

# Risk of Birth Abnormalities in the Offspring of Men With a History of Cancer: A Cohort Study Using Danish and Swedish National Registries

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**Background** The potential mutagenic effects of cancer therapies and the growing number of young male cancer survivors have given rise to concern about the health of their offspring.

**Methods** We identified all singleton children born alive in Denmark between 1994 and 2004 and in Sweden between 1994 and 2005 (N = 1777765). Of the 8670 children with a paternal history of cancer, 8162 were conceived naturally and 508 were conceived using assisted reproductive technologies (ARTs) (in vitro fertilization or intracytoplasmic sperm injection). Of the 17690795 children without a paternal history of cancer, 25926 were conceived using ARTs. Associations between paternal history of cancer and risk of adverse birth outcomes of children conceived naturally or by ARTs were investigated using log-linear binomial models, yielding risk ratios (RRs) with 95% confidence intervals (CIs). All statistical tests were two-sided.

**Results** The offspring of male cancer survivors were more likely to have major congenital abnormalities than the offspring of fathers with no history of cancer (RR = 1.17, 95% CI = 1.05 to 1.31,  $P = .0043$ , 3.7% vs 3.2%). However, the mode of conception (natural conception or ARTs) did not modify the association between paternal history of cancer and risk of congenital abnormalities (natural conception, RR = 1.17, 95% CI = 1.04 to 1.31; ARTs, RR = 1.22, 95% CI = 0.80 to 1.87,  $P_{\text{interaction}} = .84$ ).

**Conclusion** We observed a statistically significant but modest increase in the risk of major congenital abnormalities among offspring of males with a history of cancer, independent of the mode of conception.

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The growing number of young male cancer survivors (MCSs) and increasing awareness of the potential mutagenic effects of radio- and chemotherapy have given rise to concerns about the health of their offspring. Previous studies of adverse pregnancy outcomes, congenital abnormalities, genetic disease, and childhood cancer in children born to men with a history of cancer have in general been reassuring, both in terms of pregnancy outcome and rate of congenital malformations (1–6). However, these studies have been limited in statistical power and have focused solely on children conceived naturally.

Both cancer and its treatment are associated with sperm DNA damage, although treatment-induced DNA damage has been shown to be transient (7–13). However, sperm with seriously impaired DNA integrity that are unable to fertilize an egg naturally may still be used to conceive children via assisted reproductive technologies (ARTs), such as in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) (14). Because cancer and its treatments can impair fertility (15), MCSs are consequently expected to use ARTs to a greater extent than men in the general population. Therefore, paternal history of cancer and the use of ARTs may be associated with serious health issues in offspring.

There is an increasing awareness of the importance of events occurring during fetal development for not only the risk of congenital abnormalities and pathologies occurring early in life but also for morbidity later in life (16). Consequently, any investigation of a possible link between paternal cancer and adverse health outcomes in children should consider both perinatal conditions and indices of fetal growth that can affect health later in life.

Estimating the effects of relatively rare exposures such as paternal cancer and ARTs on pregnancy outcomes requires large cohorts, particularly when the outcomes of interest occur infrequently in the general population (eg, congenital abnormalities). The unique personal identification numbers used in the Danish and the Swedish civil registration systems enabled us to conduct a large population-based register-linkage study to examine the association between paternal history of cancer and perinatal outcomes in live born children conceived naturally and those conceived using ARTs.

## Subjects and Methods

### Study Population and Data Sources

Using the Danish Civil Registration System, the Swedish Total Population Register, and the Swedish Multigenerational Register,

we identified both parents and all children born alive in Denmark between 1994 and 2004 and in Sweden between 1994 and 2005. We obtained detailed information about maternal and birth characteristics for each child from the Danish and the Swedish Medical Birth Registers; additional information about congenital abnormalities was retrieved from the Danish and the Swedish Hospital Discharge Registers and the Swedish Register of Congenital Malformations, which included follow-up until late 2007. Information about the mode of conception was retrieved from the Danish IVF Register and the Swedish Medical Birth Register. Finally, we identified fathers with a history of cancer by using the Danish and Swedish Cancer Registers (data available until the end of 2003 in Denmark and 2005 in Sweden). [For a detailed description of the national registers used (17–25), please see the Appendix 1.] This study was reviewed and approved by the Lund University Ethical Committee (Lund, Sweden) and the Danish Data Protection Agency (Copenhagen, Denmark).

