1. Characteristics of the Cohort of Children Born after Assisted Conception.*

Characteristic	Total (N=106,381)	Children in Whom Cancer Did Not Develop (N=106,273)	Children in Whom Cancer Developed (N=108)
Sex — no./total no. (%)			
Male	54,143/106,277 (51)	54,083/106,169 (51)	60/108 (56)
Female	52,134/106,277 (49)	52,086/106,169 (49)	48/108 (44)
Singleton vs. multiple birth — no. (%)			
Singleton	62,195 (58)	62,130 (58)	65 (60)
Multiple	44,186 (42)	44,143(42)	43 (40)
Birth weight — g	2864±793	2864±793	2920±782
Birth-weight category — no./total no. (%)			
<2500 g	31,294/105,469 (30)	31,263/105,361 (30)	31/108 (29)
2500–3999 g	68,189/105,469 (65)	68,121/105,361 (65)	68/108 (63)
≥4000 g	5,986/105,469 (6)	5,977/105,361 (6)	9/108 (8)
Gestational age at birth — wk	37.5±3.2	37.5±3.2	37.5±3.2
Type of assisted conception — no. (%)			
IVF	61,521 (58)	61,458 (58)	63 (58)
ICSI or other micromanipulation	42,719 (40)	42,679 (40)	40 (37)
Not recorded	2,141 (2)	2,136 (2)	5 (5)
Fresh vs. cryopreserved embryos — no./total no. (%)			
Fresh	93,689/106,243 (88)	93,596/106,135 (88)	93/108 (86)
Cryopreserved	12,554/106,243 (12)	12,539/106,135 (12)	15/108 (14)
Stage at embryo transfer — no. (%)			
Blastocyst	5,773 (5)	5,769–5,773 (5)†	<5 (0–4)†
Cleavage	57,418 (54)	57,377 (54)	41 (38)
Not recorded	43,190 (41)	43,125 (41)	65 (60)
Maternal age at birth of child — yr	34.3±4.0	34.3±4.0	33.8±4.0
Paternal age at birth of child — yr	37.2±5.8	37.2±5.8	37.6±6.7
Infertility cause — no. (%)			
Both male and female factors	18,063 (17)	18,035 (17)	28 (26)
Female factor only	27,681 (26)	27,652 (26)	29 (27)
Male factor only	24,427 (23)	24,411 (23)	16 (15)
Unexplained	33,840 (32)	33,808 (32)	32 (30)
Not recorded	2,370 (2)	2,366–2,370 (2)†	<5 (0–4)†
Duration of infertility — yr	4.9±2.9	4.9±2.9	5.2±3.3
Previous assisted-conception cycles — no./total no. (%)			
0	53,861/106,344 (51)	53,808/106,236 (51)	53/108 (49)
≥1	52,483/106,344 (49)	52,428/106,236 (49)	55/108 (51)
Previous live births — no./total no. (%)			
0	94,696/105,040 (90)	94,596/104,933 (90)	100/107 (93)
≥1	10,344/105,040 (10)	10,337/104,933 (10)	7/107 (7)

* Plus–minus values are means ±SD. ICSI denotes intracytoplasmic sperm injection, and IVF in vitro fertilization.
† When the number of children in whom cancer developed was less than 5, the number is reported as "<5" owing to protection of patient confidentiality, under the terms of the Section 251 approval (National Health Service Act 2006). In these instances, the number of children in whom cancer did not develop has been approximated accordingly.

stratification according to sex, age, birth weight, gestational age at birth, singleton versus multiple birth, parity, maternal and paternal age, type of assisted conception, fresh versus cryopreserved embryos, and cause of parental infertility (Table S4 in the Supplementary Appendix). Although we could not stratify our data according to the presence or absence of coexisting respiratory conditions, only 3 of 108 children were known to have a coexisting respiratory condition.

RISK ACCORDING TO CANCER TYPE

For leukemia, neuroblastoma, retinoblastoma, and central nervous system, renal, and germ-cell tumors, no excess risk was found in the study cohort (Table 2). One or more coexisting conditions were recorded for 21 children born after assisted conception in whom cancer subsequently developed. Three cases of leukemia were diagnosed, all in children with Down's syndrome, as compared with 1.5 cases of leukemia that would be expected on the basis of NRCT data. No child had any other coexisting condition known to be associated with the development of cancer. All cases of retinoblastoma were unilateral.

The number of hepatic tumors (ICCC-3 diagnostic group VII[28]) in the study cohort was significantly in excess of the expected number (6 vs. 1.8; standardized incidence ratio, 3.27; 95% CI, 1.20 to 7.12; P=0.03). All were hepatoblastomas, and for this subgroup, the standardized incidence ratio was 3.64 (95% CI, 1.34 to 7.93; P=0.02; absolute excess risk, 6.21 cases per 1 million person-years). This increase in risk was associated with low birth weight (Table 3). The standardized incidence ratio among children with a birth weight of less than 2500 g was 10.29 (95% CI, 3.34 to 24.02; P=0.002). Infants with a birth weight of less than 1000 g were at highest risk, with a standardized incidence ratio of 56.96 (95% CI, 6.90 to 205.77; P=0.01). Coexisting conditions, as recorded by the NRCT, occurred in 3 children and were related to prematurity; none were suggestive of an imprinting disorder.

