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The Link between IVF Children and Cancer: What Do We Know So Far?

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Abstract

Most studies on the risk for childhood cancer after *in vitro* fertilization (IVF) found no increased risk. These studies were, however, underpowered to identify a mild or moderate increase in risk. A large study from Sweden found an about 40% increased cancer risk among IVF children which reached statistical significance. This review summarizes characteristics of women undergoing IVF and their children which could possibly influence childhood cancer risk. No major confounding factor was found but some neonatal characteristics may be intermediaries for the increased risk. Further studies are needed to verify or reject the moderate risk increase. Large materials are needed in order to investigate the contribution of the neonatal morbidity which follows IVF. Some rare tumour forms which have been suggested to occur at an increased rate after IVF also need to be studied further.

Keywords: Childhood cancer; Epidemiology; Imprinting error; *In vitro* fertilization; Review

Abbreviations: CI: Confidence Interval; CNS: Central Nervous System; CPAP: Continuous Positive Airway Pressure; ICD: International Classification of Diseases; ICSI: Intracytoplasmatic Sperm Injection; IVF: *In vitro* Fertilization; LGA: Large for Gestational Age; SIR: Standard Incidence Ratio; SGA: Small for Gestational Age

Introduction

Assisted reproductive technologies including *In vitro* fertilization (IVF) play an important role in today's treatment of infertile couples. Since the beginning of the use of IVF (the first infant birth after IVF in the world was in 1978) concerns have been expressed that the IVF technique could damage the embryo with an increased morbidity of the infant born. Numerous studies have been published on both short-term and long term health effects on children born after IVF; some of them studied the cancer risk. One meta-analysis [1] found a non-significantly increased standard incidence ratio (SIR), 1.33 (95% CI 0.62-2.85) and another [2] found a SIR of 1.03 (95% CI 0.61-1.63) based on four cohort studies of any childhood cancer. Table 1 summarizes seven cohort studies – in three of them less than three cancer cases were observed [3-9]. Two studies are based on relatively large number of exposed cancer cases ([10] and [11], respectively), but one of them was studying couples with infertility problems and not specifically children conceived after IVF. Until the last study in the table was published in the year 2010, the general opinion was that no increased cancer risk existed after IVF even though one could not exclude associations with specific types of cancer. "Case-control studies suggest an increased risk of some specific cancers, although findings from cohort studies suggest essentially a null risk" [2].

Study Design in Investigation of Cancer Risk after IVF

In principle, two types of epidemiological studies have been used to investigate the possible association between IVF and childhood cancer: cohort and case-control studies. The cohort studies (as exemplified in Table 1) compare cancer risk in children conceived after IVF with other children. If we suppose that the background risk of a childhood cancer (diagnosed up to the age of 15) in a follow-up study of children born after IVF is 2 per 1000[1], a power analysis (α=0.05, β=0.80) shows that in order to demonstrate a 50% increased relative risk, one would need a cohort of about 19,300 IVF children – only one of the studies summarized in Table 1 reaches that number. A similar power analysis of a case-control study with an IVF rate of 2% and 10 controls for each case shows that about 2,200 cancer cases must be studied in order to have a reasonable chance to detect a risk increase of 1.5.

[1] In this example the true population rate is probably 3 per 1000 before the age of 15, but as the follow up time for IVF cases will be of varying length up to 15 years, a 2 per 1000 rate is more adequate for the calculation.

Authors	Publication year	Number of cancers	Number of children	Risk estimate (95% CI)
Doyle et al. [3]	1998	2	2507	-
Bruinsma et al. [4]	2000	6	5249	1.39 (0.62-3.09)
Lemer-Geva et al. [5]	2000	0	332	-
Klip et al. [6]	2001	6	8711	1.00 (0.4-2.1)
Pinborg et al. [7]	2003	2	1080	-
Brinto et al. [8]	2004	51	51063	1.14 (0.8-1.5)
Källén et al. [9]	2010	53	26692	1.42 (1.09-1.87)

[a]The study refers to infertile couples, not specifically to IVF.

Table 1: Published cohort studies of childhood cancer in children conceived by IVF or born by sub fertile parents.

