Cancer risk in children born after donor assisted reproductive technology

Journal:	*Human Reproduction*
Manuscript ID	HUMREP-17-0550.R2
Manuscript Type:	Original Article
Date Submitted by the Author:	06-Oct-2017
Complete List of Authors:	Williams, Carrie; University College London, Great Ormond Street Institute of Child Health Bunch, Kathryn; University of Oxford, National Perinatal Epidemiology Unit Murphy, Michael; University of Oxford, Nuffield Department of Obstetrics & Gynaecology Stiller, Charles; National Cancer Registration and Analysis Service Botting, Beverley; University College London, Great Ormond Street Institute of Child Health Wallace, Wiliam; Department of Reproductive and Developmental Sciences, Division of Child Life and Health,, University of Edinburgh Davies, Melanie; UCLH Foundation Trust, Reproductive Medicine Unit Sutcliffe, Alastair; University College London, Great Ormond Street Institute of Child Health
Keywords:	childhood cancer, donor treatment, cohort study, CHILD FOLLOW-UP, ASSISTED REPRODUCTION
Subject Section:	Reproductive Epidemiology

TITLE: Cancer risk in children born after donor assisted reproductive technology

RUNNING TITLE: Childhood Cancer after donor ART

Dr CL Williams[1], Mrs KJ Bunch[2], Dr MFG Murphy [3], Mr CA Stiller[4], Dr BJ Botting[1], Professor WH Wallace[5], Dr MC Davies[6], Professor AG Sutcliffe*[1].

[1.] University College London, Great Ormond Street Institute of Child Health, London, UK, WC1 1EH. [2.] National Perinatal Epidemiology Unit, University of Oxford, Oxford, UK, OX3 7LF. [3.] Nuffield Department of Obstetrics & Gynaecology, University of Oxford, Oxford, UK, OX3 9DU *[4.] National Cancer Registration and Analysis Service, Oxford, UK,* OX4 2GX*. [5]. Paediatric Oncology Department, Royal Hospital for Sick Children, University of Edinburgh, Edinburgh, UK, EH9 1LF. [6.] Reproductive Medicine Unit, Institute for Women's Health, University College London Hospitals, London, UK,* NW1 2BU*.*

**Corresponding Author: Professor A G Sutcliffe, Policy, Practice and Populations Unit, University College London, Great Ormond Street Institute of Child Health, 30 Guilford Street, London, WC1N 1EH or a.sutcliffe@ucl.ac.uk*

ABSTRACT

Study question: Do children born after donor assisted reproductive technology (ART) have an increased risk of developing childhood cancer in comparison to the general population?

Summary answer: This study showed no overall increased risk of childhood cancer in individuals born after donor ART.

What is known already: Most large population based studies have shown no increase in overall childhood cancer incidence after non-donor ART; however other studies have suggested small increased risks in specific cancer types, including haematological cancers. Cancer risk specifically in children born after donor ART has not been investigated to date.

Study design, size, duration: This retrospective cohort study utilized record linkage to determine the outcome status of all 12,186 children born in Great Britain (1992-2008) after donor ART. The cohort included -12,137 members contributed 95,389 person-years of follow-up (average follow-up 7.86 years).

Participants, setting, methods: Records of all children born in Great Britain (England, Wales, Scotland) after all forms of donor ART (1992-2008) were linked to the UK National Registry of Childhood Tumours (NRCT) to determine the number who subsequently developed cancer by 15 years of age, by the end of 2008. Rates of overall and type specific cancer (selected a priori) were compared with age, sex and calendar year standardised population-based rates, stratifying for potential mediating/moderating factors including sex, age at diagnosis, birth weight, multiple births, maternal previous live births, assisted conception type, and fresh/ cryopreserved cycles.