### Paternal History of Cancer Designation

Children were categorized according to paternal history of cancer (our primary exposure of interest) and mode of conception (natural, IVF, or ICSI). We considered all diagnoses reported to the Danish or Swedish Cancer Registers, including diagnoses reportable in only one of the two countries, to be cancer diagnoses. A child was considered to have a paternal history of cancer if the father was first diagnosed with cancer at least 1 year before the child's birth (to ensure that the father's cancer had developed before the child was conceived). We did not restrict our analysis to the first child born to each father, but rather included all singletons born during the study period. If a MCS fathered children both before and after his cancer diagnosis, those children fathered before his diagnosis were considered not to have a paternal history of cancer. We excluded twins and other multiples because ARTs conceptions more frequently result in multiple births compared with natural conceptions, and multiple births tend to have more adverse pregnancy outcomes, including congenital abnormalities, than singleton gestations (20,26).

For purposes of subanalyses, paternal history of cancer was further divided into seven groups based on the *International Classification of Diseases (ICD)*, version 7, and codes were assigned to paternal cancer diagnoses as follows: 1) respiratory, digestive, and urogenital tract cancers (excluding testicular cancer) (*ICD-7* codes 141.0–163.9, 177.0–177.9, 179.0–181.9, 195.5); 2) testicular cancer (*ICD-1* codes 178.0–178.9); 3) skin cancers (*ICD-7* codes 140.0–140.9, 190.0–191.9); 4) eye and central nervous system cancers (*ICD-7* codes 192.0–193.1); 5) bone and soft tissue cancers (*ICD-7* codes 193.3, 193.8, 193.9, 196.0–197.9); 6) hematological malignancies (*ICD-7* codes 200.0–209.9); and 7) all other cancer diagnoses (*ICD-7* codes 164.0–164.9, 170.1, 170.2, 194.0–194.9, 195.0–195.9, 199.1–199.9). The registers do not contain information on treatment, but specific diagnostic groups were expected to have received specific treatments. For example, patients who were treated for a hematological malignancy most likely received chemotherapy. A subgroup of men who were presumed to have received radiotherapy was identified—standard treatment for seminomatous testicular cancer stage I during the study period was abdominal irradiation—and we identified 480 Swedish men who

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## CONTEXT AND CAVEATS

### Prior knowledge

Many cancer treatments could potentially damage the DNA in the sperm of male cancer survivors, creating concern that their offspring may be at increased risk for birth defects. Previous studies have not been large enough to determine if the mode of conception could have an effect on the potential risk of birth abnormalities in these offspring.

### Study design

Danish and Swedish registers were used to perform a population-based linkage study to investigate the risk of birth abnormalities in the offspring of 8670 male cancer survivors conceived naturally or by assisted reproductive technologies.

### Contribution

The incidence of major congenital birth abnormalities was higher in the offspring of male cancer survivors compared with fathers with no history of cancer, although the mode of conception did not contribute to this increased risk.

### Implications

Male cancer survivors have a slightly increased risk of producing offspring with major birth abnormalities regardless of the mode of conception.

### Limitations

The effect of different treatments on the risk of birth abnormalities could not be analyzed because information about specific cancer treatments for each patient was not available from the registries. The potential selective diagnosis of malformations in the offspring of male cancer survivors because of underlying patient concern is unknown.

*From the Editors*

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were diagnosed with seminomatous testicular cancer, of whom 80%–85% (27) can be assumed to have had stage I tumors and therefore to have been treated with radiotherapy.

Sperm from MCSs used for ARTs can either be banked pre-treatment sperm or fresh posttreatment sperm. Information about the sperm source was not available in the registers, but it was obtained directly from fertility clinics for 205 of the 249 Swedish children conceived using ARTs. Because data suggest that DNA damage induced by oncological treatment is only transient (9,12,28–30), the naturally conceived children of MCSs were also categorized according to whether they were born 1–2 years after their father was diagnosed with cancer or more than 2 years after diagnosis. ARTs children were omitted because the timing of semen collection (cryopreserved or fresh) was not always known and is not related to when the child was conceived. The children of MCSs were further subdivided by the father's age at diagnosis (<18 years of age [childhood cancer] vs ≥18 years of age).

### Birth Outcomes

Perinatal outcome data included gestational length, birth weight, weight for gestational age, and the presence and type, if any, of congenital abnormalities. For analytic purposes, the following dichotomous outcomes were defined: preterm delivery (gestational

age at birth <37 completed weeks), very preterm delivery (gestational age at birth <32 completed weeks), low birth weight (birth weight <2500 g), very low birth weight (birth weight <1500 g), and small for gestational age (birth weight < 10th percentile for gestational week and sex). Congenital abnormalities were defined in multiple ways: 1) any congenital abnormality, which included any child with any malformation registered in Denmark or Sweden, no matter how minor; 2) major abnormalities, from which children with minor abnormalities (preauricular appendices, patent ductus arteriosus in children born preterm, single umbilical artery, minor skin malformations [mainly nevi]) and inconsistently registered conditions (undescended testicles, congenital hip subluxation) were excluded; and 3) specific groups of abnormalities.

