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Original Paper

Adult Cancer Risks Among the Mothers of Children with Cancer

B. Gustafsson, J. Ludvigsson and J. Carstensen

We investigated cancer risk among mothers of 2365 children who were diagnosed with cancer between 1973 and 1989 in Sweden. From the date of birth of the child until 31 December 1989, 38 cases of cancer were diagnosed among the mothers. The expected number of cases, according to national rates, was 30.9. Cancer of the thyroid was the only site showing a significantly increased risk among the mothers (observed = 6, expected = 1.2, $P < 0.01$), but two cases were medullary cancer associated with an inheritable syndrome, and inherited by their children.

Key words: cancer, children–mothers–cluster, incidence, thyroid cancer
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INTRODUCTION

CURRENT THEORIES propose that a tumour suppressor gene is commonly damaged in human malignancies, and that this might be mediated by both exogenous and endogenous factors [1]. A sequence of genetic mutations leads to the formation of a cancer cell with the capacity for uncontrolled growth. Should one or more of the mutations be present at conception, or an individual be susceptible to an elevated rate of chromosome breakage, or lack an effective DNA repair mechanism, the risk of cancer is likely to be elevated. If such a trait is shared by several members of a pedigree, familial clustering may occur [2]. Only 3% of childhood cancers are known to be due to inherited genetic mutations. The most frequently recorded diagnosis is bilateral retinoblastoma [2].

From clinical experience, there is an impression that parents of children with cancer often have or develop a malignant disease close in time to the diagnosis of the child, but without any indication of inherited genetic cancer. This suggests that some exogenous factor influences the manifestation of malignancy in both the child and parent simultaneously.

With this background, we studied cancer incidence among biological mothers of children with cancer. We chose to study mothers since reliable information was available from the Swedish Medical Birth Registry, which is a standardised set of medical records introduced in Sweden since 1973.

PATIENTS AND METHODS

A total of 2474 cancer cases among children born between 1973 and 1989 were reported to the Swedish Cancer Registry up to 1989. The age limit for childhood is less than 18 years of age. Since there is compulsory registration of cancers in Sweden, practically all cases of malignancies during this period are included. Using the identification numbers of the children, the Swedish Medical Birth Registry was searched using the identification numbers of the biological mothers. 109 mothers were missing and a total of 2365 mother/child couples were available (the missing mothers probably delivered their children outside Sweden or were not Swedish citizens). Using the Swedish Cancer Registry, we determined whether they had been registered as mothers having a malignancy.

The number of years at risk for each mother was calculated from the birth of the child until 31 December 1989. The total number of mother years at risk was divided into groups, defined according to age at risk of the mother (5 year group) and the time interval from the date of diagnosis of the child. The age-adjusted expected numbers of cases of cancers of the mothers were computed by multiplying the numbers of years at risk with corresponding age-specific national rates. Levels of significance and confidence intervals were estimated on the assumption that the observed numbers of cancer cases had a Poisson distribution.

RESULTS

The number of children with different types of cancer are listed in Table 1. Among the 2365 children, 32% were reported as having leukaemia, 9% with lymphomas and 30% with a malignancy of the nervous system.

During the period from date of birth of the child to 31 December 1989, 40 cases of cancer were diagnosed among the mothers. The preliminary analysis showed a particularly increased incidence within 6 months before and after the diagnosis of the child. 8 cases were observed versus 2.3 expected ($P < 0.01$). A review of these files showed 2 cases of metastasis, and when the analysis was repeated excluding these 2 cases, there was no longer a statistically significant increase of tumours in this group.