Main results and the role of chance: In our cohort of 12,137 children born after donor assisted reproductive technology (52% male, 55% singleton births), no overall increased risk of cancer was identified. There were 12 cancers detected compared to 14.4 expected (standardised incidence ratio (SIR) 0.83; 95% confidence interval (CI) 0.43-1.45; *P*=0.50). A small, significant increased risk of hepatoblastoma was found, but the numbers and absolute risks were small (<5 cases observed; SIR

10.28; 95%CI 1.25-37.14; *P*<0.05). This increased hepatoblastoma risk was associated with low birthweight.

Limitations, reasons for caution: Although this study includes a large number of children born after donor ART, the rarity of specific diagnostic sub-groups of childhood cancer results in few cases and therefore wide confidence intervals for such outcomes. As this is an observational study, it is not possible to adjust for all potential confounders; we have instead used stratification to explore potential moderating and mediating factors, where data were available.

Wider implications of the findings: This study is the first to investigate cancer risk in children born after donor ART. Although based on small numbers, results are reassuring for families and clinicians. The small but significant increased risk of hepatoblastoma detected was associated with low birthweight, a known risk factor for this tumour type. It should be emphasised that the absolute risks are very small. However, an on-going investigation with a longer follow-up is needed.

Study funding/competing interest(s): This work was funded by Cancer Research UK (C36038/A12535) and the National Institute for Health Research (405526) and supported by the National Institute for Health Research Biomedical Research Centre at Great Ormond Street Hospital for Children NHS Foundation Trust and University College London. The work of the Childhood Cancer Research Group (CCRG) was supported by the charity CHILDREN with CANCER UK, the National Cancer Intelligence Network, the Scottish Government and the Department of Health for England and Wales. There are no competing interests.

Trial registration number: N/A

Key Words: childhood cancer, assisted reproductive technology, donor treatment, cohort study, epidemiology, data linkage.

INTRODUCTION

Donor ART treatment cycles utilize donor sperm, oocytes or embryos and result in approximately 10% of all births after ART in the UK (Human Fertilisation & Emryology Authority 2013). Given that most donors have few, if any, fertility problems, children born after donor ART represent a subtly different population than children born after non-donor ART. This inherent difference, together with the increasing use of donor ART cycles and the extra uncertainty faced by couples using donor gametes, places greater importance on follow-up studies differentiating between children born after donor and non-donor ART.

The possibility of an increased risk of childhood cancer in individuals born after ART has been suggested previously (Hargreave et al. 2013; Puumala et al. 2012; Schieve et al. 2004; Sutcliffe and Ludwig 2007; Kallen et al. 2010). Systematic reviews have provided conflicting evidence (Raimondi, Pedotti, and Taioli 2005; Hargreave et al. 2013; Reigstad et al. 2017), with a recent meta-analysis suggesting a small but significant increased risk of cancer in children born after ART (Relative Risk 1.33; 95%CI 1.08-1.63) (Hargreave et al. 2013). Two large, population based studies, published since, reported no overall increased risk and no increased risk in haematological cancers (Sundh et al. 2014; Williams et al. 2013). However, these studies did not include children born after donor ART (Sundh et al. 2014; Williams et al. 2013). A further, smaller, population based study showed no overall increased risk of childhood cancer, but did find a significant increase in leukaemia and Hodgkin lymphoma (Reigstad et al. 2016). This study did include some children born after donor ART but did not estimate risk in this group separately (Reigstad et al. 2016).

We conducted a large population-based linkage study, aiming to provide risk estimates for childhood cancer overall and for specific diagnostic subgroups (chosen a priori), in individuals born after donor ART.

MATERIALS AND METHODS

Population and cohort participants

All records relating to 12,186 children born between January 1st 1992 and December 31st 2008 in Great Britain (England, Wales and Scotland) after donor ART were identified by the Human Fertilization and Embryology Authority (HFEA). Donor ART is defined as 'all treatments or procedures including in-vitro handling of both human oocytes and sperm, or embryos, for the purpose of establishing a pregnancy' using donor oocytes, sperm or embryos (Zegers-Hochschild et al. 2009). The HFEA is legally required to record treatment and outcome details of all ART cycles in the UK, including those using donor gametes or embryos. Thus the dataset is considered effectively complete (HFEA act 2008).

