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Article



ARTICLE

# Risk of Congenital Malformations in Children Born Before Paternal Cancer

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## Abstract

**Background:** Increased risk of congenital malformations in children fathered by men treated for cancer might be due to mutagenicity of cancer therapies. Finding of increased malformation prevalence in offspring born before paternal cancer would indicate a treatment-independent mechanism.
**Methods:** Through national registries, we obtained data on singletons born in Sweden from 1994 to 2014 (n = 1 796 160) and their fathers and mothers (1 092 950/1 092 011). Men with cancer (n = 23 932) fathered 26 601 and 9926 children before and after cancer diagnosis, respectively. Associations between paternal cancer, diagnoses retrieved from the Swedish Cancer Register, and offspring malformations, based on Swedish Medical Birth Register data, were estimated by logistic regression.
**Results:** Children conceived before paternal cancer had a statistically significantly increased risk of all malformations (odds ratio [OR] = 1.08, 95% confidence interval [CI] = 1.02 to 1.15, $P = .016$, 3.8% vs 3.4%) and major malformations (OR = 1.09, 95% CI = 1.01 to 1.18, $P = .03$, 2.4% vs 2.1%). Eye and central nervous system cancers were associated with the highest risk of all malformations (OR = 1.30, 95% CI = 1.04 to 1.61, $P = .02$, 4.5% vs 3.4%). A similar trend was seen for testicular cancer. The malformation rates among children conceived before and after paternal cancer diagnosis were similar.
**Conclusions:** The association between paternal cancer and risk of malformations in the offspring is not solely due to mutagenic effects of cancer therapy. The increase in prevalence of birth anomalies among children of fathers with malignancy might be due to cancer per se or a common underlying paternal factor, for example, genomic instability.

There is concern that the mutagenic effects of cancer therapies can lead to congenital malformations in the offspring of cancer patients (1,2). A register study including all singleton children born in Denmark and Sweden between 1994 and 2004 showed a statistically significant increase in the rate of major congenital malformations in children born to fathers with a history of cancer (3). The mutagenic effects of irradiation and cytotoxic drugs have been well documented in animal studies, and some indications of mutagenicity has been found in humans (4–12). A plausible explanation for the increased rate of malformations might be adverse genetic or epigenetic alterations of sperm DNA by oncological treatments, leading to an increased rate of malformations in children conceived after cancer treatment. Conversely, the register study also indicated an increase in malformation risk among children of fathers with cancers most commonly treated with surgery only, such as skin neoplasms (3). This prompted the hypothesis that the observed increase in malformation rate could be linked to the cancer per se or a common risk factor, rather than to its treatment (13).

If the increase in congenital malformations cannot be attributed solely to cancer therapies, one might expect that there is an elevated risk of birth abnormalities in children born to men with cancer diagnosed after the conception of the child. If preclinical malignancy has an adverse impact on the sperm genome, this effect might be most pronounced immediately before the clinical manifestation of the cancer. Therefore, the main aim of this study was to estimate the malformation risk in newborns conceived by men who were subsequently diagnosed with cancer. Secondary aims were to investigate if the paternal cancer type and time elapsed to paternal cancer influence