In the following analysis, only the 38 cases are included. The

Correspondence to Dr B. Gustafsson at the Department of Paediatrics, Faculty of Health Sciences, University Hospital, S-581 85 Linköping, Sweden.
B. Gustafsson and J. Ludvigsson are at the Department of Paediatrics, Faculty of Health Sciences, University Hospital, Linköping; and J. Carstensen is at the Department of Oncology, Faculty of Health Sciences, University Hospital, Linköping and the Department of Health and Society, Linköping's University, Linköping, Sweden.
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Table 1. Classification of the different childhood cancers

Category	No. of cases	(%)
Leukaemias	750	32
Acute lymphocytic	601	
Acute non-lymphocytic	79	
Chronic myeloid leukaemia	8	
Other specified leukaemia	8	
Undifferentiated and unspecified leukaemia	54	
Lymphomas and other reticulo-endothelial neoplasms	213	9
Hodgkin's disease	46	
Non-Hodgkin's disease	110	
Histiocytosis X	57	
Brain and nervous system	708	30
Sympathetic nervous system	52	2
Neuroblastoma	52	
Retinoblastoma	83	4
Renal tumours	180	8
Wilms' tumour	178	
Kidney, unspecified	2	
Hepatic tumours	31	1
Malignant bone tumour	62	3
Soft tissue sarcomas	118	5
Germ-cell, trophoblastic and other gonadal neoplasms	48	2
Carcinoma and other malignant epithelial neoplasms	60	3
Others	60	3
Total	2365	

Table 2. Number of cancer cases among the mothers of 2365 children with a cancer diagnosed between 1973 and 1989 in Sweden

	Observed No. of cancers	Expected No. of cancers	Ratio of obs./exp.	(95% confidence limits)
Total	38	30.92	1.23	(0.87–1.69)
Mother's diagnosis before the child's				
>5 years	3	2.92	1.03	(0.21–3.00)
2–5 years	6	3.53	1.70	(0.63–3.70)
0–2 years	8	4.05	1.98	(0.85–3.89)
Mother's diagnosis after the child's				
0–2 years	3	4.74	0.63	(0.13–1.85)
2–5 years	8	5.94	1.35	(0.58–2.65)
>5 years	10	9.74	1.03	(0.49–1.89)
Diagnosis				
Breast	9	9.79	0.92	(0.42–1.75)
Cervical carcinoma	3	4.14	0.73	(0.15–2.12)
Ovarian carcinoma	4	2.22	1.81	(0.49–4.62)
Melanoma	3	2.29	1.31	(0.27–3.83)
Nervous system	4	1.90	2.11	(0.57–5.40)
Thyroid	6	1.24	4.82*	(1.77–10.5)
Other	9	9.34	0.96	(0.44–1.82)

*$P < 0.01$; obs., observed; exp., expected.

expected number of cases, according to national rates, was 30.92 (Table 2). There was a slight increase of cancers among mothers before the child's diagnosis. 25 cases (before or after) were observed within 5 years from the child's diagnosis. The expected number of cases in this group was 18.3. Cancer of the thyroid was the only diagnosis showing a significantly increased risk among the mothers (Table 2).

Review of cases of thyroid tumours among the mothers

The different thyroid tumours mother/child couples are detailed in Table 3. We collected their personal records and histological data from the clinics in which they were treated. All patients underwent some form of thyroid surgery and the diagnosis was based upon histological diagnosis. 2 of these cases were medullar cancer, inherited by their children. The children developed their cancers within 5 and 3 years after their mothers' diagnosis.

Patient 1 (Table 3) was reported as having medullar thyroid carcinoma at the age of 44. Fifty-six months later her child, a girl, was diagnosed as having a medullar thyroid carcinoma at the age of 13. From personal data, we learned that the mother belonged to a family in the southern part of Sweden who had the genetically inheritable Sipple Syndrome, inherited from her father. This disease is associated with pheochromocytoma, medullar thyroid carcinoma and, in approximately half of the reported cases, parathyroid hyperplasia [3]. Clinical manifestations of the disease occurred first when the mother was 34 years of age when she underwent the removal of the right adrenal cortex. The child had two older half siblings, of whom one was reported as having medullar cancer as part of Sipple Syndrome.