### Statistical Analyses

We evaluated the potential associations between paternal history of cancer, mode of conception, and the above-mentioned outcomes using log-linear binomial models, which yielded effect estimates as risk ratios (RRs) with 95% confidence intervals (CIs). We first assessed the effects of paternal history of cancer and mode of conception separately for Denmark and Sweden, adjusting for year of birth (1-year categories), maternal age at birth (5-year categories), maternal parity (0, 1, 2+ children), and maternal smoking during early pregnancy (self-reported at first prenatal checkup, in gestational week 10–12) (yes or no), all previously shown to affect birth outcomes (26,31–33). For outcomes with similar country-specific risk ratios, we repeated the analyses on the combined data, with paternal history of cancer and mode of conception in the same model, and adjusted for country and the above-mentioned covariates.

We conducted additional analyses of the effect of various aspects of paternal history of cancer on the risk of major congenital abnormalities in the offspring. We examined the effects of timing of paternal cancer (childhood cancer vs cancer in adulthood), semen source (cryopreserved pretreatment semen vs posttreatment semen), time since paternal cancer diagnosis, and specific cancer diagnosis categories. In addition, we investigated whether mode of conception modified the effect of paternal history of cancer on the risk of major abnormalities by including an interaction term (paternal history of cancer X mode of conception) in the multivariable model. Because similar associations were observed for IVF and ICSI, results for the two ARTs groups are presented together.

To examine whether including more than one child per father in the analyses biased our results, we conducted supplementary analyses restricted to one child per father. Because the results of these analyses did not differ appreciably from the results of our primary analyses (data not shown), we present the results from analyses including all singleton children born to each man.

All analyses were performed using SAS, version 9.1.3, software (SAS Institute, Inc, Cary, NC). *P* values were calculated using a two-sided Wald test; values less than .05 were considered to be statistically significant.

## Results

### Study Population

A total of 1 777 765 singletons were born in Denmark and Sweden between January 1, 1994, through December 31, 2004 (Denmark

and December 31, 2005 (Sweden). Of these, 1 743 169 were conceived naturally and had no paternal history of cancer, 8162 were conceived naturally and had a paternal history of cancer, 25 926 were conceived using ARTs and had no paternal history of cancer, and 508 were conceived using ARTs and had a paternal history of cancer. The distribution of selected parental characteristics and birth outcomes among these children is presented in Table 1.

Among the 8670 children with a paternal history of cancer, the mean paternal age at cancer diagnosis was 26.4 years (26.3 years among children conceived naturally, and 28.9 and 28.3 years among children conceived using IVF and ICSI, respectively). Most (98.8%) MCSs who had fathered study children had only been diagnosed with a single cancer (Table 2). Additional paternal characteristics for children born to MCSs are presented in Table 2.

### Birth Weight, Gestational Length, and Weight for Gestational Age

Paternal history of cancer was not associated with low birth weight (RR = 0.97, 95% CI = 0.86 to 1.09), very low birth weight (RR = 0.86, 95% CI = 0.62 to 1.19), preterm delivery (RR = 0.94, 95% CI = 0.85 to 1.04), or very preterm delivery (RR = 0.85, 95% CI = 0.66 to 1.09). Danish children with a paternal history of cancer had a decreased risk of being born small for gestational age compared with children whose fathers had never been diagnosed with cancer (RR = 0.89, 95% CI = 0.80 to 0.99). In contrast, a paternal history of cancer was not associated with weight for gestational age in Swedish children (RR = 0.99, 95% CI = 0.90 to 1.10, *P* = .90).

Compared with natural conception, conceptions via both IVF and ICSI were associated with increased risks of low birth weight (IVF, RR = 1.54, 95% CI = 1.44 to 1.63, *P* < .001; ICSI, RR = 1.53, 95% CI = 1.41 to 1.67, *P* < .001), very low birth weight (IVF, RR = 1.88, 95% CI = 1.62 to 2.17, *P* < .001; ICSI, RR = 1.84, 95% CI = 1.51 to 2.23, *P* < .001), preterm birth (IVF, RR = 1.55, 95% CI = 1.47 to 1.64, *P* < .001; ICSI, RR = 1.39, 95% CI = 1.29 to 1.49, *P* < .001), very preterm birth (IVF, RR = 1.86, 95% CI = 1.66 to 2.08, *P* < .001; ICSI, RR = 1.75, 95% CI = 1.49 to 2.05, *P* < .001), and being born small for gestational age (IVF, RR = 1.03, 95% CI = 0.99 to 1.08, *P* = .17; ICSI, RR = 1.10, 95% CI = 1.04 to 1.16, *P* = .001).