Table 2. Observed vs. Expected Cancers for All Cancers and According to Cancer Type.*

Cancer Type and ICCC-3 Group†	No. of Person-Years of Follow-up	No. of Observed Cancers‡	No. of Expected Cancers	Standardized Incidence Ratio (95% CI)
All cancers: groups I to X	700,705	108	109.7	0.98 (0.81–1.19)
Leukemia: group I	701,047	34	37.5	0.91 (0.63–1.27)
CNS tumors: group III	701,138	22	25.8	0.85 (0.54–1.29)
Neuroblastoma: group IV	701,165	9	10.2	0.88 (0.40–1.68)
Retinoblastoma: group V	701,193	<5	—	0.59 (0.12–1.73)
Renal tumors: group VI	701,162	8	8.5	0.94 (0.41–1.86)
Hepatic tumors: group VII	701,165	6	1.8	3.27 (1.20–7.12)§
Bone tumors and extraosseous sarcomas: groups VIII and IX	701,134	20	8.6	2.34 (1.43–3.61)¶
Osteosarcoma: group VIIIa	701,206	<5	—	2.95 (0.61–8.62)
Ewing's sarcoma: groups VIIIc and IXd, divisions 1 and 2	701,202	<5	—	2.47 (0.67–6.32)
Rhabdomyosarcoma: group IXa	701,162	10	3.8	2.62 (1.26–4.82)§
Other sarcomas: groups VIIIb; VIIId; VIIIe; IXb; IXc; IXd, divisions 3–11; and IXe	701,205	<5	—	1.42 (0.29–4.15)
Germ-cell tumors: group X	701,203	<5	—	0.56 (0.07–2.03)

* CNS denotes central nervous system.
† Cancers were classified according to the International Classification of Childhood Cancer, third edition (ICCC-3).[28]
‡ For cancers with fewer than 5 observed cases, the number is reported as "<5" (and the number of expected cancers is not shown), owing to protection of patient confidentiality, under the terms of the Section 251 approval (National Health Service Act 2006).
§ P<0.05.
¶ P<0.01.

Table 3. Risks of Hepatoblastoma and Rhabdomyosarcoma, with Stratification According to Potential Mediating or Moderating Factors.

Mediating or Moderating Factor	Hepatoblastoma		Rhabdomyosarcoma	
	No. of Person-Years of Follow-up	Standardized Incidence Ratio (95% CI)	No. of Person-Years of Follow-up	Standardized Incidence Ratio (95% CI)
Overall	701,165	3.64 (1.34–7.93)*	701,162	2.62 (1.26–4.82)*
Sex				
Male	359,108	3.19 (0.66–9.32)	359,107	1.78 (0.49–4.57)
Female	342,058	4.42 (0.88–12.43)	342,055	3.82 (1.40–8.31)*
Age at diagnosis				
<1 yr	100,541	1.28 (0.03–7.16)	100,541	0.00 (0.00–6.55)
1–4 yr	308,062	6.21 (2.02–14.49)†	308,068	2.68 (0.98–5.83)
5–9 yr	219,070	0.00 (0.00–54.22)	219,062	3.21 (0.66–9.38)
10–14 yr	73,492	0.00 (0.00–354.53)	73,491	5.54 (0.03–5.96)
Birth weight				
<2500 g	218,240	10.29 (3.34–24.02)†	218,257	2.59 (0.53–7.56)
2500–3999 g	440,482	0.95 (0.02–5.28)	440,462	2.49 (0.91–5.42)
≥4000 g	36,645	0.00 (0.00–32.03)	36,644	4.75 (0.12–26.49)
Gestational age at birth				
≤31 wk	43,442	30.02 (6.19–87.67)†	43,462	4.38 (1.11–24.23)
32–36 wk	161,264	5.51 (0.67–19.92)	161,260	3.46 (0.71–10.11)
≥37 wk	488,281	0.86 (0.02–4.76)	488,267	1.87 (0.61–4.37)
Singleton vs. multiple birth				
Singleton	396,834	2.09 (0.25–7.55)	396,840	1.83 (0.50–4.72)
Multiple	304,332	5.80 (1.58–14.84)*	304,323	3.66 (1.34–7.96)*
Previous live births				
0	644,688	4.06 (1.49–8.83)*	644,685	2.87 (1.38–5.27)*
≥1	52,495	0.00 (0.00–19.97)	52,495	0.00 (0.00–9.99)
Type of assisted conception				
IVF	469,995	5.18 (1.68–12.08)*	470,000	2.01 (0.65–4.70)
ICSI or other micromanipulation	220,674	1.56 (0.04–8.71)	220,665	3.94 (1.28–9.19)*
Not recorded	10,496	0.00 (0.00–85.57)	10,496	0.00 (0.00–46.67)
Fresh vs. cryopreserved embryos				
Fresh	623,876	3.44 (1.12–8.02)*	623,865	2.95 (1.42–5.43)†
Cryopreserved	76,218	5.24 (0.13–29.21)	76,227	0.00 (0.00–7.11)
Not recorded	1,071	0.00 (0.00–1381.02)	1,071	0.00 (0–545.27)

* P<0.05.
† P<0.01.

