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Case-control study of congenital anomalies in children of cancer patients

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Abstract

Objectives—To determine whether the offspring of cancer survivors are at an increased risk of congenital anomalies and whether cancer therapy before conception is associated with such an increase.

Design—Case-control study using computerised record linkage.

Setting—Ontario, Canada.

Subjects—Parents of children born during April 1979 to December 1986 who had a congenital anomaly diagnosed within the first year of life (45 200 mothers and 41 158 fathers) and a matched sample of parents whose children did not have a congenital anomaly (45 200 mothers and 41 158 fathers).

Main outcome measures—Cancer diagnosed in either parent before conception and radiotherapy to the pelvis or abdomen or chemotherapy with an alkylating agent.

Results—Among the mothers, 54 cases and 52 controls were identified as having had cancer diagnosed in Ontario (relative risk=1.04, 95% confidence interval 0.7 to 1.5) and among the fathers, 61 cases and 65 controls were identified (0.9, 0.7 to 1.4). No significant associations were found between congenital anomalies in the offspring and any type of cancer treatment in either the mothers or the fathers.

Conclusions—The risk of congenital anomalies among liveborn offspring whose parents have had cancer or been treated for cancer is not higher than that in the general population.

Introduction

The survival rate for children and young adults with cancer have improved substantially over the past few decades^{1,2} largely because of advances in treatment. In the 1970s, chemotherapeutic drugs used in combination were shown to increase complete remission rates. Thus, many children or young adults treated for cancer in the past 10-15 years will have received multiple chemotherapeutic drugs, possibly in addition to radiotherapy.³ Because much of the treatment is known to be mutagenic and is designed to interfere with the DNA and normal cellular function, there may be adverse effects on reproduction.

Although some animal studies support the relation between radiation and chemical exposure and abnormalities in the offspring,⁴⁻⁶ evidence in humans is inconclusive. The higher rates of adverse reproductive outcomes, including congenital anomalies, found among mothers treated with radiotherapy before con-

ception are thought to be primarily due to radiation induced uterine damage rather than to germ cell mutations.⁷⁻⁹ Although most studies have not found an association between cancer therapy and congenital anomalies in the offspring,^{7,10-11} the power to detect moderate increases in risks has generally been limited and few have looked specifically at conditions that might be expected to result from a therapy induced germ cell mutation.

We conducted a case-control study to determine the association between congenital anomalies in the children of those who had cancer diagnosed or treated before conception. We also examined the risks associated with specific cancer therapies and the risks of specific anomalies that could be produced by a new mutation.

Subjects and methods

The figure summarises the methods used in the study. Cases were defined as the parents of children who were recorded in the database of the Canadian

Design of study

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congenital anomalies surveillance system. This database includes children with congenital anomalies diagnosed at birth or cited as a reason for admission to hospital within the first year of life. Children also had to meet the following eligibility criteria: live born in Ontario during 1 April 1979 and 31 December 1986; one or more diagnosis of congenital anomaly according to the ninth revision of the International Classification of Diseases (ICD 740-0-759-9)¹³; and mother a resident of Ontario at the time of the child's birth. A total of 50 032 children were eligible, reflecting a rate of congenital anomaly of about 5% of the total births in Ontario during this period.

Information on the parents of these children was retrieved from birth certificates by computerised linkage with the Ontario birth file. By using the generalised iterative record linkage system,¹³ followed by abstraction from paper files we found a birth certificate for 97% of the records in the anomaly database.

For each set of case parents, one set of control parents was randomly selected from the Ontario birth file. Parents were matched for year of birth of the child, birth order of the child (first birth, second to third, and fourth or greater), exact maternal age, marital status of the mother (single versus not single), and birthplace of each parent (born in Ontario versus not born in Ontario). Some of these matching variables were selected to ensure that cases and controls would have an equal likelihood of linking to the Ontario cancer registry, if they had had cancer. For example, a parent who had had cancer may be more likely to be in the Ontario cancer registry if born in Ontario than a parent not born in Ontario. Identifiers were abstracted from paper copies of the certificates, as for case parents.