The importance of study size can be illustrated with data from three studies of the same but growing cohort of children conceived by IVF in Sweden. In the first study [12], 5,856 children born after IVF were followed – 11 cancer cases were identified against 12.5 expected which gave a risk estimate of 0.88 (95% CI 0.49-1.59). In the second study [13], 16280 children born after IVF were followed. Now 29 cancer cases were found with an odds ratio of 1.41 (95% CI 0.98-2.03). In the third study [9], 26,692 children born after IVF were followed and the number of observed cancers had increased to 53 and the odds ratio was 1.42 (95% CI 1.09-1.87). The confidence interval of the first risk estimate thus includes the estimates from the two following studies (which are very close) and it is possible that the risk estimate of the first study was randomly low and based on an insufficient large number of cases

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(about a third of the number needed according to the power analysis given above). Not only did the number of studied children increase with each study but also the length of the follow-up time in the third study to a maximum of 23 years.

The large numbers needed to analyze the association makes it likely that hospital-based studies will hardly ever have enough power to identify moderate risks while studies utilizing health registers can have a power to permit identification of risk increases as low as 1.5 times.

At the follow-up of cohorts of children conceived by IVF, information on the presence of cancer has been obtained in different ways. In some studies, cancers among children conceived by IVF were identified from cancer registers [3,4,9] but sometimes from questionnaires or interviews of parents [7,14] when biased information and non-participation may complicate the interpretation of the findings.

The rate of cancer among a group of children depends to a large degree on the follow-up time: if all IVF children have not been followed for 15 years, the number of identified cancer cases will be less than that calculated from the total population rate of childhood cancer. It is true that the median age of diagnosis for childhood cancer is about 4 years, but cases will be diagnosed also later and some near the upper age limit.

There are complications with the use of population based health registers. Identification of children conceived by IVF may be incomplete; this will reduce the power of the study but hardly affect risk estimates. Some cancer cases may not have been registered but this error is probably random and will not affect risk estimates. Background information may be needed in the analysis in order to analyze to what extent maternal and infant characteristics can confound the analysis and such background information is often not available or is incomplete. Ideally information on death and emigration should be available because these factors may differ in children conceived by IVF and other children.

Using various national registers, a large case-control study on the risk of childhood leukemia after IVF in Greece and Sweden has been published [15]. These authors found an odds ratio of 1.62 (95% CI 1.02-2.58) for any leukemia, higher for acute lymphatic leukemia than for other types of leukemia, but the two ORs obviously did not differ (1.77, 95% CI 1.06-2.95, and 1.34, 95% CI 0.38-4.69), even though the first was statistically significant and the second was not.

If population health registers are used for the study, the difference between cohort and case-control studies is small. The power of both approaches depends mainly on the number of exposed cases, that is, the number of children conceived after IVF who develop cancer. If the outcome in the cohort study and the case definition in the case-control study is the same (e.g., any childhood cancer), these numbers will be identical. By dividing the identified cancers into subtypes, one can get data equivalent with a series of case-control studies of specific cancer types.

Why should IVF Affect Cancer Risk?

There are many different possible ways in which IVF could affect cancer risk. Couples with fertility problems which result in IVF have characteristics which may affect cancer risk. Infants born after IVF have neonatal characteristics which may also be of importance for the risk of developing cancer. Finally, a much discussed possibility is a disturbance of epigenetic mechanisms which could result in an increased risk for certain rare congenital malformations like Beckwith-Wiedemann syndrome and also of cancer. We will discuss these different possibilities.

Characteristics of women who gave birth after IVF

Maternal characteristics could affect childhood cancer risk. Certain characteristics of women who gave birth after IVF are quite obvious: a higher age and lower parity compared to other women who give birth. In one study [16] it was demonstrated that in Sweden, the odds ratio for having an IVF increased steeply from a maternal age of 30 and reached a maximum at 35-39 and then decreased (Table 2). The OR for parity 1 was of course high. These women smoked less compared to other women, had a longer education, were more often over-weighted and worked full-time more often compared to other women. They were less often of non-Swedish nationality and they had an excess of previous