A bone tumor or extraosseous sarcoma (ICCC-3 diagnostic groups VIII and IX[28]) developed in significantly more children than expected (20 observed vs. 8.6 expected cases; standardized incidence ratio, 2.34; 95% CI, 1.43 to 3.61; P=0.002). This excess was largely, but not exclusively, accounted for by an excess of rhabdomyosarcomas (10 observed vs. 3.8 expected cases; standardized incidence ratio, 2.62; 95% CI, 1.26 to 4.82: P=0.02; absolute excess risk, 8.82 cases per 1 million person-years). The risk of rhabdomyosarcoma did not differ significantly according to age at diagnosis, birth weight, or gestational age at birth (Table 3). Nevertheless, the risk was particularly evident among multiple births, which is surprising because rhabdomyosarcoma is not

known to be associated with low birth weight.[31,32] Results were similar for rhabdomyosarcoma subtypes (data not shown). No coexisting condition consistent with an imprinting disorder was recorded for any of the affected children. The number of cases of rhabdomyosarcoma among children born to fathers older than 40 years of age was significantly greater than the expected number (6 vs. 1.0; standardized incidence ratio, 5.93; 95% CI, 2.18 to 12.90; P=0.004).

DISCUSSION

No increase in the overall risk of cancer was identified in this cohort study involving 106,013 children younger than 15 years of age who were born in Britain between 1992 and 2008 after assisted conception. We detected 108 cancers as compared with 109.7 expected cancers (standardized incidence ratio, 0.98; 95% CI, 0.81 to 1.19). The narrow confidence interval suggests that a large increased cancer risk in this population is very unlikely. Similarly, no increase in risk was found for most of the childhood cancer subtypes. Significantly increased risks were found only for hepatoblastoma and rhabdomyosarcoma. However, the absolute excess risks for these rare cancers were low, and the absolute excess observed risks between assisted conception and the development of these two tumors are not evidence of causation. They may be explained by chance, underlying parental infertility, or potential mediating factors such as low birth weight, imprinting disorders, or unknown factors. These findings should therefore be interpreted with caution.

Our reported standardized incidence ratio and narrow confidence interval for overall cancer risk are consistent with a small increase in the overall risk of cancer shown in a recent systematic review (standardized incidence ratio, 1.32; 95% CI, 1.09 to 1.55)[33] and with a similar finding in a large single study (odds ratio, 1.34; 95% CI, 1.02 to 1.76).[7] There is considerable overlap between the confidence intervals that we present for overall cancer risk and those reported in the latter study. An association between hepatoblastoma and parental infertility has been described previously in a case–control study involving 58 affected children (relative risk, 9.2; 95% CI, 2.1 to 31.5).[34] Only 1 of the children was confirmed to have been born after assisted conception; 3 were born after unspecified fertility treatment, and 2 were triplets presumed to have been conceived after fertility treatment. Subsequent analysis of these data suggested that low birth weight, a known risk factor for the development of hepatoblastoma,[32,34,35] is a potential mediating factor.[8] Children born after assisted conception have consistently been shown to be at higher risk for low birth weight and prematurity than children born after spontaneous conception.[2,3] Similarly, in our study, low birth weight appeared to mediate the association between assisted conception and hepatoblastoma; children with a birth weight of less than 1000 g were at greatest risk. In most cases, low birth weight was related to preterm birth; only 2 of the 6 children with hepatoblastoma had a birth weight below the 10th percentile for gestational age at birth.

A higher risk of imprinting disorders such as the Beckwith–Wiedemann syndrome, caused by epigenetic aberrations (specifically, loss of methylation at the differentially methylated region within *KCNQ1* [*KvDMR1* locus]), has been reported among children born after assisted conception, as compared with children born after spontaneous conception.[14-19] Weksberg et al.[36] reported an association between this specific cause of the Beckwith–Wiedemann syndrome and the development of both hepatoblastoma and rhabdomyosarcoma but not Wilms' tumor (which is more commonly associated with uniparental disomy or hypermethylation of a different region of the same gene). Imprinting disorders were also suggested as a potential mediating factor in a previously described association between assisted conception and hepatoblastoma.[8]

In our study, none of the 16 children in whom rhabdomyosarcoma or hepatoblastoma developed had an imprinting disorder or a coexisting condition consistent with such a disorder, according to the NRCT data. If imprinting disorders are mediating the association between these two rare tumors and assisted conception, they either are undiagnosed subclinical presentations or have not been reported by physicians.

The main strengths of this study are a large sample, high-quality data from two population-based data sets, and meticulous linkage of these data sets. Reporting to the HFEA is mandatory,[26] and the NRCT data are virtually complete.[27] Therefore, any child born in Britain between 1992 and 2008 after assisted conception in whom cancer developed before December 31, 2008, is highly likely to have been identified.

Limitations of the study include a lack of censoring for the competing risks of death and

emigration, which are likely to be small. Extrapolation from national data for survival to 15 years of age[37] suggests that, under normal circumstances, around 600 members of the original cohort (0.6%) would have died during the study period. Estimation of the numbers lost to follow-up as a result of emigration is more difficult, but it would be reasonable to assume that not more than 2% emigrated. There is no evidence to suggest that these competing risks occur at a greater frequency among children born after assisted conception than among spontaneously conceived children.

NRCT cancer registrations were used to calculate the expected incidence of cancer. This rate therefore includes children born after assisted conception, who accounted for 0.5% of all births in Britain in 1992 but for 1.8% in 2008. Because no data were available for deaths and emigrations in the assisted-conception cohort, it was not possible to calculate rates for spontaneously conceived children alone, as a comparison group. We are confident, however, that using overall population rates for comparative purposes has not materially altered our findings.