Ethical approval

Approval for the study was obtained from the National Information Governance Board and the London Research Ethics Committee including approval for the restricted use of data without individual written informed consent. One of the conditions attached to approval of this study prevents the publication of cells containing less than five individuals. Patients can withdraw consent for their HFEA data to be used for research. At the time of the study, 0.3% of all families using ART had done so; their data were not included.

Outcome data

Details of cancer incidence were obtained from the National Registry of Childhood Tumours (NRCT). During the study period, the NRCT was the largest national population-based childhood cancer registry world-wide, ascertaining validated information from multiple sources about children, under 15 years, diagnosed with cancer in the UK (Kroll et al. 2011). The NRCT is considered almost complete for the study period(Kroll et al. 2011). The International Classification of Childhood Cancer 3rd edition (ICCC3), was used to categorise cancers (Steliarova-Foucher et al. 2005). Co-morbidities, known at the time of a child's cancer diagnosis, were reported to the NRCT by the registering oncology centre, and data are reasonably complete for major congenital anomalies.

Data linkage

Ethical regulations stipulated that identifiable data were only viewed directly by HFEA staff. Therefore data linkage was undertaken by two members of HFEA staff independently from each other, following a robust data linkage protocol, developed to maximize linkage sensitivity and specificity, used and described in another similar study (Williams et al. 2013). Linkage was directly overseen by CLW, KJB and BB. A total of 12,186 eligible HFEA records of children born after donor ART 1992-2008 were linked to all 14,896 NRCT eligible records of children documented as having been born 1992-2008, and having developed cancer before January 1st 2009. All potential matches using this inclusive linkage protocol were anonymously reviewed by CLW and KJB. BB reviewed any cases where the validity of the match was questionable (n=2, both unanimously rejected by all three reviewers).

Statistical analyses and calculation of expected rates

Person-years at risk were calculated from date of birth until the soonest of cancer diagnosis date, December 31, 2008 or the child's 15th birthday. There were 49 children (0.4%) excluded from the analyses as no valid date of birth was available and therefore person-years at risk could not be determined. Expected cancers in the cohort were calculated by multiplying person-years at risk by the corresponding national incidence rates (1-year age bands by calendar year and sex) for children born and diagnosed in Great Britain. Standardized Incidence Ratios (SIR) were calculated comparing observed cancers within the cohort to expected values. Exact 95% confidence intervals and two-sided P values were calculated assuming a Poisson distribution (Breslow and Day 1987). Analyses were performed using STATA software, version 12 (Stata Corp 2013).

RESULTS

Included in this study were 12,137 children who contributed 95,389 person-years follow-up, with an average duration of 7.86 years. Cohort demographics are detailed in Table 1.

Twelve children were linked to NRCT records and therefore identified as having developed cancer. Baseline demographics appeared broadly similar for cohort members who did and did not develop cancer (data not shown separately given the small numbers). The median age at cancer diagnosis was 2.6 years (inter-quartile range 1.2-5.2). There were no children with more than one cancer diagnosis. There were 14.4 cancers expected within the cohort, resulting in an unadjusted SIR of 0.83 (95% CI 0.43-1.45; Table 2). Sensitivity analysis including the two potential cases rejected during data-linkage did not substantially alter the results (SIR 0.97; 95% CI 0.53- 1.63; data not shown). The results did not change appreciably when stratified by sex, age at diagnosis, birthweight, birth multiplicity, maternal parity, type of ART, and fresh versus cryopreserved embryos (Table 2), although the small number of events in some strata have resulted in wider confidence intervals.