### Congenital Abnormalities

Children with a paternal history of cancer had an increased risk of any congenital abnormality (RR = 1.12, 95% CI = 1.02 to 1.24, *P* = .0183) and an increased risk of major abnormalities (RR = 1.17, 95% CI = 1.05 to 1.31, *P* = .0043), compared with children without a paternal history of cancer, with 3.7 vs 3.2 incidents of major abnormalities per 100 offspring. When we examined paternal histories of childhood and adulthood cancer separately (Table 3), the children of childhood cancer survivors had a greater risk of major abnormalities than the children of fathers diagnosed in adulthood, although the difference was not statistically significant (RR = 1.19, 95% CI = 0.89 to 1.59, *P* = .24). When we stratified on time between cancer diagnosis and the child's birth, the effect of a paternal history of cancer on the risk of major abnormalities was stronger among children born within 2 years of their father's cancer diagnosis (RR = 1.27, 95% CI = 0.89 to 1.80) than among children born to fathers conceiving later (>2 years after diagnosis)

**Table 1.** Parental characteristics and birth characteristics for singleton children born in Denmark (1994–2004) and Sweden (1994–2005), by paternal history of cancer and mode of conception (N = 1 777 765)\*

Characteristic	No paternal history of cancer			Paternal history of cancer		
	Natural	IVF	ICSI	Natural	IVF	ICSI
Total No. of children,† (%)	1 743 169 (98.5)	16 536 (0.9)	9 390 (0.5)	8 162 (94.1)	205 (2.4)	303 (3.5)
<b>Parental characteristics</b>						
Mean maternal age at birth, y	29.9	34.2	33.3	31.6	34.5	32.8
Mean paternal age at birth, y	32.6	36.3	36.4	35.6	37.6	36.5
Maternal smoking early in pregnancy, No. (%)						
No	1 362 907 (78.2)	13 390 (81.0)	7 962 (84.8)	6 593 (80.8)	163 (79.5)	258 (85.2)
Yes	280 480 (16.1)	2 097 (12.7)	833 (8.9)	1 089 (13.3)	22 (10.7)	24 (7.9)
Missing	99 782 (5.7)	1 049 (6.3)	595 (6.3)	480 (5.9)	20 (9.8)	21 (6.9)
Maternal parity, No. (%)						
Nulliparous	739 048 (42.4)	12 288 (74.3)	7 157 (76.2)	3 194 (39.3)	149 (72.7)	210 (69.3)
Parous, 1 child	647 858 (37.2)	3 445 (20.8)	1 842 (19.6)	3 202 (39.2)	47 (22.9)	82 (27.1)
Parous, ≥2 children	356 262 (20.4)	803 (4.9)	391 (4.2)	1 766 (21.6)	9 (4.4)	11 (3.6)
Missing	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
<b>Birth characteristics</b>						
Sex, No. (%)						
Male	895 333 (51.4)	8 746 (52.9)	4 610 (49.1)	4 185 (51.3)	110 (53.7)	148 (48.8)
Female	847 825 (48.6)	7 790 (47.1)	4 780 (50.9)	3 977 (48.3)	95 (46.3)	155 (51.2)
Missing	11 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gestational age at birth, No. (%), wk						
≤32	15 237 (0.9)	348 (2.1)	169 (1.8)	61 (0.8)	5 (2.4)	6 (2.0)
33–36	67 825 (3.9)	1 093 (6.6)	540 (5.8)	302 (3.7)	14 (6.8)	23 (7.6)
≥37	1 653 984 (94.9)	15 080 (91.2)	8 677 (92.4)	7 773 (95.2)	186 (90.7)	274 (90.4)
Missing	6 123 (0.4)	15 (0.1)	4 (0.04)	26 (0.3)	0 (0.0)	0 (0.0)
Birth weight, No. (%), g						
<1500	9 279 (0.5)	240 (1.5)	113 (1.2)	35 (0.4)	3 (1.5)	6 (2.0)
1500–2499	46 294 (2.6)	811 (4.9)	427 (4.6)	219 (2.7)	10 (4.9)	13 (4.3)
≥2500	1 678 211 (96.3)	15 390 (93.1)	8 803 (93.8)	7 859 (96.3)	191 (93.2)	282 (93.1)
Missing	9 385 (0.5)	95 (0.6)	47 (0.5)	49 (0.6)	1 (0.5)	2 (0.7)
Weight for gestational age, No. (%)						
≤10th percentile	1 71 226 (9.8)	2 091 (12.7)	1 202 (12.8)	742 (9.1)	21 (10.2)	32 (10.6)
>10th percentile	1 558 502 (89.4)	14 341 (86.7)	8 138 (86.7)	7 350 (90.1)	183 (89.3)	269 (88.8)
Missing	13 441 (0.8)	104 (0.6)	50 (0.5)	70 (0.9)	1 (0.5)	2 (0.7)
Any congenital abnormality, No. (%)						
No	1 666 732 (95.6)	15 646 (94.6)	8 873 (94.5)	7 772 (95.2)	188 (91.7)	290 (95.7)
Yes	76 437 (4.4)	890 (5.4)	517 (5.5)	390 (4.8)	17 (8.3)	13 (4.3)
Major congenital abnormality, No. (%)						
No	1 687 074 (96.8)	15 930 (96.3)	9 024 (96.1)	7 863 (96.3)	192 (93.7)	293 (96.7)
Yes	56 095 (3.2)	606 (3.7)	366 (3.9)	299 (3.7)	13 (6.3)	10 (3.3)

\* ICSI = intracytoplasmic sperm injection; IVF = in vitro fertilization.