Only information from the earliest selected birth was included in the study, regardless of whether the parent was a case or control at this time to avoid non-independence affecting the results. Parents who were resident outside Ontario at the time of the index child's birth and those who were adoptive parents were also excluded. This left 45 200 case mothers and 41 158 case fathers and their matched controls in the study file. Mothers outnumbered fathers because the father was not always named on the birth certificate when the mother was unmarried.

The generalised iterative record linkage system was used to link the study file to the Ontario cancer registry to identify parents who had had cancer diagnosed before the index birth. The Ontario cancer registry contains data on all patients with malignant tumours (except non-melanoma skin cancer) diagnosed in Ontario since 1964. Sample size calculations predicted that, under the null hypothesis, about 300 parents would link to the cancer registry. This estimate accounted for the reduced fertility expected among cancer patients¹⁴ and the possibility of emigration out of Ontario after cancer was diagnosed.

Only parents with cancer diagnosed before the date of conception, estimated from the date of birth and length of gestation reported on the birth certificate, were included. Initially, 316 possible links to the cancer registry were identified. Medical records of these 316 parents were reviewed to establish both the link to the cancer registry and the diagnosis of cancer. Linkage was confirmed for 233 parents. Although four of these had no medical records available, the quality of agreement on the identifying variables was good.

We collected data on cancer treatment from treatment centres, hospital records, and physicians' offices for all 233 parents with definite links to the registry. Information on radiotherapy included dates (starting and stopping) of each course of therapy, type of radiotherapy, and site of radiotherapy (pelvic or abdominal area versus other areas). For radiotherapy to the pelvic or abdominal area, type of machine, and

dose were noted. We also noted name, starting and stopping dates, and dose for each chemotherapeutic drug. Data were also collected on pelvic surgery.

The alkylating agents (cyclophosphamide, melphalan, and mustine) were analysed together because they are thought to have the greatest mutagenic potential; procarbazine was included with these because of its similar mode of action.¹⁵ An alkylator score was calculated to summarise subjects' exposure. For each alkylating agent received a score of one or two was assigned, depending on whether the dose was in the lower or upper 50% of the total distribution of doses (a score of 0 was given to those who did not receive that drug). These scores were summed across drugs and subjects with scores in the top 50% were considered to be in the high dose group. This scoring system assumes that each alkylating agent has the same mutagenic potential and that effects are additive.

Subjects who had received cobalt-60 radiotherapy to the pelvis or abdomen (most subjects who received radiotherapy had been treated with cobalt-60) were also divided into groups. The high dose group comprised subjects whose total dose of cobalt-60 was above the median dose for all subjects treated with radiation.

The results were also examined according to type of congenital abnormality. Congenital anomalies were divided on the basis of ICD code groupings. A child with anomalies in more than one subgroup could, therefore, contribute to several different subgroups. Subgroups were also created according to aetiology¹⁶: single gene disorders (autosomal dominant disorders, autosomal recessive disorders, and X linked disorders); chromosomal disorders (autosomal and X chromosomal disorders); multifactorial disorders; suspected genetic disorders with an unknown aetiology; and anomalies with unknown aetiology. A hierarchical approach was taken so that a child with more than one anomaly contributed to only one subgroup (the order of the hierarchy was as listed above). Classification into aetiological groups was done by DJT based on the four-digit ICD codes without knowing whether the affected child was the offspring of a cancer patient. Because the single gene disorders are thought to comprise anomalies which might be expressed in the offspring as a result of a new mutation,¹⁶ this grouping of anomalies may be more sensitive in detecting an effect of an environmental mutagen.