No significant excess risk was seen for any major ICCC3 category, with the exception of hepatic tumours (Table 3). A significant excess of hepatic tumours was detected (SIR 9.12; 95%CI 1.11-32.95; Table 3), all of which were hepatoblastomas (SIR 10.28; 95%CI 1.25-37.14; Table 3; Absolute excess risk 18.66 per million person-years at risk, 95%CI 0.24-73.39). This excess was associated with low birthweight and was only seen in children with birthweight <2500g (SIR 28.00; 95%CI 3.39-101.14; *P*= 0.02; data not shown).

DISCUSSION

No overall increased risk of childhood cancer was detected in this large and complete national population based cohort of children born after donor ART. This is in line with two similar recently published cohort studies of children born after non-donor ART (Sundh et al. 2014; Williams et al. 2013). The recently published study combining data on 91,796 children born after non-donor ART in

four Nordic countries found no significant increase in overall cancer rates (adjusted Hazard Ratio 1.08; 95%CI 0.91-1.27) (Sundh et al. 2014). Similarly our previous study of 106,013 children born after non-donor ART over the same study period and from the same population as our current study, did not show an overall increased risk of cancer (SIR 0.98; 95%CI 0.81-1.19) (Williams et al. 2013).

This study is the first, to our knowledge, to explore cancer risk in children born after donor ART and uses high quality data from two population-based data sets. NRCT data are virtually complete for the study period (Kroll et al. 2011) and reporting to the HFEA is mandatory (HFEA act 2008). Whilst this study is the first to investigate cancer risk after donor ART, it is based on previously published methodology (Williams et al. 2013). There were very few cases with uncertain linkage (n=2), and sensitivity analysis including these did not substantially alter results.

Although this is a population-based study covering the whole of Great Britain over a 17 year time period which includes a large number of children born after donor ART, the rarity of specific diagnostic sub-groups of childhood cancer and thus the small number of cases reported in this study result in wide confidence intervals for individual outcomes. As this is an observational study, it is not possible to adjust for all potential confounders. We have instead used stratification to explore the role of a number of potential moderating and mediating factors, where data are available. Additionally, this study was not able to compensate for deaths and emigrations within this cohort. However, given the age of the cohort and extrapolating from national data (Office for National Statistics 2010), we would estimate under normal circumstances not more than 69 members of the original cohort would have died during follow-up (0.6%). Emigration rates are harder to estimate, but we assume not more than 2% are likely to have emigrated during follow-up. It was not possible to adjust for socio-economic status (SES) as no measure of SES was available for the cohort as a whole. It is also possible that there were other unknown potential confounding factors, which we were unable to take into account. Whilst the overall numbers of children born after oocyte donation,

sperm donation or embryo donation were available, these data were not available for analysis at an individual level. Our study had an average follow-up of 7.86 years. Therefore we are not able to comment definitively on risk of cancer subtypes with a peak age of onset beyond 7 years.

A significantly increased risk of hepatoblastoma was detected in this study of children born after donor ART, and was associated with low birthweight. A similar increased risk of hepatoblastoma, associated with low birthweight, was seen in our previous study of children born after non-donor conception (SIR 3.64; 95% CI 1.34-7.93) (Williams et al. 2013). The Nordic group found a 2- fold increase risk of hepatic tumours in children born after non-donor ART; although this was based on small numbers and confidence intervals were wide and included 1, they did find a hazard ratio of 2.61 (aHR2.61 (0.74-9.26; adjusted for country, maternal age, parity, sex, gestational age and birth defects) (Sundh et al. 2014). Beckwith-Wiedemann syndrome (BWS) is also a risk factor for hepatoblastoma (Puumala et al., 2012), and children born after ART are at increased risk of BWS (Amor and Halliday 2008). There was a small number of children (less than five) in our cohort with BWS, but there were no cases of hepatoblastoma in children with BWS or related anomalies.