Although we were able to investigate many potential mediating factors by means of stratification, we were not able to adjust for such factors. Maternal age, parity, smoking status, status with respect to previous miscarriages, and body-mass index have previously been shown not to affect cancer risk in this population.[7] Children from multiple births, including those born after assisted conception, are at significantly lower risk than are singletons.[31,38,39] The previously identified potential mediating factors of low birth weight and premature delivery[7] were explored in our study. However, it was not possible to adjust for respiratory diagnoses, shown previously to have a possible effect on cancer risk among children conceived after assisted conception,[7] or to investigate this potential association systematically. However, only 3 of the 108 children in our cohort in whom cancer developed had a coexisting respiratory condition according to the NRCT data.

Our study had an average follow-up of 6.6 years. Because most cases of many types of childhood cancer, including leukemia and all types of embryonal tumors, occur before 6.6 years of age, this study provides good evidence that the risk of these types of tumors among children born after assisted conception is no different than that in the general population. However, for a few diagnostic categories (particularly Hodgkin's lymphoma and bone tumors), the peak incidence occurs in later childhood and adolescence. Therefore, this study provides weaker evidence of the risk of these types of tumors among children born after assisted conception.

In conclusion, our population-based cohort study showed no increase in the overall risk of cancer among children younger than 15 years of age who were born after assisted conception, as compared with the expected risk. This is reassuring for couples considering assisted conception, children conceived in this way, and their families and clinicians. The weaker evidence that we present for increased risks of rare specific cancers needs further exploration to validate these findings and investigate potential causality. These increased risks could be chance findings, but possible alternative explanations include underlying parental infertility and mediation by either low birth weight or imprinting disorders.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Williams CL, Bunch KJ, Stiller CA, et al. Cancer risk among children born after assisted conception. N Engl J Med 2013;369:1819-27. DOI: 10.1056/NEJMoa1301675

Supplemental Appendix

Cancer risk in children born after assisted conception, Williams CL et al.

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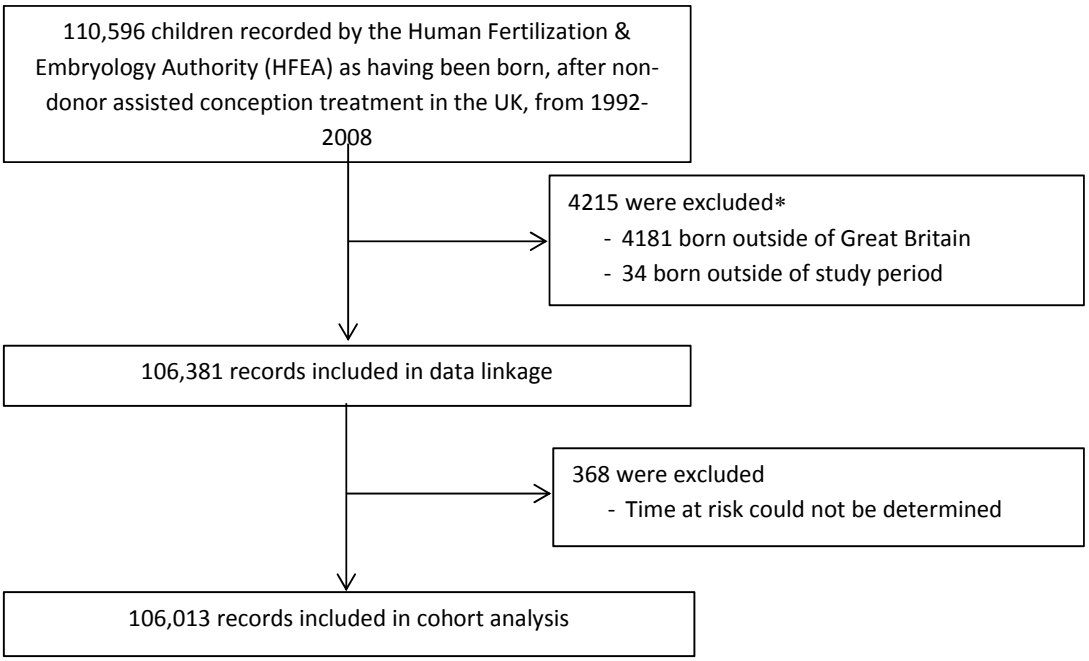

Figure S1. Number of children recorded on the HFEA registry, included in data linkage and included in analysis. * Linkage separately performed on excluded records for further validation of linkage process- no matches found

Planned analyses and post-hoc analyses

Planned Analyses

Comparison of the number of cases in the cohort to the number expected, based on annual age-specific incidence rates in Britain for childhood cancer 1992-2008 was planned. Analyses were planned to consider: -

1. All cancers as a group
2. A priori selected cancers: - Leukemia, Neuroblastoma, Retinoblastoma
3. All cancers as diagnostic subgroups (ICCC3 group codes): - Leukaemia (I), CNS tumors(III), Neuroblastoma and peripheral nerve tumours (IV), Retinoblastoma (V), Renal tumours (VI), Hepatic tumours (VII), Sarcomas (VII and IX), Germ Cell Tumours (X).

When considering all cancers, analyses were planned to stratify for: - sex, age, birth weight, gestation, multiple births, maternal parity, type of assisted reproduction (inc. fresh vs. frozen cycles), and cause of parental infertility.

