Cancer Risk in Children and Young Adults Conceived by In Vitro Fertilization

WHAT'S KNOWN ON THIS SUBJECT: No clear-cut increase in cancer risk after IVF has been found, but most studies were too small to answer the question. There are characteristics of children who are conceived by IVF that could increase cancer risk.

WHAT THIS STUDY ADDS: This study is large enough to demonstrate that a slight but statistically significant cancer risk exists for children who are conceived by IVF. An interesting finding is the seeming increase in the risk for histiocytosis.

abstract

FREE

OBJECTIVES: Studies conducted so far have found no statistically significant increased risk for cancer among children who are born after in vitro fertilization (IVF).

METHODS: We followed 26 692 children who were born after IVF during the years 1982–2005 by using the Swedish Cancer Register and compared the number of children who had cancer and were born after IVF with children who were not conceived by IVF. Adjustment was made for year of birth.

RESULTS: Maternal age, parity, smoking, subfertility, previous miscarriages, BMI, and multiple births did not significantly affect cancer risk in offspring. High birth weight, premature delivery, and the presence of respiratory diagnoses and low Apgar score were risk factors for cancer. We identified 53 cases of cancer in children who were born after IVF against 38 expected cases: 18 of them with hematologic cancer (15 of them acute lymphoblastic leukemia), 17 with eye or central nervous system tumors, and 12 with other solid cancers. There were 6 cases of Langerhans histiocytosis against 1.0 expected. The total cancer risk estimate was 1.42 (95% confidence interval: 1.09–1.87).

CONCLUSIONS: We found a moderately increased risk for cancer in children who were conceived by IVF. Putative intermediary factors could be preterm birth and neonatal asphyxia. *Pediatrics* 2010;126: e270–e276

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KEY WORDS

childhood cancer, histiocytosis, in vitro fertilization, leukemia, brain tumor

ABBREVIATIONS

IVF—in vitro fertilization
CI—confidence interval
ALL—acute lymphoblastic leukemia
OR—odds ratio
LGA—large for gestational age
ICSI—intracytoplasmic sperm injection

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Children who are born after in vitro fertilization (IVF) have an increased risk for perinatal complications and congenital malformations.[1] Some studies have also demonstrated a continued increased morbidity during at least the first years of life. The question of cancer risk in children who are conceived by IVF has been discussed in some articles. Bruinsma et al[2] studied 5249 births by using population-based registers and found 6 cancer cases against 4.33 expected. Klip et al[3] investigated cancer risk among 9484 children who were born after IVF or other related fertility techniques (85% were IVF) and found 16 cancers against 15.5 expected. Information was based on questionnaires with only 67% response rate. Three previous studies from Sweden[4–6] did not find any statistically significantly increased cancer risk. In the latest Swedish report, which was based on a follow-up of 16 280 infants by using national health registers, a risk estimate of 1.42 (95% confidence interval [CI]: 0.98–2.03) was found (based on 29 reported tumor cases against 21.4 expected). After adjustment for maternal age, parity, and smoking, the risk estimate decreased only slightly (1.35 [95% CI: 0.93–1.97]). One study found an association with maternal subfertility and an increased risk for acute lymphoblastic leukemia (ALL).[7] This study expands the follow-up time of the previously studied children who were conceived by IVF[6] and adds a number of children who were born after the end of the latest previous study (2001).

METHODS

Children who were born after IVF in Sweden were identified from reports from all IVF clinics in Sweden.[1,8] Perinatal information was obtained by linkage with the Swedish Medical Birth Register.[9] Information on cancer development was obtained from the Swedish Cancer Register[10] up to and including 2006. Thus, the definition of a patient having cancer is that the individual has been registered at least once in the Cancer Register.

Linkage was made by using the personal identification number that is assigned to each person who lives in Sweden. The first infant who was born after IVF in Sweden was born in 1982. The study was restricted to infants who were born in the period 1982–2005, because no cancer case was yet (in 2006) identified in the cancer register among infants who were born later. The proportion of infants who were born after IVF among all infants who were born in Sweden increased from <1 per 1000 before 1988 up to 2% to 3% from 1997 onward.