There is a known, consistent, inverse association between birth weight and hepatoblastoma risk (O'Neill et al. 2015; Heck et al. 2013; de Fine Licht et al. 2012; Ansell et al. 2005; Spector et al. 2009; Spector et al. 2008; Ikeda, Matsuyama, and Tanimura 1997; McLaughlin et al. 2006; Tanimura et al. 1998). Children born after ART are known to have significantly lower birth weight than children born after spontaneous conception (McDonald et al. 2010; Helmerhorst et al. 2004). Unfortunately as we were unable to adjust for birth weight, instead stratifying for this factor in both studies, we are unable to determine whether children in these studies have increased risk of hepatoblastoma mediated solely due to their low birth weight or whether children with low birth weight born after ART are at higher risk than they would be if born after spontaneous conception. The Nordic study did

not adjust for birth weight directly, but adjusted for gestational age, which did not materially alter their rate estimate for hepatic tumours (Sundh et al. 2014).

In conclusion, this study provides evidence against an increased risk of overall childhood cancer in individuals born after donor ART, which is reassuring for parents and clinicians alike. For the majority of individual diagnostic subgroups, risk estimates were not significantly raised. A significant increased risk of hepatoblastoma was observed, in line with that found in our recent study of children born after non-donor ART. This was associated with low birth weight, itself a known risk factor for hepatoblastoma. Although this finding was not observed in non-UK studies (Sundh et al. 2014; Kallen et al. 2010), further investigation is warranted. However it should be emphasised that the absolute risks are very small.

ACKNOWLEDGEMENTS

We would like to acknowledge the help and support of Dr Helen Klip (Department of Epidemiology, The Netherlands Cancer Institute) and of the UK Human Fertilisation and Embryology Authority (HFEA).

AUTHORS' ROLES

Dr Williams jointly conceptualized and designed the study, devised the linkage protocol, supervised the linkage and carried out the analysis, drafted the initial manuscript and approved the final manuscript as submitted.

Mrs Bunch jointly conceptualized and designed the study, devised the linkage protocol, jointly supervised the linkage and carried out the analysis, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Mr Charles Stiller jointly conceptualized and designed the study, interpreted data, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Dr Michael Murphy jointly conceptualized and designed the study, interpreted data, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Dr Beverley Botting jointly conceptualized and designed the study, review data linkage, interpreted data, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Professor Hamish Wallace jointly conceptualized and designed the study, interpreted data, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Dr Melanie Davies jointly conceptualized and designed the study, interpreted data, reviewed and revised the manuscript, and approved the final manuscript as submitted.

Professor Alastair Sutcliffe jointly conceptualized and designed the study, interpreted data, reviewed and revised the manuscript, and approved the final manuscript as submitted.

FUNDING

This work was funded by Cancer Research UK (C36038/A12535) and the National Institute for Health Research (405526) and supported by the National Institute for Health Research Biomedical Research Centre at Great Ormond Street Hospital for Children NHS Foundation Trust and University College London. The work of the Childhood Cancer Research Group (CCRG) was supported by the charity CHILDREN with CANCER UK, the National Cancer Intelligence Network, the Scottish Government and the Department of Health for England and Wales.

CONFLICT OF INTEREST

There are no conflicts of interest.

REFERENCES

Amor DJ and Halliday J. (2008) A review of known imprinting syndromes and their association with assisted reproduction technologies. Hum Reprod; 23 2826-34.

Ansell P, Mitchell CD, Roman E, Simpson J, Birch JM, and Eden TO. Relationships between perinatal and maternal characteristics and hepatoblastoma: a report from the UKCCS. *Eur J Cancer* 2005; 41 741-8.

Breslow NE and Day NE. *Statistical Methods in Cancer Research*. Volume II, 1987. International Agency for Research on Cancer, Lyon, France.

de Fine Licht S, Schmidt LS, Rod NH, Schmiegelow K, Lahteenmaki PM, Kogner P, Trager C, Stokland T, and Schuz J. Hepatoblastoma in the Nordic countries. *Int J Cancer* 2012; 131 E555-61.