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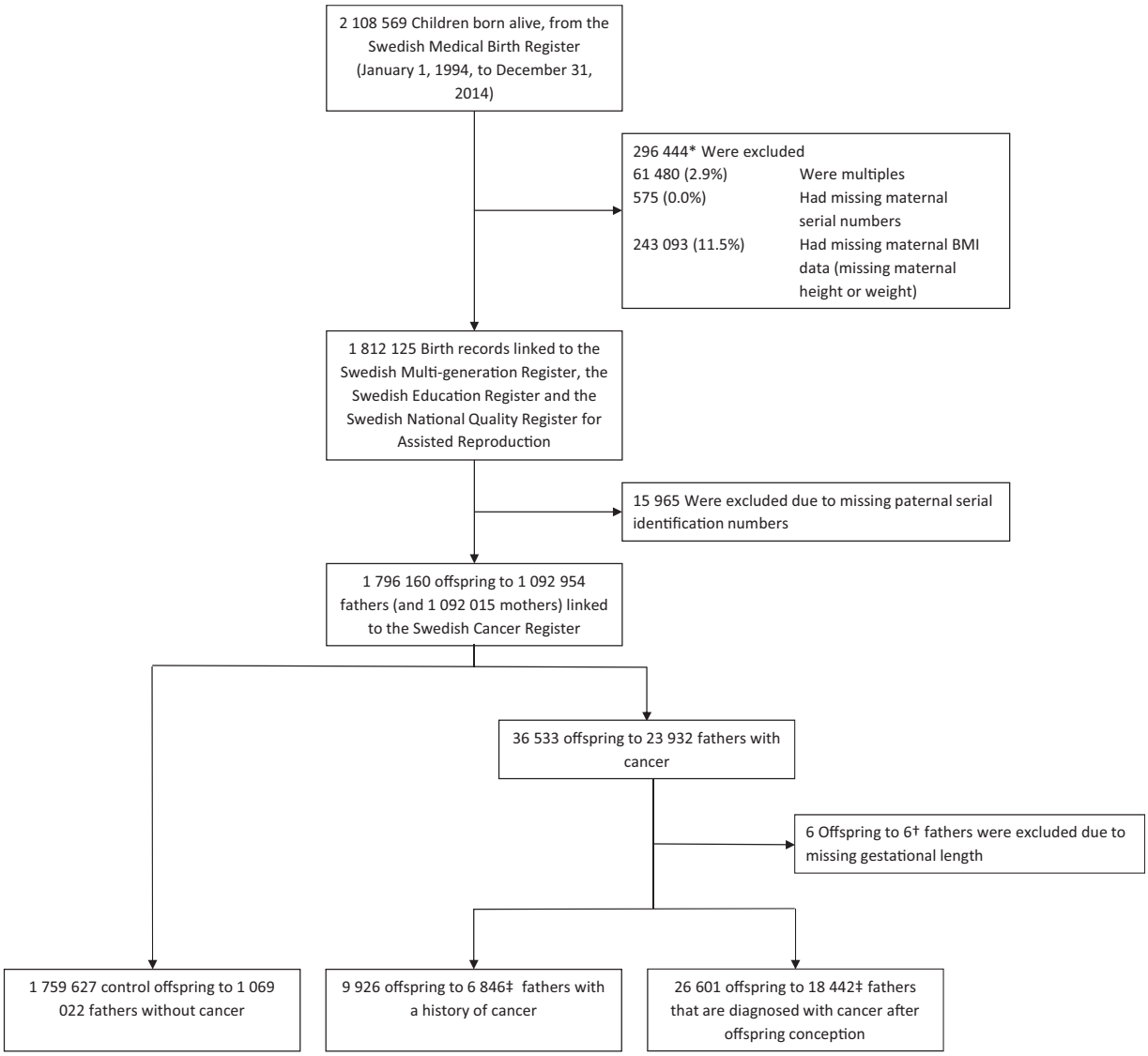


**Figure 1.** Identification of the study population and register linking. *Exclusions do not add up to 296 444 because of cases with missing data on multiple variables. †Fathers who had another child who did not have a missing gestational age were re-included in the analysis; therefore six offspring to four fathers were excluded. ‡Fathers do not add up to the number of total fathers with cancer, as 1360 fathers conceived children before and after cancer. BMI = body mass index.

offspring malformation risk, as well as to compare the malformation risk for the children born after paternal cancer with those born before malignancy. To answer these questions, we have utilized Swedish national registries to achieve sufficient power to detect even modest risk differences (14–16).

## Methods

### Study Design and Data Sources

The cohort was defined as all children registered in the Medical Birth Register and born alive in Sweden during 1994–2014 (n = 2 108 569), based on the Swedish Total Population Register and the Swedish Multigenerational Register. All children and parents in the cohort were given a unique serial number linked to their Swedish Personal Identity Number. The Personal Identity Numbers and linked serial numbers were sent to the Swedish National Board of Health and Welfare so that excerpts from relevant registries could be obtained. Finally, the Personal Identity Numbers were redacted to mask personal information. All multiples and children with missing parental serial numbers or missing maternal body mass index (BMI) data were excluded. Children with paternal cancer (n = 6) and missing gestational length were also excluded, resulting in 1 796 154 singletons with 1 092 950 fathers, and 1 092 011 mothers included (Figure 1).

Maternal and perinatal characteristics including mode of conception were gathered for each child from the Swedish Medical Birth Register and the Swedish National Quality Register for Assisted Reproduction. All paternal cancer diagnoses registered during the period 1958–2014 were retrieved from the Swedish Cancer Register. Parental education levels and date of death were sourced from the Swedish Register of Education and the Cause of Death register, respectively.

The study was approved by the regional ethical board of Lund (No: 2015/670).

### Congenital Malformations

The Swedish Medical Birth Register supplied neonatal diagnoses listed in the Swedish version of the International Classification of Diseases 9 (ICD-9-SE) for 1994–1997 and ICD-10-SE for 1998–2014. All congenital abnormalities were defined as ICD-9-SE 740-759 and ICD-10-SE Q00-Q99. Major and minor malformations were defined according to the European Surveillance of Congenital Anomalies coding guide (17), minor exceptions being diagnoses where ICD-10 codes could not be directly translated into ICD-9-SE (Section 1, Supplementary Material, available online). Additionally, to elucidate whether the types of malformations differed between children born before and after paternal cancer diagnosis, a post hoc analysis, based on the cause (chromosomal vs nonchromosomal) or location, was performed.