Maternal characteristics	OR	95% CI	Adjusted for
Maternal age			Year of birth, parity, smoking
20-24	0.03	0.02-0.03	
25-29	0.23	0.22-0.25	
30-34	2.18	2.09-2.28	
35-39	6.49	6.24-6.75	
40-44	3.34	3.03-3.69	
≥ 45	0.47	-	
Parity			Year of birth, age, smoking
1	5.09	4.88-5.31	
≥ 2	1.00	Reference	
Smoking			Year of birth, age, parity
No	1.00	Reference	
<10 cigarettes/day	0.94	0.87-1.01	
≥ 10 cigarettes/day	0.72	0.62-0.83	
Education			Year of birth
<Compulsory school	0.63	0.51-0.78	
Compulsory school	0.78	0.71-0.85	
Gymnasium[a]	1.00	Reference	
<2 years post gymnasium	1.17	1.05-1.29	
≥ 2 years post gymnasium	1.40	1.33-1.47	
Graduate studies	1.46	1.10-1.93	
Body mass index			Year of birth, age, parity, smoking
<19.8	0.74	0.67-0.82	
19.8-25.9	1.00	Reference	
≥ 26	1.13	1.07-1.20	
Previous miscarriage			Year of birth, age, parity, smoking
None	1.00	Reference	
1	1.12	1.06-1.18	
2	1.16	1.03-1.29	
≥ 3	1.23	1.03-1.44	
Work outside home			Year of birth, age, parity, smoking
None	0.67	0.62-0.71	
Full-time	1.00	Reference	
Part-time	0.82	0.77-0.87	
Non-Swedish nationality			Year of birth, age, parity, smoking
In none of the parents	1.00	Reference	
In any parent	0.61	0.55-0.84	

[a]Swedish gymnasium is approximately equivalent to upper secondary school in UK and senior high school in the USA.

Table 2: Some maternal characteristics of women who give birth after IVF [15]. Odds ratios (OR) with 95% confidence intervals (95% CI) estimated with Mantel-Haenszel technique. For maternal age, each age class was compared with all other age classes.

miscarriages (only for women who had standard IVF). An analysis of the use of medical drugs in early pregnancy showed an excess use of drugs for some chronic diseases like diabetes, intestinal inflammations, thyroid disease, and asthma but also of a number of drugs related to pregnancy like multivitamins. Psychoactive drugs, for instance antidepressants, were used less often compared with other women.

Pregnancy and delivery complications were more frequent in women who had IVF than in other women with an increased risk for early pregnancy bleeding, ovarian torsion, thromboembolic disease, preeclampsia, placental abruption, placenta previa, premature rupture of membranes, and bleeding in association with vaginal delivery. Induction of labor and caesarean section was performed more often in IVF pregnancies than in other pregnancies. Most of these pregnancy complications were seen both in singleton, in twin pregnancies and in higher order pregnancies [16].

Characteristics of infants conceived by IVF

Also neonatal characteristics of the infant can affect cancer risk. A strong characteristic of IVF infants is to have been born in multiple births, a consequence of the method to transfer more than one embryo in order to increase pregnancy rates. The proportion of twins and higher births order will therefore be a consequence of the use of multiple embryo transfer. In Sweden, a change towards single embryo transfer has taken place, notably during the last few years. Therefore, the rate of twin pregnancies has gone down from a maximum in the early 1990s of about 30% to a little more than 5% in 2006 and the high number of triplets or quadruplets seen in the early 1990s (about 30 each year) has changed to only single cases each year in 2005-2006 [17].

A high rate of multiple birth results in a high rate of preterm births and low birth weight infants. Also among singletons born after conception with IVF, the rate was increased for preterm birth, low birth weight infants, and small for gestational age (Table 3). Such infants also showed an excess of low Apgar score (<7 at 5 minutes) and an increased risk for cerebral hemorrhage, neonatal convulsions, respiratory problems which led to an increased use of mechanical ventilation and continuous positive airway pressure (CPAP) treatment, neonatal sepsis, and congenital malformations (Table 3). The increased risk for cerebral hemorrhage, convulsions, and neonatal sepsis could be linked to the high risk for multiple births [18].

Many of these neonatal characteristics have been less marked in later cohorts of IVF children [17], but our study of cancer risk is nearly exclusively based on births before 2006.