Post Hoc Analyses

It was decided post hoc to consider different types of sarcoma and hepatic tumours individually. Additionally, post hoc decisions were made to stratify for maternal and paternal age and to stratify for potential mediating/

Figure S2; Details of planned and post-hoc analyses. Extracts from protocol/ analysis plan

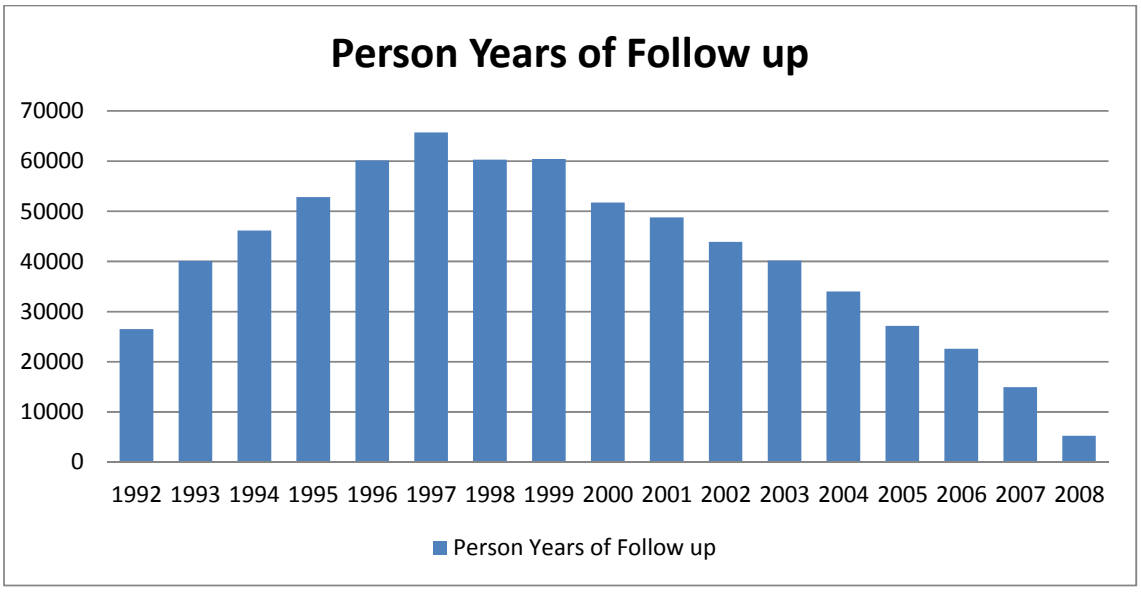

Figure S3; Person Years of Follow up. Cohort of children born after assisted reproduction; contribution of each birth year cohort to total person years of follow up.

Variable	No. records where field is valid	No. records where field is invalid*, 'NULL' or blank	% Valid
Date of birth	110,204	392	99.6%
Sex of Child	Male- 56,265, Female-54,219	112	99.9%
Birth weight	109, 157	1439**	98.7%
Child's Surname	12,332	98,264	11.2%
Child's Forename	11,402	99,194	10.3%
Child's Town of Birth	70,738	39,858	64.0%
Child's District of Birth	18,833	91,763	17.0%
Child's Town ***or*** District of Birth	71,650	38,946	64.8%
Country of Birth	'UK'- 43,886, 'England'- 20,520, 'Scotland'- 2,100, 'Wales'- 1,048	43,042	61.1%
Mother's Surname	110,596	0	100%
Mother's Forename	110,588	8	100.0%
Mother's Surname at Birth	51,237	59,359	46.3%
Mother's Forename at Birth	3,323	107,273	3.0%
Mother's Date of Birth	110,569	27	100.0%
Father's Surname	110,450	146	99.9%
Father's Forename	110,384	212	99.8%
Father's Date of Birth	110,282	314	99.7%
Mother's Town or District of Birth	62,505	48,091	56.5%
Mother's Country of Birth	64,396	46,200	58.2%
Father's Town or District of Birth	61,143	49,453	55.3%
Father's Country of Birth	63,100	47,496	57.1%
Treatment Cycle Start Date	110,596	0	100%
Treatment Centre No/ Name	110,594	2	100.0%

Table S1: Human Fertilization & Embryology Authority Meta Data on all 110,596 live born children born following non- donor assisted conception. Completeness of HFEA variables available for matching. * 'Invalid' data' refers to records which contain unusable information for the variable in question, most commonly variations of 'Not known', 'Unknown'. **905 records with documented birth weights were considered as invalid information for the purpose of deterministic linkage. Whilst a small number of these birth weights recorded as

being <600g are likely to be correct, many more are likely to be data errors within the HFEA database. All actual recorded birth weights were used when manually viewing potential matches.