### Paternal Cancers

Paternal cancer cases were stratified into the following previously described groups (3): a) digestive, respiratory, and urogenital tract cancers (ICD-7: 141.0–163.9, 177.0–177.9, 179.0–181.9, 195.5); b) testicular cancer (ICD-7: 178.0–178.9); c) skin cancers (ICD-7: 140.0–140.9, 190.0–191.9); d) central nervous system and eye cancers (ICD-7: 192.0–193.1); e) soft tissue and bone cancers (ICD-7: 193.3, 193.8, 193.9, 196.0–197.9); f) hematological and lymphatic cancers (ICD-7: 200.0–209.9); and g) all other cancer diagnoses (ICD-7: 164.0–164.9, 170.1, 170.2, 194.0–194.9, 195.0–195.9, 199.1–199.9).

### Statistical Analyses

Associations between paternal cancer and congenital malformations were evaluated using a multivariable binary logistic regression model, yielding odds ratios (ORs) with 95% confidence intervals (CIs). The offspring to fathers without a cancer diagnosis were used as controls in all analyses unless otherwise stated. The model was adjusted for the child's year of birth (five-year categories), maternal age at childbirth (five-year categories), paternal age at offspring birth (five-year categories), maternal BMI (<20, ≥20 to <25, ≥25 to <30, ≥30 to <35, ≥35 kg/m$^2$), maternal parity (0, 1, 2+ children), self-reported maternal smoking at first prenatal visit (nonsmoker, 1–9 cigarettes per day, ≥10 cigarettes per day, or missing data), and maternal and paternal years of formal education as an indicator of socioeconomic status (≤10, >10–≤14, ≥15 or missing data). These covariates were chosen because they have been previously shown to affect birth outcomes (18–23).

To investigate if children born before paternal cancer have a statistically different risk of congenital malformations compared with children born after paternal cancer diagnosis, a post hoc logistic regression analysis was performed. In this analysis, children born to fathers with a history of cancer were used as controls, as it has been shown previously that they do have an increased risk of severe congenital malformations (3). The model was adjusted for the above covariates.

In logistic regression analyses, fathers can contribute more than one child. To adjust for any intercase dependence on outcome that this may introduce, the analysis was also performed using the generalized estimating equation method, using the father as a cluster, assuming an exchangeable correlation structure, and using a robust variance estimator. Further post hoc sensitivity analysis excluded children (n = 38 454) conceived by assisted reproduction techniques (ART) due to lack of information on possible use of donor or cryopreserved spermatozoa.

To investigate whether the rate of malformations was highest in children conceived shortly before the cancer diagnosis—indicating a direct effect of malignancy on the spermatozoal genome—the malformation events were plotted using locally weighted scatterplot smoothing (span = 0.66). For this purpose, the date of conception was estimated from gestational length information.

Our hypothesis was that there is a common causative paternal factor underlying both paternal cancer and malformations in the offspring, independently of when the offspring is born in relation to the paternal cancer. Therefore, logistic regression was deemed appropriate. However, we also estimated the association between the birth of a child with a malformation and the father's subsequent cancer risk using Cox regression analysis. In this model, fathers were followed from the date of offspring conception until they developed cancer, died, or until the end of follow-up (December 31, 2014). If a father had multiple children, he was counted once for every child. The model was adjusted for the father's age and paternal education level. Fathers were grouped according to whether their offspring had a major congenital malformation to calculate the hazard ratio for developing cancer.

All analyses and data management were performed by the first author, as discussed with the other authors. Analyses were conducted using SPSS, version 24.0.0.1 (IBM Corp, Armonk, NY), R, version 3.4.0, with ggplot2 package (R Foundation for Statistical Computing, Vienna, Austria), and Python, version 3.6.1 (Python Software Foundation, python.org). All statistical analyses were two-sided; *P* values of less than .05 were considered statistically significant.

## Results

### Study Population

A total of 1 796 154 children born in Sweden between January 1, 1994, and December 31, 2014, were included. Among the children, 1 759 627 had fathers without cancer, 9926 had fathers with a history of cancer, and 26 601 had fathers who were diagnosed with cancer after the conception of the child. The distribution of selected parental characteristics and birth outcomes among these children is presented in Table 1. The 6846 fathers diagnosed with cancer before offspring conception had a mean age at the birth of the child of 35.7 years. Among the 18 442 fathers who had cancer after offspring conception, the mean age was 36.4 years. Selected parental and neonatal characteristics for subgroups defined according to the time from conception to cancer diagnosis are presented in Table 2.

### Congenital Malformations

Children born before paternal cancer had a statistically significantly increased risk of having a congenital malformation (OR = 1.08, 95% CI = 1.01 to 1.15, *P*= 0.02, 3.8% vs 3.4%) as well as having a major malformation (OR = 1.09, 95% CI = 1.01 to 1.18, *P*= 0.03, 2.4% vs 2.1%).