Neonatal characteristics	OR	95%CI
Preterm birth (<37 weeks)[a]	1.58	1.48-1.69
Low birth weight (<2500g)[a]	1.61	1.49-1.74
Small for gestational age[a]	1.30	1.19-1.43
Low Apgar score (<7 at 5 minutes)[a]	1.29	1.11-1.50
Cerebral hemorrhage	3.35	2.48-4.53
Neonatal convulsions	1.39	1.02-1.80
Respiratory problems	2.51	2.37-2.65
Mechanical ventilation	2.72	2.18-3.40
Use of CPAP	3.38	3.03-3.76
Neonatal sepsis	1.48	1.12-1.78
Congenital malformations[b]	1.44	1.32-1.57

[a]Only singletons
[b]Restricted to relatively severe malformations
CPAP = continuous positive airway pressure

Table 3: Some neonatal characteristics of infants conceived by IVF [13].

Imprinting errors in infants conceived by IVF

There is an ongoing discussion on the possibility that IVF increases the risk for imprinting errors [19], a theory supported by animal studies. This idea is mainly based on the observation of some rare congenital malformation syndromes which sometimes are due to imprinting errors, e.g., Prader-Willli syndrome, Russel Silver syndrome, and Beckwith-Wiedemann syndrome. The total rate of syndromes caused by imprinting errors has been estimated less than one in 12000 [20]. In an analysis of congenital malformations among more than 15000 infants conceived by IVF, we found a doubling of the rate of malformation syndromes according to ICD-10 codes [poo1], based on 14 cases In the total material of infants conceived by IVF (nearly 32000 infants) we identified seven with a syndrome which at least sometimes is due to imprinting errors [21].

Imprinting errors may be a link to cancer risk. Epigenetically altered genes have been identified in many human cancers [22], also in pediatric cancers including Wilms tumor [23] and retinoblastoma [24].

Maternal and Infant Characteristics of Children Developing Childhood Cancer

Numerous studies have tried to identify maternal and infant characteristics which could affect general or specific childhood cancer risk. As many childhood cancers are diagnosed during the first few years of life, it has been suggested that prenatal or perinatal conditions can play a role in their etiology.

It should be realized that such associations may vary between different cancer types but the strongest impact on total childhood cancer risk would be from the most common types, acute lymphatic leukemia and central nervous system (CNS) tumors.

Maternal age and parity

An increased risk for childhood acute leukemia with young maternal age (<20 years) was described and this was indicated also for non-Hodgkin lymphomas but not for CNS tumors or neuroblastomas [25]. Another study found no association between maternal age and acute lymphatic leukemia but found one for acute myeloid leukemia [26]. No maternal age or parity effect was seen for leukemias, lymphomas, CNS tumors or other solid tumors [27,28]. An increased risk for any childhood cancer at maternal age ≥ 35 years was found, significant also for leukemias [29]. A positive trend with maternal age was also found for all childhood cancers, leukemias, lymphomas, CNS tumors, neuroblastomas, Wilms tumors, bone tumors, and soft tissue sarcomas [30]. A higher risk for first parity was seen for non-Hodgkin lymphomas but not for acute lymphatic leukemia, CNS tumors or neuroblastomas [25]. No association was seen between parental age and the risk for childhood brain tumors but belonging to a family with three or more children or three or more adults was a risk factor for childhood brain tumor but first parity was not [31]. A study of childhood acute leukemia indicated an increased risk for parity ≥ 4 [32].

Maternal reproduction history, disease and drug use

An increased risk for CNS tumors in children whose mothers had a miscarriage before the birth of the child was found in two studies [31,33] but not in another [25] and not in a study of childhood leukemia [28]. One study identified an association between the risk for childhood leukemia and 3 years birth interval [26].

No association was found between assisted reproduction and risk for CNS tumors [33].

Preeclampsia was found to be associated with non-Hodgkin lymphoma, severe hyperemesis with leukemia, polyhydramniosis and anaemia with acute myeloid leukemia [34]. Some studies linked cancer risk with maternal anaemia during pregnancy [35,36], hormonal treatment for infertility [25], influenza/pneumonia and sexually transmitted diseases [36] while one study found no association between maternal infections and childhood leukemia [37]. Respiratory tract infections during pregnancy and use of antibiotics were associated with an increased risk for "other solid tumors" but no association was found with preeclampsia or excessive vomiting [28]. An association between maternal renal disease and childhood lymphatic leukemia has been postulated [38].