Linkage	Deterministic Linkage (DL)	Probabilistic Linkage (PL)	Details
M1	i) Birth weights matching within 100g OR Birth weight = Null OR Birth weight <600g *AND* ii) Date of Birth matching within 3 days OR Date of Birth matching in 2 out of 3 parts (i.e. day, month and year- to compensate for potential input errors) OR Date of Birth Null	Probabilistic linkage then applied to all 4,674,445 potential matches for the following variables: i) Father's Surname ii) Father's Forename iii) Mother's Forename For each variable, a probability of match produced (max = 1, min=0) for each potential match. Scores added together to form a total JW score (max 3, min 0).	*Potential matches from DL*= 4,674,445 *Viewed manually after PL (accuracy threshold of 2.35 used)* = 507 *New matches* = 102
M2	i) Birth weights matching within 100g OR Birth weight = Null OR Birth weight <600g *AND* ii) Date of Birth matching within 3 days OR Date of Birth matching in 2 out of 3 parts (i.e. day, month and year- to compensate for potential input errors) OR Date of Birth Null *AND* iii) Mother's date of birth recorded by the HFEA exactly matches NRCT mother's date of birth either from the child's birth record or the marriage certificate.	As M1, but only those not previously viewed were considered (i.e. JW total score ≤ 2.35).	*Potential matches from DL*= 244 *Viewed manually after PL*= 244 *New matches*= 1
M3	i) Birth weights matching within 100g OR Birth weight = Null OR Birth weight <600g *AND*	As M1, but only those not previously viewed were considered (i.e. JW total score ≤ 2.35).	*Potential matches from DL*= 212

	ii) Date of Birth matching within 3 days OR Date of Birth matching in 2 out of 3 parts (i.e. day, month and year- to compensate for potential input errors) OR Date of Birth Null *AND* iii) Father's date of birth recorded by the HFEA exactly matches NRCT Father's date of birth either from the child's birth record or the marriage certificate.		*Viewed manually after PL*= 212 *New matches* = 0
M4	i) Birth weights matching within 100g OR Birth weight = Null OR Birth weight <600g *AND* ii) Date of Birth matching within 3 days OR Date of Birth matching in 2 out of 3 parts (i.e. day, month and year- to compensate for potential input errors) OR Date of Birth Null *AND* iii) Mother's forename perfect or partial match (using NRCT 'Mother's Forename' recorded on birth record) *AND* iv) Mother's surname or mother's surname at birth as recorded by the HFEA, perfect match to any of NRCT mother's surname (surname, alternative surname, previous surname, maiden name).	As M1, but only those not previously viewed were considered (i.e. JW total score ≤ 2.35).	*Potential matches from D L*= 27 *Viewed manually after PL* = 27 *New matches* = 1
M5	i) Birth weights matching within 100g OR Birth weight = Null OR Birth weight <600g *AND* ii) Date of Birth matching within 3 days OR Date of Birth matching in 2 out of 3 parts (i.e. day, month and year- to compensate for potential input errors) OR Date of Birth Null *AND* iii) Father's forename perfect or partial match (using NRCT 'Father's Forename' recorded on birth record) *AND*	As M1, but only those not previously viewed were considered (i.e. JW total score ≤ 2.35).	*Potential matches from DL* = 20 *Viewed manually after PL* = 20 *New matches* = 2

	iv) Father's surname or mother's surname at birth as recorded by the HFEA, perfect match to any of NRCT Father's surname (surname, alternative surname, previous surname, maiden name).		
M6	i) Birth weights matching within 100g OR Birth weight = Null OR Birth weight <600g *AND* ii) NRCT birth weight not NULL *AND* iii) Date of Birth exact match	As M1, but only those not previously viewed were considered (i.e. JW total score ≤ 2.35).	*Potential matches from DL = 0* *Viewed manually after PL* - N/A *New matches* - N/A
M7	i) Birth weights matching within 100g OR Birth weight = Null OR Birth weight <600g *AND* ii) Date of Birth matching within 3 days OR Date of Birth matching in 2 out of 3 parts (i.e. day, month and year- to compensate for potential input errors) OR Date of Birth Null *AND* iii) Mothers forename 'reverse' partial match (e.g. HFEA: Louisa matches to NRCT: Claire Louisa)	As M1, but only those not previously viewed were considered (i.e. JW total score ≤ 2.35).	*Potential matches from DL* = 15 *Viewed manually after PL* = 15 *New matches* = 0
M8	i) Birth weights matching within 100g OR Birth weight = Null OR Birth weight <600g *AND* ii) Date of Birth matching within 3 days OR Date of Birth matching in 2 out of 3 parts (i.e. day, month and year- to compensate for potential input errors) OR Date of Birth Null *AND* iii) Fathers forename 'reverse' partial match (e.g. HFEA: James matches to NRCT: Peter James)	As M1, but only those not previously viewed were considered (i.e. JW total score ≤ 2.35).	*Potential matches from DL* = 10 *Viewed manually after PM* = 10 *New matches* = 0
M9	i) Birth weights matching within 100g OR Birth weight = Null OR Birth weight <600g *AND*	As M1, but only those not previously viewed were considered (i.e. JW total score ≤ 2.35).	*Potential matches from DL* = 0