When examining the malformation risk according to the cancer subgroups for children born before paternal cancer diagnosis, eye and central nervous system cancers were associated with the highest risk of all malformations (OR = 1.30, 95% CI = 1.04 to 1.61, *P* = .02, 4.5% vs 3.4%). Furthermore, testis cancer

**Table 1.** Selected parental and perinatal characteristics for children without paternal cancer, with paternal history of cancer, and paternal cancer after offspring conception*

| Characteristic | No cancer | Paternal history of cancer | Paternal cancer after offspring conception |
|---|---|---|---|
| Total No. of children (%) | 1 759 627 (98.0) | 9926 (0.6) | 26 601 (1.5) |
| Parental characteristics | | | |
| Mean maternal age at offspring birth (SD), y | 29.8 (5.1) | 31.6 (5.0) | 31.4 (5.2) |
| Mean maternal BMI at early pregnancy (SD), kg/m$^2$ | 24.4 (4.4) | 24.5 (4.6) | 24.3 (4.3) |
| Mean paternal age at offspring birth (SD), y | 32.7 (6.1) | 35.7 (7.1) | 36.4 (7.8) |
| Nonsmoking mothers early in pregnancy, No. (%) | 1 571 503 (89.3) | 9105 (91.7) | 22 839 (85.9) |
| Mothers smoking 1–9 cigarettes/d, No. (%) | 117 620 (6.7) | 488 (4.9) | 2121 (8.0) |
| Mothers smoking more than 10 cigarettes/d, No. (%) | 46 932 (2.7) | 203 (2.0) | 1131 (4.3) |
| Missing information regarding maternal smoking, No. (%) | 23 572 (1.3) | 130 (1.3) | 510 (1.9) |
| Maternal parity, No. (%) | | | |
| Nulliparous | 765 013 (43.5) | 4061 (40.9) | 9966 (37.5) |
| Parous, 1 child | 649 562 (36.9) | 3814 (38.4) | 9797 (36.8) |
| Multiparous | 345 052 (19.6) | 2051 (20.7) | 6838 (25.7) |
| Mode of conception | | | |
| Natural | 1 722 595 (97.9) | 9132 (92.0) | 25 973 (97.6) |
| Assisted | 37 032 (2.1) | 794 (8.0) | 628 (2.4) |
| Birth characteristics | | | |
| Sex, No. (%) | | | |
| Male | 904 143 (51.4) | 5116 (51.5) | 13 673 (51.4) |
| Female | 855 480 (48.6) | 4810 (48.5) | 12 928 (48.6) |
| Missing | 4 (0.0) | 0 (0.0) | 0 (0.0) |
| All congenital abnormalities, No. (%) | 60 540 (3.4) | 357 (3.6) | 1016 (3.8) |
| Major congenital abnormalities, No. (%) | 37 785 (2.1) | 230 (2.3) | 629 (2.4) |

*BMI = body mass index.

**Table 2.** Selected parental and perinatal characteristics for groupings based on when conception occurred in relation to paternal cancer diagnosis*

| Characteristic | Paternal cancer after offspring conception | | | Paternal cancer before offspring conception |
|---|---|---|---|---|
| No. of years from offspring conception to paternal cancer diagnosis | >6 | ≤6 to >3 | ≤3 to >0 | ≤0 to >−3 |
| Total No. of children | 18 254 | 4291 | 4056 | 2630 |
| Parental characteristics | | | | |
| Mean maternal age at offspring birth (SD), y | 31.4 (5.2) | 31.5 (5.2) | 31.3 (5.1) | 31.3 (5.1) |
| Mean maternal BMI at early pregnancy (SD), kg/m$^2$ | 24.2 (4.2) | 24.5 (4.4) | 24.6 (4.5) | 24.4 (4.4) |
| Mean paternal age at offspring birth (SD), y | 36.5 (7.7) | 36.5 (8.3) | 36.0 (8.0) | 35.5 (7.5) |
| Nonsmoking mothers early in pregnancy, No. (%) | 15 381 (84.3) | 3797 (88.5) | 3661 (90.3) | 2411 (91.7) |
| Mothers smoking 1–9 cigarettes/d, No. (%) | 1596 (8.7) | 281 (6.5) | 244 (6.0) | 137 (5.2) |
| Mothers smoking more than 10 cigarettes/d, No. (%) | 886 (4.9) | 143 (3.3) | 102 (2.5) | 52 (2.0) |
| Missing information regarding maternal smoking, No. (%) | 391 (2.1) | 70 (1.6) | 49 (1.2) | 30 (1.1) |
| Maternal parity, No. (%) | | | | |
| Nulliparous | 6643 (36.4) | 1749 (40.8) | 1574 (38.8) | 1108 (42.1) |
| Parous, 1 child | 6669 (36.5) | 1558 (36.3) | 1570 (38.7) | 965 (36.7) |
| Multiparous | 4942 (27.1) | 984 (22.9) | 912 (22.5) | 557 (21.2) |
| Mode of conception, No. (%) | | | | |
| Natural | 17 895 (98.0) | 4145 (96.6) | 3912 (96.4) | 2456 (93.4) |
| Assisted | 359 (2.0) | 146 (3.4) | 144 (3.6) | 174 (6.6) |
| Birth characteristics | | | | |
| Sex, No. (%) | | | | |
| Male | 9370 (51.3) | 2183 (50.9) | 2120 (52.3) | 1342 (51.0) |
| Female | 8884 (48.7) | 2108 (49.1) | 1936 (47.7) | 1288 (49.0) |
| All congenital abnormalities, No. (%) | 681 (3.7) | 183 (4.3) | 152 (3.7) | 99 (3.8) |
| Major congenital abnormalities, No. (%) | 412 (2.3) | 119 (2.8) | 98 (2.4) | 64 (2.4) |