No statistically significant association was found between maternal drug use during pregnancy and childhood leukemia [36], but an association between use of antibiotics and "other solid tumors" was found [27]. A high prepregnancy maternal weight was associated with acute myeloid leukemia [39].

Maternal smoking

Some studies have investigated the possible association between maternal smoking during pregnancy and childhood cancer. No risk increase was found in some studies [25,40] but in one case, no association with any childhood cancer was found but an association with retinoblastoma [41] found an increased risk for acute myeloid leukemia but a protective effect for acute lymphatic leukemia [42].

Multiple births

The possible association between multiple births and cancer risk has a special interest because of the high proportion of multiple births after IVF. This subject has rarely been studied. A lower childhood cancer and leukemia risk was found in twins compared to singletons [43]. Another study found no general difference in cancer risk between children born as twins and as singletons but a borderline reduced risk for Wilms tumor and neuroblastoma, notably among children diagnosed before the age of two years. Among such children, an increased risk for fibrosarcoma was found [44]. No increased cancer risk was seen in higher order multiple births.

Gestational duration and birth weight

Gestational duration and birth weight are strongly correlated but no significant association between preterm or post term birth and CNS tumors [33] or childhood leukemia [26] was found. In the latter study an increased risk for acute lymphatic leukemia was near significance (lower 95% confidence limit 0.98).

Many studies have investigated the association between birth weight and childhood cancer. A meta-analysis and review [45] concentrating on childhood leukemia found support for the idea that high birth weight is associated with an increase in overall risk for leukemia and for acute lymphatic leukemia while the risk for acute myeloid leukemia may be elevated both at low and high birth weight. A similar U-shaped effect of birth weight seems to exist also for the risk of CNS tumors [46] but this was not seen in some earlier studies [31,33]. High birth weight and large for gestational age increased the risk for childhood rhabdomyosarcoma [47]. A relationship between head circumference at birth and brain cancer has been demonstrated and remained significant after adjustment for birth weight [48].

Some data show that birth weight corrected for gestational age is a better predictor for cancer risk than birth weight alone [29].

Neonatal morbidity

Low Apgar score (<7 at 5 minutes)a was associated with an increased risk for childhood leukemia [26,28]. Postpartum asphyxia and oxygen treatment were associated with childhood lymphatic leukemia [27,38,49,50] and with childhood brain tumors [51].

As is seen from the short summary given above, results vary between studies. There are probably many reasons for that. Differences between study populations may exist. Some studies are based on rather small materials and results are therefore, uncertain. In many studies, several different variables are studied in different subgroups and the possibility for false statistical significances as a result of multiple testing is large.

Risk factor	OR	95% CI	Adjustments
Maternal age			Year of birth, parity, smoking, previous miscarriages, sub fertility
<20	0.98	0.85-1.14	
20-24	0.96	0.90-1.02	
25-29	0.99	0.94-1.04	
30-34	1.05	0.99-1.11	
35-39	1.03	0.95-1.11	
40-44	0.89	0.73-1.08	
≥ 45	1.18	(0.49-2.86)	
Parity			Year of birth, maternal age, smoking, previous miscarriages, sub fertility
1	1.00	0.95-1.06	
2	1.00	0.95-1.06	
3	0.99	0.91-1.05	
≥ 4	1.08	0.99-1.19	
Smoking			Year of birth, maternal age, parity, previous miscarriages, sub fertility
None	1.00	reference	
<10 cigarettes/day	0.99	0.92-1.07	
≥ 10 cigarettes/day	1.08	0.99-1.19	
Previous miscarriages			Year of birth, maternal age, parity, smoking, sub fertility
None	1.00	reference	
1	0.96	0.88-1.03	
2	1.02	0.87-1.19	
≥ 3	1.06	0.82-1.38	
Sub fertility (years of unwanted childlessness)			Year of birth, maternal age, parity, smoking, previous miscarriages
None	1.00	reference	
1	1.04	0.87-1.24	
2	0.94	0.72-1.15	
3	0.91	0.69-1.20	
4	1.13	0.80-1.55	
≥ 5	1.18	0.96-1.44	
Body mass index			Year of birth, previous miscarriages, years of unwanted childlessness
<19.8	0.97	0.82-1.14	
19.8-25.9	1.00	reference	
26.0-29.9	1.02	0.89-1.16	
30.0-39.9	1.01	0.85-1.21	
≥ 40	0.97	0.49-1.95	

For maternal age and parity, each subgroup was compared with all other subgroups.