Patient 2 was reported as having medullar thyroid carcinoma 29 months before the child had the same diagnosis, medullar thyroid carcinoma. She was 33 years old when her disease was discovered, and she was also born in a family with Sipple Syndrome. She underwent surgery for medullar thyroid cancer and pheochromocytoma. Her father and her sister also had Sipple Syndrome. Her child was 10 years old at diagnosis. This family also came from the same region of Sweden. If these two cases were excluded, the increase in the incidence of thyroid cancer was no longer statistically significant ($P < 0.05$).

DISCUSSION

Because clinically, parents and their children are sometimes coincidentally diagnosed with cancer, we decided to examine whether the biological mothers of children with cancer, themselves develop cancer more often than expected, and whether this occurs closely in time to the diagnosis of the child.

The Swedish Medical Birth Registry contains information on nearly all infants born in Sweden since 1973 and who are identified by their unique personal identification number, which makes record linkage possible [4]. This investigation includes practically all known cases of childhood malignancies in Sweden during the years 1973–1989. Sweden is a country with a well-developed health and welfare service with a registry of all

Table 3. The group of mothers with thyroid cancer

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Type of cancer	Medullar t.c.	Medullar t.c.	Papillary t.c.	Papillary t.c.	Papillary t.c.	Papillary t.c.
Age at diagnosis	44	33	43	31	29	28
Treatment	Total thyroidectomy	Total thyroidectomy	Hemi-thyroidectomy	Total thyroidectomy	Hemi-thyroidectomy	Total thyroidectomy
Earlier MEN-symptoms	10 years earlier surgery for pheochromocytoma	Bilateral adrenalectomy just before surgery for t.c.				
No. of children at diagnosis	3	1	2	1	1	1
Time of diagnosis	56 months before child's	29 months before child's	160 months after child's	4 months after child's	53 months before child's	34 months before child's
Diagnosis of the child	Medullar t.c.	Medullar t.c.	Acute lymphoblastic leukaemia	Wilms' tumour	Astrocytoma	Astrocytoma
Child's age at diagnosis	13	10	3	4	6	7

t.c., thyroid carcinoma; MEN, type 11a, multiple endocrine neoplasia. MEN is associated with adrenal medullary hyperplasia or pheochromocytoma and parathyroid hyperplasia [8].

cancers. Since 1958, the Swedish Cancer Registry requires compulsory reporting of all newly diagnosed malignant tumours among Swedish residents from the physicians and from the pathologist [5]. Both these Registries are well documented and provide accurate and reliable information.

In our preliminary analysis, there was a statistically significant clustering of cancers in mother and child at 6 months before and after the diagnosis of the child, but after exclusion of two inappropriate cases, there was no significant increased incidence of cancers during this period.

There were no site-specific increased cancer risks among the mothers, except for thyroid cancer. Earlier studies have shown that women with infertility may experience an excess of thyroid cancer [6]. However, later studies lend support to another hypothesis that an increasing number of children could be a risk factor [7], which may be the case in our study. Occurrence of cancer in the same family, such as mother and child, could of course have a genetic inherited aetiology. This is certainly true for the two cases of medullar thyroid cancers that we observed in both mothers and children. Carcinoma of the thyroid accounts for approximately 10% of thyroid malignancies. The tumour can occur sporadically, but also as an autosomal dominant syndrome [8].

The childhood cancer studied most extensively for evidence of space–time clustering is leukaemia, and recently significant clustering has been found [9]. The established factors for childhood leukaemia include exposure to moderate and high doses of ionising radiation, *in utero* X-ray and chemotherapeutic agents [10]. Other risk factors that have been discussed include maternal smoking [11, 12] and parental exposure to radiation before conception [13]. A viral aetiology has been suggested [11, 14]. In our study, we did not find an increased incidence of leukaemia among mothers of leukaemic children. Our findings do not negate the viral hypothesis since the latent period could be long and variable. A common environmental agent may also affect the mother and child differently.

In summary, the present analyses revealed no general association between childhood cancer and cancer risks among mothers. We did not find any specific tumour group that had an increased incidence in the mothers, with the exception of thyroid cancer.

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