† Percentages do not add up to 100% due to rounding error.

(RR = 1.16, 95% CI = 1.03 to 1.31), although the difference was not statistically significant. Children with paternal histories of skin cancers (RR = 1.36, 95% CI = 1.08 to 1.72,  $P = .008$ ) and eye and central nervous system cancers (RR = 1.44, 95% CI = 1.08 to 1.91,  $P = .012$ ) had statistically significant increased risks of major congenital abnormalities, whereas increases that fell short of statistical significance were seen in children with paternal histories of respiratory, digestive, and urogenital tract cancers (excluding testicular cancer), and hematological malignancies. Among children with fathers belonging to these groups, a 19%–44% increased risk of major congenital abnormalities was seen compared with children without a paternal history of cancer (Table 3). In contrast, children with a paternal history of testicular cancer, as well as children born to Swedish fathers with a specific history of seminomatous testicular cancer, were no more likely than children without a paternal

history of cancer to have major abnormalities (Table 3; seminoma data not shown). When we examined specific classes of congenital abnormalities, a positive association with a paternal history of cancer was suggested for alimentary tract atresia, cleft lip, cystic kidney, hypospadias, renal agenesis/reduction defects, limb reduction, phacomatosis, pyloric stenosis, and syndactyly (Table 4).

Children conceived using ARTs had a 20% increased risk of major congenital abnormalities compared with children conceived naturally (RR = 1.20, 95% CI = 1.12 to 1.28,  $P < .001$ ). Mode of conception did not modify the association between paternal history of cancer and risk of congenital abnormalities (natural conceptions, RR = 1.17, 95% CI = 1.04 to 1.31; ARTs, RR = 1.22, 95% CI = 0.80 to 1.87;  $P_{\text{interaction}} = .84$ ). Of the children of Swedish MCSs conceived via ARTs ( $n = 249$ ), 55% ( $n = 137$ ) were conceived using fresh posttreatment semen and 27% ( $n = 68$ ) were

**Table 2.** Paternal characteristics for 8670 singleton children born at or after 1 year after a paternal cancer diagnosis, by mode of conception\*,†

Paternal characteristic	Mode of conception			Total (n = 8670)
	Natural (n = 8162)	IVF (n = 205)	ICSI (n = 303)	
Mean age at cancer diagnosis, y	26.3	28.9	28.3	26.4
Cancer diagnosis,‡ No. (%)				
Respiratory/digestive/urogenital tract§	1114 (13.6)	20 (9.8)	14 (4.6)	1148 (13.2)
Testicle	2259 (27.7)	68 (33.2)	161 (53.1)	2488 (28.7)
Skin	1687 (20.7)	39 (19.0)	18 (5.9)	1744 (20.1)
Eye and central nervous system	1054 (12.9)	13 (6.3)	10 (3.3)	1077 (12.4)
Bone and soft tissue	430 (5.3)	3 (1.5)	8 (2.6)	441 (5.1)
Blood and lymphatic system	1211 (14.8)	53 (25.9)	84 (27.7)	1348 (15.5)
All other diagnoses	407 (5.0)	9 (4.4)	8 (2.6)	424 (4.9)
No. of diagnoses (%)				
1	8065 (98.8)	204 (99.5)	293 (96.7)	8562 (98.8)
>1	97 (1.2)	1 (0.5)	10 (3.3)	108 (1.2)

\* ICSI = Intracytoplasmic sperm injection; IVF = in vitro fertilization.

† Men who fathered more than one child post-cancer diagnosis are counted multiple times.

‡ See "Exposure" in "Materials and Methods" for the *International Classification of Diseases-7* codes included in each category.

§ Testicular cancer was excluded.

conceived using cryopreserved pretreatment semen; data were missing for the remaining 18% (n = 44) of children. The prevalence of major congenital abnormalities in children conceived using fresh posttreatment semen and those conceived using cryopreserved pretreatment semen was comparable (4.4% [six of 137] and 4.4% [three of 68], respectively).

A subanalysis restricted to Swedish children and therefore including only cancer diagnoses registered in Sweden in the definition of paternal history of cancer did not appreciably alter our results (data not shown), which suggests that small differences in the registration of cancer patients in Denmark and Sweden did not affect our results.