Table 4: Some putative maternal risk factors studied in 6,458 cancer cases. Odds ratios (OR) with 95% confidence intervals (95% CI), adjustments as stated [9].

Recent Swedish Data on Risk Factors for Childhood Cancer

In order to evaluate how much confounding could be expected in a study of childhood cancer in children conceived by IVF, we investigated the possible effect of a number of maternal and neonatal characteristics on childhood cancer risk in the total population [9]. This analysis was based on 6,458 cancer cases (the majority were diagnosed before the age of 15 and were therefore childhood cancers). A summary of the results is given in Table 4. Information on the maternal and neonatal characteristics was obtained from the Medical Birth Register with data registered during pregnancy and around the time of birth and therefore prospective related to the outcome, cancer. Comparisons were made with all other births in the register (n=2417878) after exclusion of perinatally dead infants. As can be seen from Table 4, none of the studied maternal characteristics appeared to influence general childhood cancer risk in the offspring.

The absence of an effect of maternal characteristics in some and the presence in other studies may have technical explanations and be due to various biases or population characteristics. High maternal age at the first delivery, for instance, may have different significance in different populations – in some it may be an expression of subfertility while in other it may mainly be an effect of voluntary postponement of pregnancy, associated with socio-economic factors. Smoking may in different degree be associated with other abuse (alcohol and illegal drugs). Some of the associations claimed in the literature refer to specific cancer types, and, if rare, they will not affect total cancer risk in a noticeable way. In connection with the question of cancer risk after IVF, the effect of confounding must be analyzed in the population on which the study is made and with respect to total cancer risk as long as this is the main outcome studied.

The childhood cancer risk according to the number of infants in birth (reference = singletons) was 1.07 (95% CI 0.90-1.27) for twins and 1.13 (95% CI 0.87-1.49) for higher order births (based on only 4 cases). The only adjustment made was for year of birth.

Table 5 summarizes some neonatal characteristics. All odds ratios were adjusted for year of birth. An association is seen between cancer risk and preterm birth and low Apgar score. High birth weight and large for gestational age are also significant risk factors. The presence of respiratory problems in the newborn period does not show a significant risk increase.

Risk factor	OR	95% CI	Notes
Gestational duration			Only singletons
<32 weeks	1.21	0.93-1.58	
<37 weeks	1.16	1.05-1.28	
Birth weight			Only sngletons
<1500g	1.06	0.78-1.45	
<2500g	1.07	0.95-1.21	
≥ 4500g	1.21	1.07-1.38	
Growth deviation			Only singletons
SGA	0.91	0.77-1.08	
LGA	1.34	1.21-1.47	
Respiratory diagnoses, CPAP or mechanical ventilation	1.07	0.92-1.23	All infants
Low Apgar score (<7 at 5 minutes)	1.33	1.08-1.63	All infants with known

CPAP = Continuous Positive Airway Pressure
LGA = Large for Gestational Age
SGA = Small for Gestational Age

Table 5: Some putative neonatal risk factors studied in 6458 cancer cases. Odds ratios (OR) with 95% confidence intervals (95% CI), adjustments as states [9].

How Maternal and Neonatal Characteristics Related to IVF can Affect Cancer Risk

When these findings should be taken into consideration for the analyses of cancer risk in children conceived with IVF, one should first look at characteristics among women who have IVF to search for anything which could affect the cancer risk in the children. If, for instance, high maternal age is a risk factor for childhood cancer, it seems reasonable to adjust for that variable in the analysis. If maternal age is a strong determinant of the risk for an unusual cancer type, its impact on the total analysis will be small, however, and may not have to be considered.