*BMI = body mass index.

was associated with an elevated risk of major malformations (OR = 1.28, 95% CI = 1.00 to 1.64, $P = .05$, 2.7% vs 2.1%). The odds ratios for these subgroups are presented in Table 3.

When post hoc stratifying into subgroups of malformations, children born before paternal cancer had an elevated risk of chromosomal abnormalities (OR = 1.40, 95% CI = 1.08 to 1.80,

**Table 3.** Congenital malformations among offspring to fathers who were diagnosed with cancer after and before offspring conception*

| Paternal group | Crude odds ratio (95% CI) | *P* | Adjusted odds ratio (95% CI) | *P* |
|---|---|---|---|---|
| Paternal cancer after offspring conception | | | | |
| All malformations | | | | |
| All cancers | 1.11 (1.05 to 1.19) | <.001 | 1.08 (1.01 to 1.15) | .02 |
| Digestive, respiratory, and urogenital | 1.14 (1.03 to 1.25) | .01 | 1.09 (0.99 to 1.20) | .09 |
| Testicle | 1.23 (1.00 to 1.50) | .04 | 1.21 (0.99 to 1.48) | .06 |
| Skin | 1.08 (0.95 to 1.24) | .24 | 1.06 (0.92 to 1.21) | .42 |
| Central nervous system and eye | 1.32 (1.06 to 1.64) | .01 | 1.30 (1.04 to 1.61) | .02 |
| Soft tissue and bone | 1.31 (0.88 to 1.94) | .18 | 1.28 (0.86 to 1.90) | .22 |
| Hematological and lymphatic | 0.94 (0.77 to 1.15) | .55 | 0.92 (0.75 to 1.12) | .38 |
| All other cancer diagnoses | 0.93 (0.71 to 1.22) | .62 | 0.91 (0.70 to 1.19) | .51 |
| Major malformations | | | | |
| All cancers | 1.10 (1.02 to 1.20) | .02 | 1.09 (1.01 to 1.18) | .03 |
| Digestive, respiratory, and urogenital | 1.09 (0.96 to 1.23) | .17 | 1.06 (0.94 to 1.20) | .34 |
| Testicle | 1.27 (0.99 to 1.63) | .06 | 1.28 (1.00 to 1.64) | .05 |
| Skin | 1.15 (0.98 to 1.36) | .10 | 1.15 (0.98 to 1.36) | .09 |
| Central nervous system and eye | 1.23 (0.92 to 1.63) | .16 | 1.23 (0.93 to 1.64) | .15 |
| Soft tissue and bone | 1.28 (0.78 to 2.11) | .32 | 1.29 (0.78 to 2.12) | .32 |
| Hematological and lymphatic | 0.94 (0.73 to 1.21) | .64 | 0.93 (0.73 to 1.20) | .59 |
| All other cancer diagnoses | 0.90 (0.64 to 1.27) | .54 | 0.89 (0.63 to 1.26) | .52 |
| Paternal history of cancer | | | | |
| All malformations | | | | |
| All cancers | 1.05 (0.94 to 1.16) | .39 | 1.04 (0.94 to 1.16) | .47 |
| Digestive, respiratory, and urogenital | 1.05 (0.81 to 1.37) | .71 | 1.03 (0.80 to 1.35) | .80 |
| Testicle | 1.25 (1.02 to 1.53) | .03 | 1.25 (1.02 to 1.53) | .03 |
| Skin | 1.06 (0.82 to 1.36) | .66 | 1.05 (0.82 to 1.35) | .71 |
| Central nervous system and eye | 1.22 (0.92 to 1.63) | .17 | 1.22 (0.91 to 1.62) | .18 |
| Soft tissue and bone | 0.69 (0.41 to 1.15) | .15 | 0.69 (0.41 to 1.14) | .15 |
| Hematological and lymphatic | 0.82 (0.62 to 1.09) | .17 | 0.82 (0.62 to 1.08) | .16 |
| All other cancer diagnoses | 0.94 (0.63 to 1.41) | .76 | 0.93 (0.62 to 1.39) | .71 |
| Major malformations | | | | |
| All cancers | 1.08 (0.95 to 1.23) | .24 | 1.07 (0.94 to 1.22) | .32 |
| Digestive, respiratory, and urogenital | 1.04 (0.75 to 1.45) | .81 | 1.01 (0.73 to 1.41) | .94 |
| Testicle | 1.38 (1.08 to 1.76) | .01 | 1.38 (1.08 to 1.76) | .01 |
| Skin | 1.14 (0.84 to 1.54) | .40 | 1.12 (0.83 to 1.52) | .45 |
| Central nervous system and eye | 0.95 (0.63 to 1.42) | .81 | 0.95 (0.63 to 1.42) | .79 |
| Soft tissue and bone | 0.59 (0.29 to 1.18) | .14 | 0.58 (0.29 to 1.18) | .13 |
| Hematological and lymphatic | 0.90 (0.64 to 1.26) | .54 | 0.89 (0.63 to 1.25) | .50 |
| All other cancer diagnoses | 1.13 (0.71 to 1.81) | .60 | 1.11 (0.70 to 1.78) | .65 |