Comparison was made with all infants who were recorded in the Medical Birth Register, survived the perinatal period, and had an identification number in the register. Maternal and infant characteristics were studied by using the Mantel-Haenszel method with odds ratio (OR) estimates and 95% CIs estimated with Miettinen's technique. For comparisons of 2 ORs, 2-tailed z tests were made on the basis of Mantel-Haenszel χ^2 tests. Trend tests for i ORs were made as weighted linear regression analyses of the $\log(OR_i)$. The following putative maternal risk factors were analyzed: maternal age (5-year classes), parity (1, 2, 3, ≥4), maternal smoking (unknown, 0, <10 cigarettes per day, ≥10 cigarettes per day), number of previous miscarriages (0, 1, 2, ≥3), years of unwanted childlessness (unknown, 0, 1, 2, 3, 4, ≥5), BMI (unknown, <19.8, 19.8–25.9, 26.0–29.9, 30.0–34.9, 35.0–39.9, ≥40), and number of infants in birth (1, 2, ≥3). The following putative neonatal factors were analyzed in singletons: preterm birth (<32 and <37 completed weeks), low birth weight (<1500 and <2500 g), small for gestational age and large for gestational age (LGA; <2 and >2 SDs according to growth graphs on the basis of data in the Medical Birth Register[11]), presence of neonatal diagnoses of respiratory problems or use of continuous positive airway pressure, and low 5-minute Apgar score.

This statistical method used is sensitive to changes in population size with age as a result of deaths or emigration. The death rate after the perinatal period is low (0.2% among all children in the population). Emigration could not be controlled for. It is probably low for children whose mother was born in Sweden and those who had 2 parents of Swedish nationality but may be higher for children whose parents were not born in Sweden and/or did not have a Swedish nationality. A reanalysis was therefore made with exclusion of all children whose mother was not born in Sweden or had at least 1 parent who was not of Swedish nationality (18% of all). This study was performed within the responsibilities of the National Board of Health and Welfare; therefore, no ethical approval from outside ethical committees was needed.

RESULTS

Putative maternal risk factors for cancer in their children are shown in Table 1. In all analyses, adjustment was for year of birth, and additional adjustments were made as indicated in the tables.

Compared with other women, women who had IVF were older, were more often of first parity, smoked less, had fewer previous miscarriages, had a period of unwanted childlessness, more often had high BMI, and had an increased rate of multiple pregnancies.[1] None of these characteristics showed a statistically significant association with the risk for cancer in the offspring. The highest OR (1.18) was seen for a period of unwanted child-

TABLE 1 Maternal Risk Factors for Cancer in the Offspring

Variable	No. of Children		OR	95% CI	Test for Trend	
	With Cancer ($n = 6458$)	In the Population ($n = 2\,417\,878$)			z	P
Maternal age, y[a]					1.47	.14
<20	186	60 807	0.98	0.85–1.14		
20–24	1347	464 926	0.96	0.90–1.02		
25–29	2334	861 074	0.99	0.94–1.04		
30–34	1783	695 093	1.05	0.99–1.11		
35–39	699	284 173	1.03	0.95–1.11		
40–44	104	49 930	0.89	0.73–1.08		
≥45	5	1875	1.18	0.49–2.86		
Parity[a]					0.25	.39
1	2642	1 011 804	1.00	0.95–1.06		
2	2317	863 357	1.00	0.95–1.06		
3	1034	375 460	0.98	0.91–1.05		
≥4	465	167 256	1.03	0.93–1.14		
Smoking[a]					1.48	.13
Unknown	793	202 276	—			
No	4273	1 770 934	1.00	Reference		
<10 cigarettes per d	834	282 091	0.99	0.92–1.07		
≥10 cigarettes per d	558	162 577	1.08	0.99–1.19		
Previous miscarriage[b]					0.94	.26
0	5507	2 007 790	1.00	Reference		
1	737	320 300	0.96	0.88–1.03		
2	157	66 215	1.02	0.87–1.19		
≥3	57	23 573	1.06	0.82–1.38		
Years of unwanted childlessness[b]					1.18	.26
0	6051	2 267 021	1.00	Reference		
1	128	44 594	1.04	0.87–1.24		
2	95	40 135	0.94	0.77–1.15		
3	50	22 048	0.91	0.69–1.20		
4	38	13 466	1.13	0.80–1.55		
≥5	97	30 614	1.18	0.96–1.44		
BMI[c]					0.89	.27
Unknown	375	227 366	—	—		
<19.8	171	109 542	0.97	0.82–1.14		
19.8–25.9	1172	752 677	1.00	Reference		
26.0–29.9	272	180 748	1.02	0.89–1.16		
30.0–39.9	139	96 544	1.01	0.85–1.21		
≥40.0	8	6356	0.97	0.49–1.95		
No. of infants in birth[d]						
1	6295	2 358 046	1.00	Reference		
2	150	60 513	1.07	0.90–1.27		
3	4	1578	1.13	0.87–1.49		

Women with perinatally dead infants and with infants without complete identification numbers were excluded.
[a] Adjusted for year of birth and for the other variables. For maternal age and parity, each group is compared with all other groups. One infant in population lacked parity information.
[b] Adjusted for year of birth and for the other variables.
[c] Adjusted for year of birth, number of previous miscarriages, and years of unwanted childlessness. Restricted to children who were born 1992–2005.
[d] Adjusted only for year of birth.

lessness of >5 years, but it did not reach statistical significance, and there is no clear-cut trend with duration of childlessness.