The mothers and fathers were analysed separately because of the possibility of different effects of cancer therapy on the germ cells. Descriptive analyses were done by using the computer program SAS.¹⁷ Relative risks were approximated by odds ratios which, along with their confidence intervals, were calculated with the EGRET statistical software package.¹⁸ Estimates of relative risk were based on case-control pairs that were discordant with respect to a previous diagnosis of cancer and cancer treatment.¹⁹ Because the numbers of discordant pairs were small, exact methods were used to calculate confidence intervals.²⁰

Results

MOTHERS

For both the case and control mothers, the mean age at the time of the child's birth was 26.7 years; 12% (5337 cases and 5303 controls) were unmarried, 32% (14 302 cases and 14 320 controls) were born outside of Ontario, and 49% (21 989 cases and 22 011 controls) were nulliparous before the index birth. Fifty four case mothers and 52 control mothers were identified in the Ontario cancer registry as having had cancer (relative risk=1.04, 95% confidence interval=0.7-1.5). The most common types of cancer among these 106 mothers were melanoma, thyroid cancer, and breast cancer.

The mean age at diagnosis of cancer was similar among the cases (23.1 years) and controls (23.6 years). The relative risk of anomalies in the offspring decreased with increasing age at diagnosis of cancer, although none was significantly different from unity (relative risk=1.4, 1.0, and 0.7 for mothers under 20, 20 to 29, and over 29 years at the time of diagnosis).

Table I shows the relative risks and 95% confidence intervals associated with cancer treatment. The risk for each category reflects any treatment within that category, regardless of other types of treatment which may have been given. No significant change in risk was seen for any category of treatment. We could not look at the dose effect because of the small number of mothers treated with radiotherapy or chemotherapy.

TABLE I—Numbers of case and control mothers and relative risks for congenital anomalies in the offspring by cancer treatment

Cancer treatment	No of discordant pairs: case exposed, control not exposed	No of discordant pairs: case not exposed, control exposed	Relative risk	95% Confidence interval
Any radiotherapy	14	19	0.7	0.3 to 1.6
Any chemotherapy	6	10	0.6	0.2 to 1.8
Surgery only	35	27	1.3	0.8 to 2.2
Radiotherapy to pelvis	4	3	1.3	0.2 to 9.1
Chemotherapy with an alkylating agent	2	6	0.3	0.0 to 1.9

TABLE II—Numbers of case and control mothers who had had cancer and relative risks for specified congenital anomalies in the offspring

Anomaly group	No of discordant pairs: case cancer, control no cancer	No of discordant pairs: case no cancer, control cancer	Relative risk	95% Confidence interval
According to ICD 9 Code:				
Heart and circulatory system (ICD: 745-747)	14	9	1.6	0.6 to 4.1
Genital organs (ICD: 752)	8	4	2.0	0.5 to 9.1
Musculoskeletal deformities (ICD: 754)	10	12	0.8	0.3 to 2.1
Other anomalies of limbs and musculoskeletal anomalies (ICD: 755-756)	7	6	1.2	0.3 to 4.2
According to aetiology:				
Single gene disorder	4	2	2.0	0.3 to 22.0
Chromosome disorder	2	1	2.0	0.1 to 118.0
Multifactorial aetiology	26	21	1.2	0.7 to 2.3
Genetic, unknown aetiology	6	9	0.7	0.2 to 2.1
Unknown aetiology	16	19	0.8	0.4 to 1.7

TABLE III—Numbers of case and control fathers and relative risks for congenital anomalies in the offspring by cancer treatment

Cancer treatment	No of discordant pairs: case exposed, control not exposed	No of discordant pairs: case not exposed, control exposed	Relative risk	95% Confidence interval
Any radiotherapy	20	31	0.7	0.4 to 1.2
Any chemotherapy	17	14	1.2	0.6 to 2.7
Surgery only	32	29	1.1	0.7 to 1.9
Radiotherapy to pelvis	8	13	0.6	0.2 to 1.6
Chemotherapy with an alkylating agent	11	10	1.1	0.4 to 2.9

TABLE IV—Numbers of case and control fathers with a previous cancer diagnosis and relative risks of specified congenital anomalies in the offspring