*CI = confidence interval.

P = .01, 0.12% vs 0.24%). The odds ratios for these specific malformations and malformation groups are given in Table 4.

Sensitivity analyses, excluding ART and utilizing the generalized estimating equation differed negligibly from the main logistic regression (Supplementary Table 1, available online).

We did not observe any statistical differences in all or major malformation risk between children born before and after paternal cancer diagnosis (OR = 1.06, 95% CI = 0.92 to 1.21, P = .42, 3.8% vs 3.6%, and OR = 1.01, 95% CI = 0.86 to 1.20, P = .88, 2.4% vs 2.3%, respectively).

In the Cox regression analysis, 26 603 (1.5%) cancer events were observed among the total of 1 785 992 fathers followed. Of these, 38 405 had a child with a major congenital malformation. Fathering a child with a congenital malformation resulted in a statistically significant increase in the risk of developing cancer (hazard ratio = 1.10, 95% CI = 1.01 to 1.19, P = .02).

The major malformation rate for children to fathers with cancer, according to when the child is conceived in relation to the paternal cancer diagnosis, is illustrated in Figure 2. The malformation rate was elevated as compared with the control population for children conceived zero to 20 years before malignancy. There was an apparent peak in malformation rate two to three years before diagnosis of paternal malignancy. Furthermore, the children conceived more than 20 years after paternal malignancy—the median age at cancer diagnosis for these fathers was six years—also exhibited high malformation rates.

## Discussion

The main finding of this study was a statistically significant increase in the rates of all and major congenital malformations in children born before paternal cancer diagnosis. The congenital malformation rates did not differ substantially among children conceived before and after paternal cancer diagnosis. This finding points to the existence of a treatment-independent mechanism that increases the risk of malformations in children born to fathers with cancer. A Danish register study has previously shown an association between offspring born with cleft lip and

**Table 4.** Specific malformations among offspring to fathers who were diagnosed with cancer after and before offspring conception and to fathers without cancer*