Hargreave M, Jensen A, Toender A, Andersen KK, and Kjaer SK. Fertility treatment and childhood cancer risk: a systematic meta-analysis. *Fertil Steril* 2013; 100 150-61.

Heck JE, Meyers TJ, Lombardi C, Park AS, Cockburn M, Reynolds P, and Ritz B. Case-control study of birth characteristics and the risk of hepatoblastoma. *Cancer Epidemiol* 2013; 37 390-5.

Helmerhorst FM, Perquin DA, Donker D, and Keirse MJ. Perinatal outcome of singletons and twins after assisted conception: a systematic review of controlled studies. *BMJ* 2004; 328 261.

Human Fertilisation & Embryology Authority. Egg and Sperm Donation in the UK 2012-2013. (http://www.hfea.gov.uk/9370.html). Accessed: 17/5/2017

Ikeda H, Matsuyama S, and Tanimura M. Association between hepatoblastoma and very low birth weight: a trend or a chance? *J Pediatr* 1997; 130 557-60.

Kallen B, Finnstrom O, Lindam A, Nilsson E, Nygren KG, and Olausson PO. Cancer risk in children and young adults conceived by in vitro fertilization. *Pediatrics* 2010; 126 270-6.

Kroll ME, Murphy MF, Carpenter LM, and Stiller CA. Childhood cancer registration in Britain: capture-recapture estimates of completeness of ascertainment. *Br J Cancer* 2011; 104 1227-33.

McDonald SD, Han Z, Mulla S, Ohlsson A, Beyene J, Murphy KE, and Knowledge Synthesis G. Preterm birth and low birth weight among in vitro fertilization twins: a systematic review and meta-analyses. *Eur J Obstet Gynecol Reprod Biol* 2010; 148 105-13.

McLaughlin CC, Baptiste MS, Schymura MJ, Nasca PC, and Zdeb MS. Maternal and infant birth characteristics and hepatoblastoma. *Am J Epidemiol* 2006; 163 818-28.

O'Neill KA, Murphy MF, Bunch KJ, Puumala SE, Carozza SE, Chow EJ, Mueller BA, McLaughlin CC, Reynolds P, Vincent TJ, et al. Infant birthweight and risk of childhood cancer: international population-based case control studies of 40 000 cases. *Int J Epidemiol* 2015; 44 153-68.

Office for National Statistics. Interim Life Tables United Kingdom (1980-80 to 2008-2010). (https://www.ons.gov.uk/ons/rel/lifetables/interim-life-tables/2008-2010/rft-ilt-uk-2008-2010.xls). Accessed: 17/5/2017

Puumala SE, Ross JA, Feusner JH, Tomlinson GE, Malogolowkin MH, Krailo MD, and Spector LG. Parental infertility, infertility treatment and hepatoblastoma: a report from the Children's Oncology Group. *Hum Reprod* 2012; 27 1649-56.

Raimondi S, Pedotti P, and Taioli E. Meta-analysis of cancer incidence in children born after assisted reproductive technologies. *Br J Cancer* 2005; 93 1053-6.

Reigstad MM, Larsen IK, Myklebust TA, Robsahm TE, Oldereid NB, Brinton LA, and Storeng R. Risk of Cancer in Children Conceived by Assisted Reproductive Technology. *Pediatrics* 2016; 137 e20152061.

Reigstad MM, Oldereid NB, Omland AK, and Storeng R. Literature review on cancer risk in children born after fertility treatment suggests increased risk of haematological cancers. *Acta Paediatr* 2017; 106 698-709.

Schieve LA, Rasmussen SA, Buck GM, Schendel DE, Reynolds MA, and Wright VC. Are children born after assisted reproductive technology at increased risk for adverse health outcomes? *Obstet Gynecol* 2004; 103 1154-63.