Table 2 shows the impact of some neonatal characteristics on cancer risk. The only adjustment made was for year of birth. There was an increased risk for cancer associated with preterm birth before week 37, for birth weight of ≥4500 g, for LGA, and for low Apgar score. Among these characteristics, infants who were born after IVF are characterized by an increased risk for preterm birth, low birth weight, being small for gestational age, respiratory problems, and low Apgar score.

Among children who were conceived by IVF and survived the perinatal period, there were 53 cases of cancer (Table 3). Eighteen infants had hematologic neoplasms (12.3 expected), 15 of them ALL. Fifteen infants had central nervous system neoplasms (8.1 expected), 7 of them astrocytomas. Two infants had malignant retinal tumors (retinoblastoma); the expected number was 1.25. Six infants had a diagnosis of histiocytosis (expected number: 1.0).

After adjustment for year of birth, the OR for childhood cancer among infants who were born after IVF was 1.42 (95% CI: 1.09–1.87; $P = .01$). After exclusion of infants with histiocytosis from the analysis, the OR decreased to 1.34 (95% CI: 1.02–1.76). Despite that maternal age, parity, smoking, and years of unwanted childlessness did not seem to affect cancer risk in our material, we tried an adjustment for these variables besides year of birth; the resulting OR hardly changed, from 1.42 to 1.45 (95% CI: 1.10–1.91), supporting the lack of confounding. All additional analyses were therefore made after adjustment only for year of birth. When children whose mother was born outside Sweden or whose father or mother was of non-Swedish nationality were excluded, 49 cancer cases remained (5505 in the population), and the OR increased slightly to 1.52 (95% CI: 1.15–2.02).

Fifteen of the children who were conceived by IVF and had cancer had been conceived by intracytoplasmic sperm injection (ICSI). The expected number of children who were conceived by ICSI, calculated from the ICSI rate among all infants who were born after IVF and adjusted for year of birth, is 15.5.

Among the 53 children who were conceived by IVF and developed cancer, 28

TABLE 2 Neonatal Risk Factors for Cancer

Variable	No. of Children		OR	95% CI
	With Cancer ($n = 6459$)	In the Population ($n = 2\,419\,274$)		
Gestational duration, wk[a]	6435	2 413 568	—	—
<32	55	18 702	1.21	0.93–1.58
<37	444	146 120	1.16	1.05–1.28
Birth weight, g[a]	6420	2 409 373	—	—
<1500	40	15 369	1.06	0.78–1.45
<2500	288	101 899	1.07	0.95–1.21
≥4500	256	85 690	1.21	1.07–1.38
Growth deviation[a]	6246	2 342 927		
SGA, less than −2 SDs	141	54 780	0.91	0.77–1.08
LGA, >2 SDs	440	132 277	1.34	1.21–1.47
Respiratory diagnosis[b]	194	75 908	1.07	0.92–1.23
Apgar score[c]	6385	2 402 279	—	—
<7 at 5 min	93	27 313	1.33	1.08–1.63

Perinatally dead infants and infants without complete identification numbers were excluded. OR adjusted only for year of birth. Numbers for each variable give number of infants with relevant information. SGA indicates small for gestational age.
[a] Only singletons with known gestational duration or birth weight; for growth deviation, known gestational duration, birth weight, and infant gender.
[b] Includes infants who were treated with continuous positive airway pressure or mechanical ventilation. All infants.
[c] All infants with known 5-minute Apgar score.

were younger than 3 years at cancer diagnosis, 14 were aged 3 to 5 years, 7 were 6 to 10 years, and 4 were older than 10 years (1 was 19 years). The expected numbers calculated from the age distribution of all cancers and adjusted for year of birth was 26.3, 15.4, 8.1, and 3.2, respectively. The distribution of age at onset in children who were conceived by IVF thus agrees well with that of other children. The OR among children who were conceived after IVF and received a cancer diagnosis before the age of 3 was 1.87 (95% CI: 1.27–2.77) and from age ≥3 years was 1.32 (95% CI: 0.89–1.96). These 2 estimates do not differ significantly, however ($z = 1.23$, $P = .19$), so it is not certain that the risk actually decreases after the age of 3.