## Discussion

In this study, Danish and Swedish registries including 1 777 765 singleton children born between 1994 and 2004 (Denmark) and 2005 (Sweden) were used to investigate the relationship between paternal history of cancer and the mode of conception on perinatal outcomes in offspring. A paternal history of cancer was not associated with either low birth weight or preterm delivery. However, a paternal history of cancer was associated with a 17% increased risk of major congenital malformations, an association that was not modified by mode of conception. Apart from results from a recent study that found that first-born children of MCSs had an increased risk of congenital abnormalities (RR = 1.5, 95% CI = 1.1 to 2.3)

**Table 3.** Prevalence and risk ratios for the association between paternal history of cancer and the risk of major congenital abnormalities, by type of paternal cancer, paternal age at cancer diagnosis, and time between cancer diagnosis and birth\*

Characteristic	No.	Prevalence, %	Adjusted† RR (95% CI)
No paternal history of cancer (N = 1 769 095)	57 067	3.2	1.00 (referent)
Any paternal history of cancer (8670 total patients)	322	3.7	1.17 (1.05 to 1.31)
Paternal history of specific cancer types			
Respiratory/digestive/urogenital tract‡	45	3.9	1.26 (0.94 to 1.68)
Testicle	76	3.1	0.98 (0.78 to 1.22)
Skin	77	4.4	1.36 (1.08 to 1.72)
Eye and central nervous system	47	4.4	1.44 (1.08 to 1.91)
Bone and soft tissue	8	1.8	0.54 (0.26 to 1.12)
Blood and lymphatic system	51	3.8	1.19 (0.90 to 1.57)
All other diagnoses	18	4.3	1.30 (0.82 to 2.07)
Paternal age at cancer diagnosis, y			
<18 (n = 1337)	56	4.2	1.36 (1.05 to 1.77)
≥18 (n = 7333)	266	3.6	1.14 (1.01 to 1.29)
Time between cancer diagnosis and birth, y§			
≤2 (n = 774)	31	4.0	1.27 (0.89 to 1.80)
>2 (n = 7388)	268	3.6	1.16 (1.03 to 1.31)

\* CI = confidence interval; RR = risk ratio.

† Adjustments were made for country (Denmark vs Sweden), year of birth (1-year categories), maternal age at birth (5-year categories), maternal parity (0, 1, ≥ 2), maternal smoking during early pregnancy (yes or no), and mode of conception (natural, IVF, or ICSI).

‡ Testicular cancer was excluded.

§ Only naturally conceived children were included.

**Table 4.** Paternal history of cancer and risk of specific congenital abnormalities in children born in Denmark (1994–2004) and Sweden (1994–2005) (N = 1 777 765) (34)\*

Type of congenital abnormality	Paternal history of cancer				RR (95% CI)†	P‡
	Yes (n = 8670)		No (n = 1 769 095)			
	No. of patients	Prevalence, %	No. of patients	Prevalence, %		
Any	420	4.84	77844	4.40	1.12 (1.02 to 1.24)	.018
Any major	322	3.71	57067	3.23	1.17 (1.05 to 1.31)	.004
Selected groups of congenital abnormalities§						
Abdominal wall	3	0.03	511	0.03	1.2 (0.4 to 3.7)	.76
Alimentary tract atresia	14	0.16	1704	0.10	1.7 (1.0 to 2.8)	.054
Cardiovascular	88	1.01	17772	1.00	1.0 (0.9 to 1.3)	.92
Central nervous system	8	0.09	1915	0.11	0.9 (0.4 to 1.7)	.65
Chromosomal, non-Down	2	0.02	1179	0.07	0.3 (0.1 to 1.4)	.13
Cleft lip	17	0.20	2731	0.15	1.3 (0.8 to 2.0)	.33
Cleft palate	8	0.09	1410	0.08	1.2 (0.6 to 2.3)	.68
Club foot	15	0.17	2657	0.15	1.2 (0.7 to 1.9)	.58
Craniosynostosis	5	0.06	967	0.05	1.1 (0.4 to 2.5)	.90
Cystic kidney	7	0.08	547	0.03	2.6 (1.2 to 5.5)	.012
Diaphragmatic hernia	1	0.01	447	0.03	0.5 (0.1 to 3.2)	.43
Down syndrome	5	0.06	1941	0.11	0.5 (0.2 to 1.3)	.15
Hypospadias	27	0.31	4506	0.25	1.2 (0.8 to 1.8)	.30
Kidney dysgenesis, agenesis or hypoplasia	5	0.06	440	0.02	2.3 (1.0 to 5.6)	.061
Limb reduction	10	0.12	912	0.05	2.2 (1.2 to 4.2)	.011
Neural tube	5	0.06	777	0.04	1.3 (0.5 to 3.2)	.54
Phacomatosis	4	0.05	336	0.02	2.4 (0.9 to 6.5)	.078
Polydactyly	7	0.08	1659	0.09	0.8 (0.4 to 1.8)	.69
Pyloric stenosis	13	0.15	1493	0.08	1.8 (1.0 to 3.1)	.04
Skeletal	2	0.02	375	0.02	1.1 (0.3 to 4.4)	.91
Syndactyly	11	0.13	1510	0.08	1.5 (0.8 to 2.7)	.19

\* CI = confidence interval; RR = risk ratio.