	ii) Date of Birth matching within 3 days OR Date of Birth matching in 2 out of 3 parts (i.e. day, month and year- to compensate for potential input errors) OR Date of Birth Null **AND** iii) Mothers HFEA forename perfect or partial match to NRCT mothers alternative forename *AND* iv) Mothers surname or mothers surname at birth as recorded by the HFEA, perfect match to any of NRCT mother's surname (surname, alternative surname, previous surname, maiden name).		*Viewed manually after PL* -N/A *New matches*- N/A
M10	i) Birth weights matching within 100g OR Birth weight = Null OR Birth weight <600g *AND* ii) Date of Birth matching within 3 days OR Date of Birth matching in 2 out of 3 parts (i.e. day, month and year- to compensate for potential input errors) OR Date of Birth Null *AND* iii) HFEA mothers forename at birth perfect or partial match to NRCT mothers forename *AND* iv) Mothers surname or mothers surname at birth as recorded by the HFEA, perfect match to any of NRCT mother's surname (surname, alternative surname, previous surname, maiden name).	As M1, but only those not previously viewed were considered (i.e. JW total score ≤ 2.35).	*Potential matches after DL* = 0 *Viewed manually after PL- N/A* *New matches- N/A* N/A
M11	i) Birth weights matching within 100g OR Birth weight = Null OR Birth weight <600g *AND* ii) Date of Birth matching within 3 days OR Date of Birth matching in 2 out of 3 parts (i.e. day, month and year- to compensate for potential input errors) OR Date of Birth Null	As M1, but only those not previously viewed were considered (i.e. JW total score ≤ 2.35).	*Potential matches from DL* = 0 *Viewed manually after PL*- N/A

	AND iii) HFEA mothers forename at birth perfect or partial match to NRCT mothers alternative forename *AND* iv) Mothers surname or mothers surname at birth as recorded by the HFEA, perfect match to any of NRCT mother's surname (surname, alternative surname, previous surname, maiden name).		*New matches* - N/A
M12	i) Birth weights matching within 100g OR Birth weight = Null OR Birth weight <600g *AND* ii) Date of Birth matching within 3 days OR Date of Birth matching in 2 out of 3 parts (i.e. day, month and year- to compensate for potential input errors) OR Date of Birth Null *AND* iii) HFEA Fathers forename perfect or partial match to NRCT Fathers alternative forename *AND* iv) Fathers surname or mothers surname at birth as recorded by the HFEA, perfect match to any of NRCT father's surname (surname, alternative surname, previous surname, maiden name).	As M1, but only those not previously viewed were considered (i.e. JW total score ≤ 2.35).	*Potential matches from DL* = 0 *Viewed manually after PL – N/A* *New matches*- N/A
M13	i) Birth weights matching within 100g OR Birth weight = Null OR Birth weight <600g *AND* ii) Date of Birth matching within 3 days OR Date of Birth matching in 2 out of 3 parts (i.e. day, month and year- to compensate for potential input errors) OR Date of Birth Null *AND* iii) Mothers forename perfect or partial match (using NRCT 'Mothers Forename' recorded at diagnosis not on Birth	As M1, but only those not previously viewed were considered (i.e. JW total score ≤ 2.35).	*Potential matches from DL* = 10 *Viewed manually after PL* = 10 *New matches* = 0

	record) *AND* iv) Mothers surname or mothers surname at birth as recorded by the HFEA, perfect match to any of NRCT mother's surname (surname, alternative surname, previous surname, maiden name).		
M14	i) Birth weights matching within 100g OR Birth weight = Null OR Birth weight <600g *AND* ii) Date of Birth matching within 3 days OR Date of Birth matching in 2 out of 3 parts (i.e. day, month and year- to compensate for potential input errors) OR Date of Birth Null *AND* iii) Fathers forename perfect or partial match (using NRCT 'Fathers Forename' recorded at diagnosis not as appears on birth record) *AND* iv) Fathers surname or mothers surname at birth as recorded by the HFEA, perfect match to any of NRCT Fathers surname (surname, alternative surname, previous surname, maiden name).	As M1, but only those not previously viewed were considered (i.e. JW total score ≤ 2.35).	*Potential matches from DL* = 6 *Viewed manually after PL* = 6 *New matches* = 0
M15	i) Mothers forename full or partial match *AND* ii) Mothers surname (HFEA) full match to any NRCT mother surname (including as recorded at diagnosis, as recorded at mothers birth and as recorded at child's birth) *AND* iii) Birth-weight NOT NULL or 'effectively' NULL	No JW criteria applied to this match	*Potential matches from DL* = 147 *Viewed manually*= 147 *New matches* = 11
M16	i) Mothers forename full or partial match *AND*	No JW criteria applied to this match	*Potential matches from DL* = 4

	ii) Mothers surname (HFEA) full match to any NRCT mother surname (including as recorded at diagnosis, as recorded at mothers birth and as recorded at child's birth) *AND* iii) Birth-weight NOT NULL or 'effectively' NULL *AND* iv) Date of Birth exact match		*Viewed manually*= 4 *New matches* = 0
M17	i) Birth weights matching within 100g *AND* ii) Mothers forename perfect or partial match (using any recorded NRCT 'Mothers Forename') recorded on birth record) *AND* iii) Mothers surname or mothers surname at birth as recorded by the HFEA, perfect match to any of NRCT mother's surname (surname, alternative surname, previous surname, maiden name). *AND* iv) Date of birth is NOT NULL	JW Total score (for mothers forename, fathers forename, fathers surname scores combined as in M1) less than 2.35	*Potential matches from DL* = 2384 *Viewed manually after PL* = 2384 *New matches* = 0
M18	i) Date of Birth matching within 3 days OR Date of Birth matching in 2 out of 3 parts (i.e. day, month and year- to compensate for potential input errors) OR Date of Birth Null *AND* ii) Mother forename partial reverse match (e.g. 'Sarah Jane' on the NRCT birth record matches to 'Jane' on the HFEA record) *AND* iii) Mothers surname or mothers surname at birth as recorded by the HFEA, perfect match to any of NRCT mother's surname (surname, alternative surname, previous	No JW criteria applied to this match	*Potential matches from DL* = 69 *Viewed manually* = 69 *New matches* = 0

	surname, maiden name).		
M19	i) Birth weights matching within 100g *AND* ii) Mothers forename perfect or partial match (using any recorded NRCT 'Mothers Forename') recorded on birth record) *AND* iii) Mothers surname or mothers surname at birth as recorded by the HFEA, perfect match to any of NRCT mother's surname (surname, alternative surname, previous surname, maiden name). *AND* iv) Date of birth is NOT NULL	JW Total score (for mothers forename, fathers forename, fathers surname scores combined as in M1) less than 2.35	*Potential matches from DL* = 294 *Viewed manually after PL* = 294 *New matches* = 0