Even if evidence was lacking in our material for an effect of maternal age, parity, smoking, or years of unwanted childlessness on cancer risk, we tried to adjust for these variables. The estimated odds ratio actually increased slightly (from 1.42 to 1.45, 95% CI 1.10-1.91), supporting the idea that the variables did not confound the analysis. Removal from the analysis of children whose mothers were born outside Sweden or whose mother or father was of non-Swedish nationality also increased the odds ratio somewhat (to 1.52, 95% CI 1.15-2.02) probably explained by a higher emigration rate among such children which made identification of cancer cases incomplete.

For neonatal characteristics, which are important for cancer risk one could reason differently. If, for instance, IVF increases the risk for neonatal morbidity which in turn increases the cancer risk, neonatal morbidity is an intermediary and should not be adjusted for. On the other hand, it could be of interest to see if an increased cancer risk among children conceived after IVF is solely due to neonatal morbidity which can be studied after adjustment for such factors.

The associations found or suggested may affect cancer risk in children conceived by IVF in opposite ways. Thus, for instance, infants born after IVF have more often than other infants with a low Apgar score and need neonatal oxygen treatment. This could increase their cancer risk but they are also less often large for gestational age and of high birth weight, which would have the opposite effect. It is difficult to estimate the net effect only direct observations can show if the cancer risk is lower, normal, or increased after IVF compared with non-IVF children.

A number of other factors have been discussed as associated with an increased childhood cancer risk, e.g., infections during pregnancy and exposure for X-ray or electromagnetic fields during pregnancy. Such factors are unlikely to be associated with IVF and are therefore uninteresting as putative confounders in the present context.

Types of Cancer in Children Conceived by IVF

As seen in Table 1, the only large cohort study of cancer risk in children conceived by IVF is the Swedish study [9]. Table 6 summarizes the different cancer types among the observed 53 cancers. Two types dominate: acute lymphatic leukemia and CNS tumors (60%) which usually make up the majority of childhood cancers. Most specific types with the exception of acute lymphatic leukemia and histiocytosis occur in single instances. Pilocytic astrocytoma in the cerebellum occurred in three, unspecified malignant retinal neoplasm in two, and mature testicular teratoma in two cases.

From such limited numbers, it is impossible to state whether the cancer type distribution is the normal one or if an excess of a specific

Cancer type	Standard IVF	ICSI	Unknown	Total
Hematologic cancer	10	7	1	18
Acute lymphatic leukemia	7	7	0	15
Other leukemia	3	0	0	3
Langerhans histiocytosis	4	2	0	6
CNS or eye cancer	12	5	0	17
Soft tissue neoplasma	3	0	0	3
Adenocarcinomas	2	1	0	3
Other neoplasms	6	0	0	6

CNS = Central Nervous System

Table 6: Main types of cancer in 53 children, conceived after IVF and observed in the latest Swedish cancer study [9].

type occurs. The only unusual condition was histiocytosis with six cases, a finding which will be discussed separately.

It is to be expected that observations of rare cancer types, notably of embryonic tumors, will be made in children conceived by IVF. One such example is the recent description of an atypical teratoid/rhabdoid brain tumor in an infant of an IVF pregnancy [52]. This tumor type is rare and aggressive but it is of course impossible to draw conclusions on causality from single case reports. Other such relatively rare tumors which have been observed in children conceived via IVF are hepatoblastoma [10] and retinoblastoma [53]. Retinoblastoma may be of a special interest because of a link with imprinting errors. The original observation referred to five cases of retinoblastoma after IVF in the Netherlands during 1995-2002 and by comparison with the rate in the population, a risk increase of more than five times was estimated. Other studies could not verify a high rate of retinoblastoma and a follow-up study in the Netherlands revealed no significant increase in risk in the years 2002-2007 [14]. It should, however, be noticed that the 95% upper confidence limit for the latter study period was 4.66 and an increased risk is still possible. A recent French case-control study [11] found no association between IVF and childhood retinoblastoma but an increased risk was seen when the time to pregnancy was more than 2 years. In our material, there were only two malignant retinal tumors, close to the expected number. In an analysis of seven retinoblastomas in children conceived by IVF in Netherlands, two causative RB1 mutations were found but no hypermethylation of the RB1 promotor was seen [54].