| Paternal cancer | No | Yes | | | | | |
|---|---|---|---|---|---|---|---|
| | No paternal cancer | Paternal history of cancer | | | Paternal cancer after offspring conception | | |
| Selected congenital malformation groups | No. of children (%) | No. of children (%) | Adjusted odds ratio (95% CI) | *P* | No. of children (%) | Adjusted odds ratio (95% CI) | *P* |
| All malformations | 60 540 (3.44) | 357 (3.60) | 1.04 (0.94 to 1.16) | .47 | 1016 (3.82) | 1.08 (1.01 to 1.15) | .02 |
| Major malformations | 37 785 (2.15) | 230 (2.32) | 1.07 (0.94 to 1.22) | .32 | 629 (2.36) | 1.09 (1.01 to 1.18) | .03 |
| Chromosomal malformations | 2199 (0.12) | 10 (0.10) | 0.68 (0.37 to 1.27) | .23 | 64 (0.24) | 1.40 (1.08 to 1.80) | .01 |
| Chromosomal, non-Down syndrome | 499 (0.03) | 0 (0.00) | 0.00 (0.00 to 0.00) | .97 | 17 (0.06) | 1.58 (0.96 to 2.59) | .07 |
| Down syndrome | 1700 (0.10) | 10 (0.10) | 0.87 (0.47 to 1.62) | .66 | 47 (0.18) | 1.34 (1.00 to 1.80) | .05 |
| Abdominal wall | 267 (0.02) | 0 (0.00) | 0.00 (0.00 to 0.00) | .98 | 3 (0.01) | 0.91 (0.29 to 2.85) | .87 |
| Alimentary tract atresia | 701 (0.04) | 4 (0.04) | 1.04 (0.39 to 2.77) | .94 | 8 (0.03) | 0.76 (0.38 to 1.54) | .45 |
| Cardiovascular | 12 423 (0.71) | 77 (0.78) | 1.10 (0.88 to 1.38) | .41 | 215 (0.81) | 1.09 (0.95 to 1.25) | .23 |
| Central nervous system | 473 (0.03) | 4 (0.04) | 1.46 (0.54 to 3.90) | .46 | 11 (0.04) | 1.32 (0.72 to 2.42) | .37 |
| Cleft lip | 1614 (0.09) | 11 (0.11) | 1.23 (0.68 to 2.23) | .50 | 25 (0.09) | 1.00 (0.67 to 1.49) | .99 |
| Cleft palate | 997 (0.06) | 3 (0.03) | 0.52 (0.17 to 1.63) | .26 | 19 (0.07) | 1.20 (0.76 to 1.90) | .44 |
| Craniosynostosis | 195 (0.01) | 1 (0.01) | 0.90 (0.13 to 6.42) | .92 | 5 (0.02) | 1.63 (0.66 to 3.99) | .29 |
| Cystic kidney | 2012 (0.11) | 19 (0.19) | 1.46 (0.93 to 2.29) | .10 | 17 (0.06) | 0.73 (0.45 to 1.18) | .20 |
| Diaphragmatic hernia | 243 (0.01) | 2 (0.02) | 1.41 (0.35 to 5.69) | .63 | 4 (0.02) | 0.90 (0.33 to 2.44) | .84 |
| Hypospadis | 4166 (0.24) | 21 (0.21) | 0.89 (0.58 to 1.36) | .58 | 52 (0.20) | 0.91 (0.69 to 1.20) | .50 |
| Kidney dysgenesis* | 361 (0.02) | 3 (0.03) | 1.39 (0.45 to 4.34) | .57 | 2 (0.01) | 0.41 (0.10 to 1.67) | .22 |
| Limb reduction | 649 (0.04) | 7 (0.07) | 2.00 (0.95 to 4.23) | .07 | 8 (0.03) | 0.80 (0.40 to 1.62) | .54 |
| Neural tube | 318 (0.02) | 3 (0.03) | 1.91 (0.61 to 5.95) | .27 | 10 (0.04) | 1.61 (0.85 to 3.06) | .14 |
| Patent ductus arteriosus | 1708 (0.10) | 22 (0.22) | 2.31 (1.52 to 3.52) | <.001 | 34 (0.13) | 1.15 (0.82 to 1.63) | .41 |
| Phacomatosis | 20 (0.00) | 0 (0.00) | 0.00 (0.00 to 0.00) | .98 | 0 (0.00) | 0.00 (0.00 to 0.00) | .96 |
| Polydactyly | 1798 (0.10) | 15 (0.15) | 1.50 (0.90 to 2.49) | .12 | 31 (0.12) | 1.19 (0.83 to 1.70) | .34 |
| Skeletal | 99 (0.01) | 1 (0.01) | 1.72 (0.24 to 12.42) | .59 | 4 (0.02) | 1.81 (0.65 to 5.03) | .26 |
| Syndactyly | 1415 (0.08) | 8 (0.08) | 1.01 (0.51 to 2.03) | .97 | 23 (0.09) | 1.08 (0.71 to 1.63) | .72 |
| Undescended testicle | 7230 (0.41) | 37 (0.37) | 0.90 (0.65 to 1.25) | .53 | 108 (0.41) | 0.98 (0.81 to 1.19) | .84 |

*Diagnosis codes according to International Classification of Diseases 9 (ICD-9-SE) and ICD-10-SE. All congenital abnormalities: ICD-9-SE 740-759 and ICD-10-SE Q00-Q99; major malformations: see Section 1 in the supplement; all chromosomal: 758 or Q90–Q99 ;chromosomal, non-Down: 758 (excluding 758A) or Q91–Q99; Down syndrome: 758A or Q90; abdominal wall: 756H or Q79.2–Q79.5; alimentary tract atresia: 750D or 751C-D/Q39 or Q41–42; cardiovascular: 745–747 (excluding 747A or 747F) or Q20–Q28 (excluding Q25 and Q27); central nervous system: 742B or 742D-X or Q02-Q04 or Q06; cleft lip: 749B-C or Q36–Q37; cleft palate: 749A or Q35; craniosynostosis: 756A or Q75.0–Q75.1; cystic kidney: 753B or Q62; diaphragmatic hernia: 756G or Q79.0–Q79.1; hypospadias: 752G or Q54; kidney dysgenesis: agenesis or hypoplasia*: 753A or Q61; limb reduction: 755C-E or Q71–Q73; neural tube: 740–742A or Q00-Q01 or Q05; patent ductus arteriosus: 747A or Q250; phacomatosis: 759F-G or Q85; polydactyly: 755A or Q69; skeletal: 756E-F or Q77–Q78; syndactyly: 755B or Q70; undescended testicle: 752F or Q53. CI = confidence interval.

subsequent parental cancer (24). However, to our knowledge, this is the first study showing a link between paternal malignancies per se and the general risk of congenital malformations in the offspring born before the father's cancer diagnosis.