Among children who were born after IVF and developed cancer, 7 had malformation diagnoses. One child had a cleft lip/palate, 1 had a coarctation of the aorta, 1 had an unspecified musculoskeletal malformation, 1 had an arm reduction, 1 had a kidney malformation, and 2 had Down syndrome. One of the 2 infants with Down syndrome had ALL, and the other had acute myeloid leukemia.

Twenty-five infants who developed cancer were born in multiple births (24 twins, 1 triplet); the expected number from the yearly distribution of cases and the yearly multiple birth rates among all infants who were born after IVF was 19.1. The excess is thus not statistically significant ($\chi^2 = 3.3$, $P = .09$).

DISCUSSION

This is the first study to demonstrate a statistically significant increase in cancer risk among children who are born after IVF. It is also the largest of the published studies. In our previous study,[6] which was based on 16 280 children and included 29 of the 53 cancer cases, nearly the same risk estimate was obtained as in this study (1.41 vs 1.42), but statistical significance was not reached (95% CI: 0.98–2.03).

Mothers of children who were born after IVF differ in many characteristics besides subfertility from other women who give birth: higher maternal age, high percentage of first parity, less smoking, increased number with high BMI, and fewer who were born outside Sweden. Whether such differences can confound the analysis depends on their possible effect on the risk for cancer in the offspring. In our analysis, none of the included characteristics affected the total cancer risk, and adjustment for them therefore did not change the risk estimate. For the main analysis, we therefore did not adjust for any 1 of them. Some previous studies that used different methods analyzed the possible associations between maternal characteristics and the general risk for cancer in the offspring. Low maternal age (<20) was associated with an increased risk for acute leukemia,[7] whereas high maternal age had no effect in another study[12] but was associated with acute myeloid leukemia in 1 study.[13] We saw no certain maternal age effect on the risk for cancer in the offspring. The putative effect on acute myeloid leukemia seems not to be of importance in our study, because only 1 such case occurred among the cancers in children who were born after IVF. An increased risk for childhood leukemia with parity ≥4 has been found.[14] An association between previous miscarriages and brain tumors has been described.[15]

Some articles discussed the putative effect of maternal smoking on cancer risk in the offspring, but the results varied and no clear association was seen.[16] A protective effect on ALL was described in 1 study[17] but was not found in another.[7] A specific association has been described between maternal smoking and neuroblastoma[18] or retinoblastoma[19] in the child.

Maternal education level was associated in 1 study with a decreased risk for childhood cancer.[20] The effect of maternal education on IVF is complex, but, if anything, high maternal education is associated with a higher use of IVF.[8]

Many neonatal characteristics have been associated with a generally in-

TABLE 3 Nature of the 53 Cancer Cases Observed Among Infants Who Were Born After IVF

Cancer Diagnosis and Location	No. of Cases	IVF Method Used (*n*)
Hematologic neoplasms	18	
ALL	15	Standard IVF (7), fresh testicular ICSI (6), fresh epididymal ICSI (1), unspecified (1)
Prolymphocytic leukemia	1	Standard IVF (1)
Acute myeloid leukemia	1	Standard IVF (1)
Chronic myeloid leukemia	1	Standard IVF (1)
Histiocytosis	6	
Langerhans histiocytosis	6	Standard IVF (4), fresh testicular ICSI (1), cryopreserved ejaculated ICSI (1)
Central nervous system or eye neoplasms	17	
Pilocytic astrocytoma in temporal lobe	1	Standard IVF (1)
Pilocytic astrocytoma in cerebellum	3	Fresh ejaculated ICSI (1), fresh testicular ICSI (1), cryopreserved nonejaculated ICSI (1)
Pilocytic astrocytoma, unspecified	1	Standard IVF (1)
Astrocytoma, cerebellum	1	Standard IVF (1)
Astrocytoma, brain stem	1	Standard IVF (1)
Medulloblastoma, cerebellum	1	Standard IVF (1)
Medulloblastoma, unspecified	1	Fresh testicular ICSI (1)
Glioblastoma, cerebellum	1	Standard IVF (1)
Glioblastoma, unspecified	1	Fresh ejaculated ICSI (1)
Unspecified brain stem neoplasm	1	Standard IVF (1)
Plexus papilloma	1	Cryopreserved standard IVF (1)
Ependymoma, spinal cord	1	Standard IVF (1)
Unspecified malignant optic nerve neoplasm	1	Standard IVF (1)
Unspecified malignant retinal neoplasm	2	Standard IVF (2)
Soft tissue neoplasms	3	
Fibrosarcoma	1	Standard IVF (1)
Pleomorphic sarcoma upper limb	1	Standard IVF (1)
Unspecified soft tissue neoplasm	1	Standard IVF (1)
Adenocarcinomas	3	
Adenopapilloma in appendix	1	Cryopreserved nonfresh ICSI (1)
Squamous cell cancer in larynx	1	Standard IVF (1)
Cancer in situ, vulva	1	Standard IVF (1)
Other neoplasms	6	
Craniopharyngeoma	1	Standard IVF (1)
Malignant melanoma lower limb	1	Standard IVF (1)
Hepatoblastoma	1	Standard IVF (1)
Mature testicular teratoma	2	Standard IVF (2)
Medullary cancer in thyroid gland	1	Standard IVF (1)