† The estimates for “any congenital abnormality” and “any major congenital abnormality” are adjusted for mode of conception, country, year of birth, maternal age at birth, maternal parity, and maternal first-trimester smoking; the class-specific estimates are unadjusted.

‡ P values were calculated using two-sided Wald test.

§ *International Classification of Diseases (ICD-9)* codes (Sweden)/*ICD-10* codes (Denmark): abdominal wall, 756H/Q79.2–Q79.5; alimentary tract atresia, 750D or 751C-D/Q39 or Q41–42; cardiovascular, 745–747, excluding 747A and 747F/Q20–Q28, excluding Q25.0 and Q27.0; central nervous system, 742B or 742D-X/Q02–Q04 or Q06; chromosomal, non-Down, 758, excluding 758A/Q91–Q99; cleft lip, 749B-C/Q36–Q37; cleft palate, 749A/Q35; club foot, 754F/Q66.0; craniosynostosis, 756A/Q75.0–Q75.1; cystic kidney, 753B/Q62; diaphragmatic hernia, 756G/Q79.0–Q79.1; Down syndrome, 758A/Q90; hypospadias, 752G/Q54; kidney dysgenesis, agenesis or hypoplasia, 753A/Q61; limb reduction, 755C-E/Q71–Q73; neural tube, 740–742A/Q00–Q01 or Q05; phacomatosis, 759F-G/Q85; polydactyly, 755A/Q69; skeletal, 756E-F/Q77–Q78; syndactyly, 755B/Q70.

(35), our findings with respect to congenital abnormalities are contrary to those reported in previous studies (2,6,36–40). However, our study is the largest of its kind, to our knowledge, and was better powered to detect modest associations between paternal history of cancer and congenital abnormalities than previous studies because of the relatively large number of patients.

Concern for the health of the offspring of MCSs is founded mostly on the theoretical adverse effects cancer treatment may have on sperm quality. In animal models, chemotherapy administered in doses equivalent to those received by humans undergoing treatment for cancer has been shown to be mutagenic (41). In addition, both radio- and chemotherapy have been shown to induce DNA damage in human sperm, albeit only transiently, with both decreased DNA integrity (8,9,11) and chromosomal damage (10,28,42) observed. However, increased damage to sperm DNA has also been shown in cryopreserved pretreatment semen from cancer patients (8,12,13,43), suggesting that the cancer itself may also diminish sperm quality.

We were unable to directly examine the effect of paternal history of specific treatments for cancer on birth outcomes because

neither national cancer register contains complete information on treatment (eg, the Danish Cancer Register only contains information on treatment completed within 4 months of diagnosis). However, specific groups of cancers can generally be expected to be treated in standard ways. Consequently, in subanalyses, we examined the effect of paternal histories of specific groups of cancer diagnoses that were presumed to have received the same treatment, as a proxy for the effect of a paternal history of specific cancer treatments. Although we recognize that use of such a coarse proxy measure was not ideal and our results must be interpreted with caution, our findings are suggestive nonetheless.

Whereas paternal history of hematological malignancy, generally treated with chemotherapy, was associated with a non-statistically significant increased risk of congenital abnormalities compared with children with no paternal history of cancer, no such increased risk was seen among children with a paternal history of testicular seminoma, the majority of which would have been treated with radiotherapy (stage I disease) (27). In contrast, a paternal history of skin cancer, for which the standard treatment is surgical excision only, conferred an almost 40% increased risk of

such abnormalities. The role of chance should always be considered when multiple subanalyses are performed, and no clear conclusions in relation to specific diagnoses should be drawn. However, these findings suggest that the increased risk of congenital abnormalities may be related more to paternal disease than to treatment for said disease. Although we cannot rule out that the observed increase in risk of congenital abnormalities among children fathered by MCSs may be due to treatment-induced sperm DNA damage, this modest increase in risk could be due either to a direct effect of cancer itself on sperm DNA quality or to a constitutional genetic instability that contributed to the risks of both developing cancer early in life and conceiving a child with a birth defect. The latter possibility is supported by the fact that the rate of congenital abnormalities among ARTs children with a paternal history of cancer was similar using either pretreatment (“unexposed”) or post treatment (“exposed”), although this information was only available for a small number of children.