Anomaly group	No of discordant pairs: case cancer, control no cancer	No of discordant pairs: case no cancer, control cancer	Relative risk	95% Confidence interval
According to ICD 9 Code:				
Heart and circulatory system (ICD: 745-747)	19	13	1.5	0.7 to 3.2
Genital organs (ICD: 752)	7	15	0.5	0.2 to 1.2
Musculoskeletal deformities (ICD: 754)	11	13	0.9	0.3 to 2.1
Other anomalies of limbs and musculoskeletal anomalies (ICD: 755-756)	12	8	1.5	0.6 to 4.2
According to aetiology:				
Single gene disorder	6	3	2.0	0.4 to 12.4
Chromosome disorder	3	3	1.0	0.1 to 7.5
Multifactorial aetiology	29	27	1.1	0.6 to 1.9
Genetic, unknown aetiology	3	4	0.8	0.1 to 4.4
Unknown aetiology	20	28	0.7	0.4 to 1.3

No significant increase in risk was seen in the four ICD anomaly subgroups with the most cases (table II). Results for each subgroup were based on all case-control pairs for which the case's child had an anomaly within that subgroup. The relative risks of treatment with either radiotherapy or chemotherapy associated with anomalies of the heart and circulatory system and anomalies of the genital organs were 2.0 (0.4 to 18.0) and 4.0 (0.3 to 7.0) respectively.

Table II also shows the results of the analyses according to aetiological groupings of anomalies. The number of subjects in the group with single gene disorders was small and therefore, although the risk was increased, the confidence interval was wide. None of the subjects in this subgroup who had had cancer were treated with an alkylating agent or radiotherapy to the pelvis or abdomen.

FATHERS

Among the fathers, 61 cases and 65 controls were found to have had cancer (relative risk=0.9, 95% confidence interval 0.7 to 1.4). The most common cancers were Hodgkin's disease, testicular cancer, melanoma, and brain cancer. About half of the cases (32) and 29 of the controls had not received chemotherapy or radiotherapy for their cancers. The mean ages at diagnosis were 28.0 years for the cases and 25.4 years for the controls. The risk of a congenital anomaly among the offspring did not decrease with increasing age at diagnosis (relative risk=0.5, 1.0, and 1.2 for fathers under 20, 20-29 years, and over 29 years at the time of diagnosis). Not enough subjects were diagnosed and treated before the age of puberty (when the germ cells are inactive) to evaluate risk in this subgroup.

The risk associated with the various forms of cancer therapy and anomalies in the offspring did not differ significantly from unity (table III). There was no evidence that the risk of congenital anomalies among the offspring rises with increasing dose of alkylating agents, although the confidence intervals were wide (relative risk 1.2, 95% confidence interval 0.3 to 4.2 for those in the lower dose group and 1.0, 0.2 to 5.4 for those in the higher dose group). The risk did not increase with dose of cobalt-60 radiotherapy directed at the pelvis or abdomen. The relative risk was 0.8 (0.2 to 3.7) for those in the low dose group (≤ 25 Gy) and 0.6 (0.1 to 2.3) for those in the high dose group (> 25 Gy).

No significant increase in relative risk was seen for any of subgroups of anomalies (table IV). Although the increase in risk for those with a single gene disorder was not significant, three of the six case fathers who had had cancer in this subgroup had been treated with an alkylating agent or radiotherapy to the pelvis or abdomen, or both, whereas none of the three controls in this subgroup had received either of these therapies.

Discussion

Our results are consistent with the previous epidemiological studies designed to investigate the risk of congenital anomalies in children of cancer patients, most of which have found no association. While most of the previous studies have followed cohorts of cancer patients and observed their offspring, we used a case-control method and computerised record linkage. The validity of our results depends, in part, on the accuracy with which the record linkage identified cases and controls with a previous cancer diagnosis. Incorrect matches (false positives) or incorrect non-matches (false negatives) in either of the record linkages used in this study could potentially bias the results.