The present study has some interesting biological and clinical implications. From a biological perspective, the link between cancer in fathers and malformations in the children gives some clue regarding possible shared pathogenetic factors.

Genetic instability, which may be genetically or environmentally induced, could be an underlying cause of both offspring birth abnormalities and cancer development. Genetic instability is a hallmark of cancer progression, although its involvement in carcinogenesis is speculative. However, if genetic instability is present to a higher extent in some men, this could explain an increased congenital malformation rate in children fathered by these men many years before their cancer diagnosis, as seen in Figure 2. Supporting this mechanism, it has been shown that that the number of mutations passed down to offspring through the paternal germline differs by more than two-fold between fathers; and that the same mutational processes are present in the soma where these processes generate the majority of precancerous mutations (25).

In a post hoc analysis, we found that children born to fathers before the father's cancer diagnosis had a marked increased risk of chromosomal abnormalities. This could further support that these men have higher levels of genetic instability, as it has been shown that unrepaired sperm DNA damage can be incorrectly repaired by the oocytes DNA repair machinery, resulting in chromosomal structural aberrations and ultimately in chromosomally abnormal offspring (26).

Fathers diagnosed with cancer after offspring conception become fathers on average four years later than the control population, possibly due to some degree of impaired fertility. The association between infertility and subsequent cancer has been previously described (27). Subfertility is a complex disease that might in some cases be a symptom of other underlying disorders; a contributing factor might be that these men have been exposed to a variety of genetic, environmental, or lifestyle factors that may cause cancer, as well as offspring congenital malformations via an as yet unknown pathway. However, excluding fathers that had undergone ART treatment did not attenuate the malformation risk, indicating that increased use of ART is not an explanation for the higher malformation risk in offspring of fathers diagnosed with cancer. Furthermore,


**Figure 2.** The rate of major malformation vs the time from offspring conception to paternal cancer diagnosis. Presented as major malformation rate (%) with 95% prediction interval (shaded). Horizontal straight line indicates control level malformation rate. Vertical straight line indicates the date of paternal cancer diagnosis.

paternal age is a weak predictor for offspring congenital malformations when compared with maternal characteristics. Nevertheless, the adjusted analyses did not differ substantially from the crude values, indicating that the observed risk increases are not affected through these covariates.

Apart from genetic instability, other biological mechanisms should be considered. Accordingly, it cannot be excluded that early, preclinical stages of malignancy could have a negative impact on the genome of spermatozoa and cause congenital malformations through unknown mechanisms. Increased sperm DNA damage has been observed in cryopreserved pretreatment sperm from cancer patients (9,28,29), which suggests that cancer per se can adversely affect sperm quality, although other studies could not find this association (30). The fact that the malformation risk was increased even in children born more than 10 years before paternal cancer diagnosis seems to contradict such a mechanism. However, testis cancer, which affects the germinal cells, was associated with major malformations, which might be due to a direct effect of preclinical testicular cancer, especially as testis cancer is assumed to arise in early fetal life (31). However, this mechanism would not be applicable for other cancer types.

As the malformation risks were not higher for children born post-treatment as compared with the children born before paternal cancer diagnosis, it is possible that the elevated risks associated with being conceived post–cancer treatment, which have been previously reported, could be due to the same treatment-independent mechanism. However, these results do not exclude the possibility of a transient treatment effect.

From a clinical perspective, it should be noted that the increases in risk estimates are so modest that fathers of children born with malformations should not worry about an increased cancer risk. Similarly, fathers conceiving children post-treatment should not worry about increased risks of malformations.

The strength of this study was the use of national Swedish registries. Reporting to these registries is mandatory in Sweden, which gives the study both sufficient statistical power and high-quality data, both with respect to paternal cancer diagnoses and neonatally diagnosed malformations in the offspring. More than 1.8 million births and more than 1 million fathers could be included. It has been estimated that more than 98% of cancer diagnoses in Sweden are reported to the national register (14,15), ensuring a complete assessment of all cancer diagnoses. For infant diagnoses in the Medical Birth Register, the underreporting is estimated to be about 10% and is considered random (16). A weakness of this study is that the level of underreporting and prenatal testing might be influenced by previous paternal cancer, especially regarding chromosomal abnormalities; however, this is unlikely to be the case for children born before the diagnosis of malignancy in their fathers. Furthermore, even with the current size of the cohort, the study is underpowered to study specific malformations and specific conception time intervals in relation to paternal cancer.

In summary, this study showed a modest but statistically significant increased risk of congenital malformations in children born before paternal cancer diagnosis. This finding indicates a link between cancer and congenital malformations that is not mediated by cancer therapy.

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## Notes

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LR and AG designed and supervised the study. YA prepared and analyzed the data. YA, LR, OS, and AG interpreted the analyzed data. YA prepared the manuscript. YA, LR, OS, and AG discussed and revised the manuscript. YA and GA had access to the raw data. All authors approved the final version of the manuscript.

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