342 Spector LG, Johnson KJ, Soler JT, and Puumala SE. Perinatal risk factors for hepatoblastoma. *Br J*
343 *Cancer* 2008; 98 1570-3.
344
345 Spector LG, Puumala SE, Carozza SE, Chow EJ, Fox EE, Horel S, Johnson KJ, McLaughlin CC, Reynolds P,
346 Behren JV, et al. Cancer risk among children with very low birth weights. *Pediatrics* 2009; 124 96-104.
347
348 Stata Statistical Software: Release 12. College Station TX: Stata Corp LP, City.
349
350 Steliarova-Foucher E, Stiller C, Lacour B, and Kaatsch P. International Classification of Childhood
351 Cancer, third edition. *Cancer* 2005; 103 1457-67.
352
353 Sundh KJ, Henningsen AK, Kallen K, Bergh C, Romundstad LB, Gissler M, Pinborg A, Skjaerven R,
354 Tiitinen A, Vassard D, et al. Cancer in children and young adults born after assisted reproductive
355 technology: a Nordic cohort study from the Committee of Nordic ART and Safety (CoNARTaS). *Hum*
356 *Reprod* 2014; 29 2050-7.
357
358 Sutcliffe AG and Ludwig M. (2007) Outcome of assisted reproduction. Lancet; 370 351-9.
359
360 Tanimura M, Matsui I, Abe J, Ikeda H, Kobayashi N, Ohira M, Yokoyama M, and Kaneko M. Increased
361 risk of hepatoblastoma among immature children with a lower birth weight. *Cancer Res* 1998; 58
362 3032-5.
363
364 Human Fertilisation and Embryology Authority Act 2008
365 (http://www.legislation.gov.uk/ukpga/2008/22/contents). Accessed: 17/5/2017
366

Williams CL, Bunch KJ, Stiller CA, Murphy MF, Botting BJ, Wallace WH, Davies M, and Sutcliffe AG. Cancer risk among children born after assisted conception. *N Engl J Med* 2013; 369 1819-27.

Zegers-Hochschild F, Adamson GD, de Mouzon J, Ishihara O, Mansour R, Nygren K, Sullivan E, van der Poel S, International Committee for Monitoring Assisted Reproductive T, and World Health O. The International Committee for Monitoring Assisted Reproductive Technology (ICMART) and the World Health Organization (WHO) Revised Glossary on ART Terminology, 2009. *Hum Reprod* 2009; 24 2683-7.

Table I. Cohort Characteristics.

Variable	Frequency (%)[1]
N	12,186
Sex	
Male	6,326 (52)
Female	5,851 (48)
Multiple births	
Singletons	6,697 (55)
Multiple Births	5,489 (45)
Birth weight	
Mean (SD) g	2,807 (812)
Birth weight group (g)	
≤2499	3,980 (33)
2500g-3999	7,379 (61)
≥4000	679 (6)
Gestational age at birth	
Mean (SD)	37.1 (3.3)
Type of donor treatment	
Donated oocytes	5209 (43)
Donated sperm	6508 (53)
Donated embryos	469 (4)
Type of ART	
IVF	9,764 (80)
ICSI and other micromanipulation[2]	2,110 (17)
Not recorded	310 (3)
Fresh/ frozen cycles	
Fresh Cycle	10,207 (84)
Cryopreserved Cycle	1,949 (16)
Stage at embryo transfer	
Blastocyst	5,402 (44)
Cleavage	370 (3)
Not recorded	6,414 (53)
Maternal age at birth of child	
Mean (SD) years	37.8 (6.2)
Paternal age at birth of child	
Mean (SD) Years	40.3 (7.4)
Infertility cause	
Both Male & Female	2,734 (22)
Female Factor only	2,847 (23)
Male Factor only	4,706 (39)
Unexplained	740 (6)
Not recorded	1,159 (10)
Duration of infertility	
Mean (SD) years	6.1 (4.1)
Previous maternal ART cycles	
0	4,799 (39)
≥1	7,385 (61)
Previous maternal live births	
0	2,546 (21)
≥1	2,535 (21)
Unknown	7,105 (58)

[1]Frequencies do not always add up to 12,186, and percentages to 100, where data is unrecorded and treated as missing

[2]Intracytoplasmic sperm injection (ICSI): a procedure in which a single spermatozoon is injected into the oocyte cytoplasm; Micromanipulation: a technology that allows micro-operative procedures to be performed on the spermatozoon, oocyte, zygote, or embryo.