creased risk for cancer or for specific cancer forms in the offspring. Two of the children who were born after IVF and developed cancer had Down syndrome. A strong association exists between Down syndrome and childhood leukemia. The risk to have a child with a chromosome anomaly seems not to be increased after IVF,[21] and in that material, the risk for birth of an infant with Down syndrome after IVF was estimated to be 1.09 (95% CI: 0.73–1.62), on the basis of 27 cases (unpublished data) and adjusted for year of birth, maternal age, parity, smoking, and BMI. The other malformations that were observed among the children who were conceived by IVF and developed cancer are not known to be associated with an increased cancer risk.

Neonatal factors could act as intermediaries between the IVF procedure and cancer development. Two neonatal factors that have shown a relatively constant association with an increased childhood cancer risk are high birth weight and neonatal asphyxia. High birth weight as a risk factor has been described repeatedly[7,15,22,23] and was also seen in our material (Table 2) as a birth weight ≥4500 g, or LGA. This has been looked on as an effect of fetal growth factors.[24] If anything, infants who are born after IVF show an increased risk for intrauterine growth restriction.[25] One study found an increased risk for childhood leukemia after preterm birth,[23] which was also indicated in our material.

An increased risk for childhood cancer after neonatal asphyxia or oxygen treatment has also been described,[12,20,26–28] and this was also indicated in our material as seen for low Apgar score. This could be an intermediary in the effect of IVF on cancer risk, because an increased risk for low Apgar score and respiratory problems is seen in infants who are born after IVF.[25]

Multiple births are common complications in IVF pregnancies. There was no certain effect of multiple births on cancer risk in our material. We found a slight excess of children who were born in multiple births after IVF and developed cancer, but this was not statistically significant. One publication even suggested that twins have a lower cancer risk than singletons.[29]

Two tumors that possibly are associated with IVF have been specifically discussed. One is retinoblastoma, on the basis of a Netherlands study.[30] A more recent study of the same authors found no significant increase in retinoblastoma risk after IVF in the years after the initial observation.[31] In our material, there were only 2 malignant eye neoplasms, a number that is close to the expected number. The second condition is Langerhans histiocytosis. This has been observed only in the Swedish material, but it is not clear whether such cases would have been included in previous studies. We found a total of 6 such cases against the expected number of 1. Five of them were observed in a previous study.[6] In addition, 2 children had Letterer-Siwe disease, a closely related condition. They were

not registered in the cancer register but were identified from the hospital discharge register.[5]

The biological nature of Langerhans histiocytosis is debatable; is it a malignant neoplastic disease or a reactive process?[32–34] Little is known about the epidemiology of Langerhans histiocytosis. One study identified maternal urinary tract infections, feeding problems during infancy, and blood transfusions during infancy[35] as risk factors. Another study found increased risks associated with neonatal infections, solvent exposure, and family thyroid disease.[36] If histiocytosis is not regarded as a true malignancy, then there could be reason to exclude them from the analysis of total cancer risk; the OR then went down to 1.34 but remained statistically significant.

We can see no biological explanation for why children who are conceived after IVF would have an increased risk for histiocytosis. It is noteworthy that only 1 additional case appeared in the new data set compared with that previously published, and thus the follow-up study did not support the previous observation of an increased risk. Because the observation has not been verified in independent investigations, it is possible that it is a random event. Additional information on this putative association is needed.

CONCLUSIONS

We found a moderately increased risk for cancer in children who were conceived by IVF. This is probably not attributable to the IVF procedure itself but could be an effect of confounding from unidentified characteristics of women who undergo IVF or could act via the widely known increased risks for neonatal complication. It should be stressed that the individual risk for a child who is born after IVF to develop childhood cancer is low. Additional studies on large populations are needed to permit analysis of such a rare outcome as cancer and notably of specific types.

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