Table S2: Data Matching Process. Details of matching process including variables used, accuracy thresholds and numbers of potential matches viewed manually.

Year of Birth	No of Children born after assisted conception	% of cohort	Cumulative % of Cohort	Person Years of follow up	Person Years as % of total
1992	1768	1.7	1.7	26491	3.7
1993	2676	2.5	4.2	40108	5.7
1994	3185	3.0	7.2	46154	6.6
1995	3925	3.7	10.9	52830	7.5
1996	4818	4.5	15.4	60124	8.6
1997	5723	5.4	20.8	65733	9.4
1998	5756	5.4	26.2	60275	8.6
1999	6371	6.0	32.2	60414	8.6
2000	6108	5.7	37.9	51747	7.4
2001	6538	6.1	44.1	48780	7.0
2002	6792	6.4	50.4	43915	6.3
2003	7332	6.9	57.3	40171	5.7
2004	7563	7.1	64.4	34020	4.9
2005	7789	7.3	71.8	27164	3.9
2006	9061	8.5	80.3	22592	3.2
2007	10005	9.4	89.7	14958	2.1
2008	10603	10.0	99.7	5228	0.7
Missing Values	368	0.3	100.0	N/A	N/A
Totals	106,381	100	100	700,705	100

Table S3; Cohort by Year of Birth and Person Years of Follow up. Cohort of Children born after assisted conception by year of birth and person years contributed to cohort analysis

Potential Mediating/ Moderating Factor		Person years of follow up	SIR	95% CI
Overall		700,705	0.98	0.81-1.19
Potential mediators	Sex			
	Male	358,853	1.00	0.77-1.29
	Female	341,852	0.96	0.71-1.27
	Age Group at Diagnosis (years)			
	0	100,532	0.85	0.50-1.37
	1-4	307,932	0.93	0.70-1.21
	5-9	218,839	1.22	0.82-1.75
	10-14	73,401	1.03	0.44-2.02
	Birth Weight			
	<1000g	15,516	0.84	0.10-3.03
	1000-1499g	28,307	0.47	0.06-1.68
	1500-2499g	174,294	1.00	0.66-1.46
	2500-3999g	440,171	0.98	0.76-1.24
	≥4000g	36,617	1.52	0.69-2.88
	Gestational Age at Birth			
	<26 weeks	6,319	1.02	0.03-5.68
	26-31 weeks	37,099	1.06	0.39-2.30
	32-36 weeks	161,139	1.08	0.71-1.58
	37-41 weeks	468,563	0.95	0.74-1.20
	42+ weeks	19,411	0.98	0.20-2.86
	Number of Infants per Birth			
	1	396,569	1.04	0.80-1.33
	2	268,651	0.95	0.68-1.30
	3	35,144	0.59	0.12-1.72
	4	341	0.00	0.00-63.62

Potential Moderators	Maternal Previous Live Births			
	0	644,270	1.00	0.81-1.21
	1	50,879	0.82	0.33-1.70
	2	1,492	0.00	0.00-11.63
	3 or more	86	0.00	0.00-193.15
	Type of Assisted conception			
	IVF	469,686	0.89	0.68-1.14
	ICSI	134,006	1.07	0.70-1.57
	Unspecified Micromanipulation	86,534	1.10	0.60-1.85
	Not recorded	10,478	2.70	0.88-6.31
	Fresh/Cryopreserved cycle			
	Fresh	623,485	0.95	0.77-1.17
	Cryopreserved	76,149	1.24	0.69-2.04
	Not recorded	1,071	0.00	0.00-18.34
	Maternal Age at Birth of Child			
	<30 years	92,325	0.98	0.54-1.65
	30-34 years	289,042	0.98	0.71-1.32
	35-39 years	264,652	1.03	0.74-1.38
	40+ years	54,423	0.80	0.32-1.65
	Paternal Age at Birth of Child			
	<30 years	49,606	0.79	0.29-1.73
	30-34 years	210,645	1.05	0.73-1.46
	35-39 years	255,613	0.80	0.54-1.12
	40+ years	183,571	1.20	0.83-1.66

	Broad Cause Parental Infertility			
	Both Male & Female factor	166,862	1.15	0.76-1.66
	Female factor only	176,555	1.04	0.70-1.50
	Male factor only	96,536	0.92	0.53-1.49
	Unexplained	250,328	0.84	0.57-1.18
	Not recorded	10,423	1.62	0.34-4.75

Table S4: Childhood Cancer Risk Stratified by Potential Mediating and Moderating Factors. Observed vs. expected cancers for 'all cancer' stratified by potential mediating/ moderating factors. *=P<0.05, **=P<0.01