ASCERTAINMENT

Incorrect matches in the first linkage (identifying the

birth record corresponding to each anomaly record) are unlikely since links were verified with information available on the paper copy of the birth certificate. Likewise, because a birth certificate was found for 97% of the children in the anomaly database, the false negative rate should be low. A likely reason why birth certificates were not found for the remaining 3% is that the birth occurred outside Ontario but the child was admitted to hospital in Ontario during the first year of life. Since this group was not eligible for the study, these omissions would not result in bias.

It is more difficult to estimate the number of parents missed in the linkage between the case-control file and the Ontario cancer registry. The number of links among fathers agreed closely with that expected under the null hypothesis. However, slightly fewer mothers than expected were linked to the registry. Some true links for mothers may have been missed because of name changes between diagnosis of cancer and the birth of the child, resulting in them being wrongly classified as not having had cancer. Because identifying information on cases and controls was comparable and the linkage to the cancer registry was done without knowledge of case-control status any misclassification should have affected cases and controls equally. Although misclassification would drive the relative risk towards unity, it is unlikely that misclassification accounted for the lack of effect observed in this study. False positive links to the cancer registry are improbable because nearly all accepted links were confirmed through data found in medical records.

Parents who had cancer diagnosed while resident outside Ontario would not appear in the Ontario cancer registry and therefore would have been incorrectly classified, as not having had cancer. Cases and controls were matched for birth place to minimise the possibility of any such misclassification biasing the results. Among both mothers and fathers, the risks associated with previous cancer and anomalies in their offspring are similar in the subgroups of parents born in and outside of Ontario. Thus the relative risks for those born outside of Ontario seem unlikely to be biased because of case-control differences in the likelihood of linking to the cancer registry.

EFFECT OF CANCER TREATMENT

The treatments most likely to be mutagenic (and therefore to be associated with anomalies in the offspring) are radiotherapy directed at the pelvis and chemotherapy with an alkylating agent. Our results do not suggest that these therapies increase the risk of anomalies in the offspring of either the mothers or the fathers. While this may mean that cancer therapy does not increase the risk of having a child with a congenital anomaly, there are other possible explanations for the observed results.

Firstly, cancer patients who have received potentially mutagenic therapy may be more likely to undergo prenatal screening than those with no history of cancer and may therefore have a higher rate of therapeutic abortion, reducing the number of offspring with anomalies. This would, however, only affect the number of offspring with chromosomal anomalies, as prenatal diagnosis for other genetic disorders was not widely available during the study period. Secondly, the adverse effects of cancer therapy may manifest themselves earlier in the reproductive process—for example, as infertility among those treated most aggressively with potentially mutagenic therapy.¹⁴ Cancer patients who have liveborn offspring may therefore have received chemotherapy and radiotherapy at relatively low doses with diminished mutagenic potential.

The effect of cancer therapy on sporadic genetic disease has not been conclusively established. Single gene disorders are important indicators of possible

germ cell mutations, but occur very rarely.^{16 21} Several investigators have looked for increased rates of single gene disorders among the offspring of cancer survivors but have not noted any.^{7 11} The fact that three of the six case fathers and none of the three controls with a previous diagnosis of cancer in this subgroup had been treated with potentially mutagenic cancer therapies supports the possibility of a genetic effect. None of the cases or control mothers in this subgroup were treated with these therapies. These findings are somewhat difficult to interpret because of the small numbers of subjects in this anomaly subgroup. In addition, the grouping of anomalies by aetiology was based on the limited information in the anomaly database, namely the four digit ICD-9 codes for anomalies recorded through the first year of life. Since family histories were not known, some of the anomalies observed in the offspring may have been familial rather than the result of a new mutation. Although the anomalies were assigned to groups by one person who was blinded to parental exposure, the lack of detailed diagnostic and familial information may have resulted in some misclassification of both cases and controls. Given the rarity of single gene disorders and the likelihood that any increase in risk will not be large, many subjects will be needed to conclusively determine the risks associated with cancer therapy and these disorders.