A recent report [55] investigated the association between parental infertility and its treatment and the occurrence of hepatoblastomas in a large US case-control study without being able to find evidence for an association.

A similar situation exists for the Swedish observation on a number of Langerhans histiocytosis cases. In the first study [12], two children with histiocytosis were identified (expected number 0.35). In addition, two children with Letterer-Siwe syndrome were identified from other sources, a rare condition with histiocytosis. In the second study [13], five such cases were reported to the Cancer Register against the expected number of 0.9. This indicated an association with IVF but in the follow-up [9], only one further case was identified. No reports on this association have been found in other studies but there is a further complication: Langerhans histiocytosis is usually not regarded as a malignant condition but is included in the Swedish cancer register. It is unclear, if it was included in previous studies of childhood cancer after IVF. It should be stressed that the increased cancer risk remained statistically significant also when cases of histiocytosis were excluded [9].

The two tumours can be examples of random clusters of diseases, which were not verified in either of the follow up studies, even though causality is still possible. A case-control study of 55 cases of Langerhans histiocytosis or retinoblastoma with 10 controls per case from a population with 2% IVF would be enough to have a chance to demonstrate a five times risk increase.

Cancer Risk in Subgroups of Children Conceived by IVF

The recent Swedish material is too small to really permit sub grouping but some such analyses are presented in Table 7. The observed number in each subgroup was compared with the expected number estimated under the assumption that the 53 cancer cases after IVF had the same distribution as all cancer cases (after adjustment of year of birth) or all IVF cases (with respect to number of infants in birth and IVF technique used) and chi-square analyses were performed. None of the studied characteristics showed a significant deviation from expected numbers. The lowest p value refers to number of infants in birth. As pointed out above, twinning seems not to represent a general increased risk for childhood cancer.

Practical Implications of an Increased Cancer Risk in Children Conceived by IVF

If we suppose that the estimate of a close to 50% over risk for childhood cancer from the Swedish study holds true, this means that the individual risk for cancer development increases from 3 to 4-5 per 1000, a risk increase which for the individual is hardly noticeable. Even if one accepts the upper confidence limit of close to a doubling in risk, it still means an absolute risk of about 6 per 1000, if the lower confidence limit is true, it is only a 9% increase in risk, that is, an individual risk of 3.3 instead of 3 per 1000. If 2% of all children born are the result of IVF conceptions, a 50% risk increase means that among all childhood cancers which will occur, IVF will cause only 1%. If a child conceived by IVF develops cancer, it is only 33% probability that a causality exists, and thus more likely that the cancer is not due to IVF.

As in all epidemiological work, a single study seldom gives a final result but has to be verified or rejected by unrelated studies. Such studies, however, must be large enough to have the power to detect a low risk increase (less than a doubling) and before beginning such a study, a power analysis should be made to see how likely it is to give meaningful results.

For investigations of possible associations between IVF and specific rare cancer types, a case-control approach may be more practical and risk increases may be much higher than for any childhood cancer.

Subgroup	Number	Expected numbe	Chi-square	P value
Child age at diagnosis			0.22	0.90
<3 years	28	26.5		
3-5 years	14	15.4		
≥ 6 years	11	11.3		
Number in birth			2.85	0.09
Singletons	28	33.9		
Multiples	25	19.1		
IVF method			0.02	0.89
Standard IVF	38	37.5		
ICSI	15	15.5		

Table 7: Occurrence of cancer in subgroups of children after IVF [9]:

When large enough materials are available and if an increased cancer risk has been verified, an analysis should be made to see if the risk is restricted to children with neonatal problems or if it is independent of such problems and perhaps linked to epigenetic phenomena. An extended material may also shed light over the suggested possibility that twins born after IVF may be more susceptible to cancer development than singletons. A reduction of twinning rate is possible by a change towards single embryo transfer as has been successfully demonstrated for instance in Sweden and which will most likely reduce other long term effects in IVF children like cerebral palsy [55]. Furthermore, the possible impact of maternal hormone treatment and specific *in vitro* techniques should be analyzed. The present material is too small even to identify different effects of standard IVF and ICSI.

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