Because ARTs can be used to conceive children in situations where the percentage of sperm with DNA strand breaks excludes the possibility of natural conception, a further increase in the risk of adverse birth outcomes could theoretically be anticipated when MCSs use IVF or ICSI to conceive their children. However, although we found independent increases in the risk of major congenital abnormalities associated with both a paternal history of cancer and conception using ARTs, the risk associated with a paternal history of cancer was not further increased in children conceived using either IVF or ICSI.

The study was based on Danish and Swedish national population-based registers, all of which have previously been extensively validated and demonstrated to have excellent coverage (17–19,21–25,36). The feasibility of combining national registers from the Nordic countries has previously been demonstrated (4).

Despite the strengths associated with the register-based nature of our study, register-based designs are also subject to certain limitations, although we have attempted to minimize, or at least to delineate, their impact on our findings. Although the Scandinavian registers are known to have good coverage, the potential for misclassification due to incomplete case registration is always a concern. Registration of incident cancer patients, however, is considered to be close to complete in both Denmark and Sweden (22,25). Consequently, there is likely to have been little misclassification of a paternal history of cancer. Furthermore, subanalyses revealed that the small differences in the diagnoses registered in the two countries did not affect our results.

Similarly, registration of birth characteristics such as birth weight and gestational age by the Danish and Swedish Medical Birth Registers is also considered close to complete (18,21). However, registration of congenital abnormalities may be less complete, as many abnormalities are not immediately apparent at birth. Despite these potential limitations, we were able to extend follow-up for congenital abnormalities by up to 11 years through use of records from the Danish and Swedish Hospital Discharge Registers and the Swedish Register of Congenital Malformations.

Our results show that the risk of major abnormalities was stronger (although not statistically significantly so) among children born within 2 years of their father’s cancer diagnosis and that the strength of the association between a paternal history of cancer and

the risk of congenital abnormalities was similar for many classes of abnormalities. These results could support the theory that the offspring of MCSs, particularly those of men treated shortly before conceiving their children, may be more vigilant in having congenital abnormalities diagnosed due to concerns about their own health. However, a transient effect of treatment on sperm DNA quality could also produce the pattern seen with time between paternal cancer diagnosis and birth.

Further questions about the birth outcomes of offspring from MCSs still need to be addressed. For example, are offspring fathered by childhood cancer survivors at greater risk of congenital abnormalities than those fathered by adult cancer survivors? Furthermore, treatment data are necessary to disentangle the potential contributions of cancer itself and different treatments to the observed increased risk of congenital abnormalities among the offspring of MCSs supported by our study. However, our findings provide evidence that a paternal history of cancer may not be associated with most adverse perinatal outcomes. Furthermore, if confirmed in subsequent studies, the modest increase in risk of major congenital abnormalities associated with a paternal history of cancer may not be compounded by the use of ARTs.

## Appendix 1: Data Sources

### Denmark

Civil Registration System (23): Updated daily and includes all residents of Denmark, their civil status, links to their parents, and a unique personal identification number, allowing linkage of information from population-based health registers.

Medical Birth Register (18): Established in 1973 and contains information on all live and stillbirths in Denmark.

IVF Register (17): Established in 1994 and records all treatments with IVF, ICSI, frozen embryo replacement, and egg donation, with coverage close to 100% (mandatory reporting nationwide).

Cancer Register (25): Records information on cancer patients in Denmark since 1943, including information on site of tumor (*ICD-7* codes), histological type (*ICD-O* codes), with completeness shown to be 95%–98%.

Hospital Discharge Register (34): Contains discharge diagnoses (up to 20) for all hospitalizations (from 1978) and outpatient visits (from 1996) in Denmark.

### Sweden

Total Population Register: The civil registration of the inhabitants of Sweden, assigning all a unique personal identification number.

Multigenerational Register (24): Contains information on first-degree relatives of all Swedish citizens born after 1931 and still alive in 1961, or born in 1961 or later, with close to 100% coverage.

Medical Birth Register (21): Covers nearly all (>98%) children born in Sweden. Between 1993 and 2005, IVF and ICSI treatments were given at 18 public or private clinics, with data on all treatments leading to delivery of a baby reported to the Swedish National Board of Health, and thereby to the register.

Cancer Register (22): Mandatory reporting of cancers in Sweden since 1958, with agreement between clinical and cytological or histological diagnoses close to 100% coverage. Information includes site of tumor (*ICD-7* codes), histological type (*ICD-O/2* codes for 1994–2004 and *ICD-O/3* codes for 2005), and basis of and date of diagnosis.

Congenital malformations: Information retrieved from the Medical Birth Register, and supplemented with data from the Swedish Register of Congenital Malformations (19), and the Hospital Discharge Register (44). Records from the various registries were compared, with the most detailed diagnoses for each child used (20).

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