Studies that have examined ICD subgroups of anomalies have not shown consistent associations with any particular subgroup. However, Green *et al*²² recently reported a possible association between women treated with dactinomycin and cardiac defects among their offspring. We found that relative risks for the subgroup of cardiac anomalies were moderately but not significantly increased in both the mothers and the fathers, although no association was found with dactinomycin.

CONFOUNDING

Studies that use data collected for other purposes are limited by the information available in the databases. In this study, confounder information comprised that available from birth certificates. We were therefore able to match (and control for) some potential indicators of socioeconomic status (parental age, marital status), although residual confounding with socioeconomic status may exist. Other potential confounders were not available on the birth certificate—for example, smoking, alcohol. Since most of the cases of cancer were diagnosed by early adulthood, it is not unlikely that these factors would be strongly related to the development of cancer. It seems reasonable to assume that few, if any, other factors would be strongly related to both congenital anomalies in the offspring and cancer in a parent. The known advantages of using existing data—that is, the ability to study large numbers of subjects at a relatively low cost—outweighed the possibility of a small amount of bias associated with the lack of information on potential confounding variables.

A recent study of occupational exposure to ionising radiation among fathers and leukaemia in their children suggested that the observed increased risk was due to a cell mutation which was leukaemogenic in the offspring.²³ The results also suggested that exposure during the six months before conception may be the most relevant. We found no evidence of increased risk among fathers treated with either radiotherapy or an alkylating agent within a year of conception, although the numbers were small. As many cancer patients are advised to wait a year after treatment before conceiving it may be difficult to analyse the risk of anomalies in the offspring among parents who are treated within a year of conception.²⁴

Our results should offer some reassurance to people who survive cancer. They suggest that, among live-

Clinical implications

- Young adults and children now commonly survive treatment for cancer and subsequently want to have a family
- Many fear that the toxic treatment they received for cancer will affect their children
- This study shows that the risk of having a child with congenital anomalies was not increased among parents who had been treated for cancer
- For live births there was no relation between increasing toxicity of treatment and congenital anomalies
- Cancer patients can be reassured that any liveborn offspring are unlikely to be affected by cancer treatment

born offspring, the probability of having a child with a congenital anomaly is not appreciably different for those who have had cancer or been treated for cancer from that for the general population.

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Factors affecting uptake of measles, mumps, and rubella immunisation

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Abstract

Objective—To study factors affecting uptake of measles, mumps, and rubella immunisation.

Design—Cohort study using data from computerised child health systems.

Setting—10 health districts in North East Thames and North West Thames regions.

Subjects—7841 children born in January to March 1990 and resident in the districts up till the end of October 1991.

Main outcome measures—Overall uptake of measles, mumps, and rubella immunisation, variation of uptake among groups of children, and odds ratio of being vaccinated against measles, mumps, and rubella.

Results—The overall uptake rate of measles, mumps, and rubella immunisation for the study cohort in the 10 districts was 82%. Wide variation was identified among children with different demographic characteristics. Lower uptake was associated with absent or incomplete primary immunisation, including omission of pertussis vaccine. Other factors affecting uptake included the type of resident district, birth order, where

registered for immunisation (general practitioner or clinic), and one parent family status.

Conclusions—Many districts have difficulties in meeting the 90% target for measles, mumps, and rubella immunisation, mainly because of the characteristics of their local population. To increase overall coverage, the health service should target families with adverse factors, especially those whose children have missed previous immunisations.

Introduction

In October 1988 the combined measles, mumps, and rubella vaccine replaced monocomponent measles vaccine in the routine childhood immunisation programme for the United Kingdom.¹ This change was partly to improve rubella coverage as well as to introduce protection against mumps into the schedule. The change was also hoped to improve uptake of measles immunisation, about which there had been widespread concern in Britain.²⁻⁵ Coverage with measles, mumps, and rubella vaccine has dramatically increased protection against measles in the country as a whole.⁶ The improved uptake of measles, mumps, and

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