Table II. Overall cancer risk stratified by potential mediating/moderating factors.

Mediating/ Moderating Factor	All Cancers[1]		
	Person years follow-up	SIR	95% CI
Overall	95,389	0.83	0.43-1.45
Sex			
Male	49,418	1.13	0.52-2.14
Female	45,970	0.47	0.10-1.36
Age group at diagnosis (years)			
0	11,734	1.29	0.27-3.78
1-4	38,917	0.82	0.30-1.79
5-9	31,688	0.82	0.18-2.57
10-14	13,051	0.00	0.00-2.14
Birth weight (g)			
<2500	33,048	0.80	0.22-2.05
2500g-3999	56,398	0.93	0.40-1.84
≥4000	4,776	0.00	0.00-4.00
Multiple Births			
Singletons	50,331	0.91	0.37-1.87
Multiple Births	45,058	0.74	0.24-1.73
Previous maternal live births			
0	18,940	1.04	0.21-3.03
1 or more	21,165	0.62	0.08-2.25
Type of ART			
IVF	83,548	0.89	0.44-1.58
ICSI and other micromanipulation	10,083	0.00	0.00-1.76
Not recorded	1,734	3.26	0.08-18.2
Fresh/ Cryopreserved cycle			
Fresh	80,153	0.83	0.40-1.52
Cryopreserved	14,830	0.88	0.11-3.18
Not recorded	406	0.00	0.00-55.7

[1]Numbers of cancers observed not given, as ethical regulations preclude publishing cells containing fewer than five cohort members.

Table III. Cohort cancer risk by specific cancer type.

Cancer Type and ICCC3 categories[2]	Person years of follow up	Standardized Incidence Ratio[1]	95% Confidence Interval
All cancers			
ICCC-3 groups I to X11	95,389	0.83	0.43-1.45
Leukaemia			
ICCC-3 group I	95,445	0.61	0.13-1.78
CNS tumours			
ICCC-3 group III	95,435	1.17	0.32-2.99
Neuroblastoma			
ICCC-3 group IV	95,464	0	0.00-2.03
Retinoblastoma			
ICCC-3 group V	95,452	3.29	0.40-11.87
Renal tumours			
ICCC-3 group VI	95,460	0.94	0.02-5.25
Hepatic tumours			
All- ICCC-3 group VII	95,454	9.12	1.11-32.95*
Hepatoblastoma, ICCC-3 group VIIa	95,454	10.28	1.25-37.14*
Bone tumours and extra osseous sarcomas			
All- *ICCC-3 groups VIII and IX*	95,464	0	0.00-2.50
Osteosarcoma- *ICCC-3 group VIIIa*	95,464	0	0.00-18.38
Ewing's Sarcoma- *ICCC-3 group-VIIIc, IXd, division 1& 2*	95,464	0	0.00-12.41
Rhabdomyosarcoma- *ICCC-3 group IXa*	95,464	0	0.00-5.91
Other Sarcomas- *ICCC-3 groups VIIIb, VIIId, VIIIe IXb, IXc, IXd divisions 3 to 11, IXe*	95,464	0	0.00-10.45
Germ cell tumours			
ICCC-3 group X	95,464	0.00	0.00-6.59

[1]Numbers of cancer observed not given, as ethical regulations preclude publishing cells containing fewer than five cohort members.
[2]Cancer type classified according to ICCC3 coding[29]
* = P<0.05. ** =P<0.01*** =P<0.001