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Original Paper

Multiple Primary Neoplasms in Childhood: Data from the German Children's Cancer Registry

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The German Children's Cancer Registry (GCCR) has documented all malignancies during the first 15 years of life in Germany since 1980. In a series of 20 388 cancer cases to the end of 1995, 127 children with multiple primary neoplasms up to the age of 15 years were identified. The children were monitored for 82 591 person-years with a mean observation time of 4.1 years. Relative and cumulative risk for the occurrence of second malignant neoplasms were estimated only for the first 15 years of life, as follow-up data beyond childhood are incomplete and valid data on the incidence of cancer in adolescents and adults are not available in Germany. The overall standardised incidence ratio for a second malignancy was 12.5 (95% CI: 10.4–14.9) which implies an absolute excess risk of 141.5 per 10^5. The estimated cumulative risk within 10 years after the first malignancy was 1.9% (95% CI: 1.5–2.3). It is expected that the risk will alter with prolongation of follow-up beyond childhood. © **1998 Elsevier Science Ltd. All rights reserved.**

Key words: multiple primary neoplasms, second primary neoplasms, childhood, cancer registry, cancer incidence, risk estimate
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INTRODUCTION

ACCORDING TO the most recent annual report of the German Children's Cancer Registry (GCCR), the incidence of cancer in children under the age of 15 years is 13.4 per 100 000 [1]. Except for the first years since the inception of this nationwide registry in 1980, it is estimated that 95% of all incident cases are reported, and the incidence rates have not changed substantially [2]. The survival rate at 5 years after diagnosis has risen continuously during the past two decades to approximately 75% due to improvements in diagnosis and treatment.

With increasing numbers of long-term survivors, the study of potential sequelae of cancer in childhood, especially late therapy effects, is of increasing importance (for an overview see [3–5]). One of the most serious and harmful events following childhood cancer is the occurrence of a second malignant neoplasm. It is well known that cancer survivors have an excess risk of developing a second malignancy, either because of an increased genetic susceptibility to multiple neoplasms or an immunosuppressive or carcinogenic effect of therapy.

Several studies have analysed the relative risk and the incidence of second malignancies leading to differing estimates of the size of the risk. Two of the largest population-based studies are those by Olsen and associates [6] who analysed the data of the cancer registries in the Nordic countries, and by Hawkins and associates [7], who described the data of the National Cancer Registration of the United Kingdom. In addition, there are studies based on registries of multicentre trials investigating late effects of therapy, such as the Italian Off-Therapy-Registry (IOTR) [8] or the registry of the Late Effects Study Group (LESG) [9]. Finally, there are a large number of studies concerned with specific first malignancies after which an increased risk of developing a second neoplasm is well known, for example, children with Hodgkin's disease [10–13] or retinoblastoma [14, 15].

Relative risk estimates, usually given by standardised incidence ratios (SIR), vary from 3.6 (Nordic Countries), over 5.8 (United Kingdom) and 10.8 (IOTR) to 15 (LESG). Since cancer in childhood is a rare event, most of the studies on second malignancies cover a long period and therefore

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usually include children diagnosed at a time in which crucial improvements in therapy had not yet been achieved. The current lack of up-to-date information necessitates further studies on the occurrence of second malignancies to give estimates for survivors of modern therapy. Risk estimates derived from population-based registries, such as the GCCR, are of special importance since, in contrast to estimates based on multicentre trials, they are less prone to various forms of bias.

In this paper, we present data on multiple primary neoplasms which have been registered by the GCCR from 1980 to the end of 1995. The main goal of our analyses is the estimation of relative and cumulative risk of developing a second malignancy by the age of 15 years. Data concerning effects of therapy schemes on the occurrence of second malignant neoplasms are not presented. However, this topic is the subject of future work.

PATIENTS AND METHODS

Since its inception in 1980 to the end of 1995, the GCCR has documented 20 388 cases of first malignant neoplasms in children less than 15 years of age resident in Germany. Data from the new federal states (Neue Bundesländer) have been included since 1991. Nearly all incident cases are reported to the registry by paediatric hospitals and centres for paediatric oncology. Although notification is voluntary, completeness of the registry has risen from an estimated 80% in the first 5 years to 95% thereafter.

Multiple malignant neoplasms are documented within the framework of the usual registration process, in close adherance to the guidelines of the IARC [16]. 90% of all children known to the registry are participants of clinical trials, for which a central review of pathological material is carried out. Altogether, approximately 99% of the recorded malignancies are verified either histologically (solid tumours) or by immunocytology (haematological malignancies).

Additionally, multiple malignancies are recognised by the long-term follow-up of the registered children. All hospitals reporting cancer cases are requested to inform the registry about the health status of the children at subsequent clinical examinations. The long-term follow-up is accomplished regardless of age, i.e. further malignant neoplasms diagnosed after the age of 15 years are also documented. However, the ascertainment of second neoplasms in older patients is incomplete, since their treatment is partly carried out in hospitals for adults which do not notify the GCCR. Thus, systematic case ascertainment beyond childhood is not guaranteed.

In 1992, in a comprehensive action, all notifying hospitals and oncological centres were explicitly asked for all known cases of multiple malignancies. It was again stressed that multiple malignancies should be notified to the registry. The data of this inquiry were linked with the cases already documented. Since then, the registry has strengthened its efforts to improve the notification of multiple malignancies. Furthermore, a study group of experienced oncologists was established by the Society for Paediatric Oncology and Haematology (GPOH) to support the GCCR in reviewing questionable diagnoses. Since 90% of all children known to the registry are participants of clinical trials, the notification of second malignancies, including haematological malignancies, is now expected to be as complete as the notification of first malignancies.

In 1995, the registry comprised 329 cases of multiple malignant neoplasms. A comprehensive description and analysis of these cases is given in Kaatsch and Michaelis [17]. In a substantial number, the first cancer was diagnosed before 1980. As notification of cancers diagnosed before the inception of the registry has been rather arbitrary and incidence rates are not available, these cases were excluded from the present study. Furthermore, we restricted our analysis to the first 15 years of life, because follow-up data beyond childhood are incomplete.

For the following statistical analyses we shall regard the registry population of 20 388 documented cases at the end of 1995 as a cohort at risk of developing a second malignancy. Children with multiple primary neoplasms were identified irrespective of the time lag between the cancers. The sequence of the neoplasms was based on the date of diagnosis. The observation period starts with the diagnosis date of the first malignancy. For children with confirmed second malignancies ($n = 127$) or death ($n = 3793$), the study endpoint was the date of diagnosis or death, respectively. However, the situation is not that clear-cut for children currently under follow-up ($n = 15\,920$) and those who are lost to follow-up ($n = 548$). As the registry contains approximately 95% of all incident cases, we decided to consider that children of the latter two groups will, in all likelihood, be reported in case of further malignancies before the age of 15 years. Neglecting the number of children lost to follow-up who have moved to other countries or have died before the age of 15 years, we regard all children of the registry population to be continuously observed up to the age of 15 years. According to this approach, all children with first malignancies contributed 82 591 person-years at risk with a mean observation time of 4.1 years.

Relative risk estimates for second malignancies are given by SIRs, i.e. the ratio of observed and expected numbers of second malignancies. The latter denotes the number of second malignancies which would have been expected if the incidence rate of childhood cancer in the general population had prevailed. Expected numbers of second malignancies were estimated by applying age/sex specific rates derived from the registry statistics between 1991 and 1995 to each observed patient-year. The absolute excess risk which denotes the difference in risks of developing a malignancy for children with and without first malignancies was calculated using these expected numbers. Confidence limits for the SIR were calculated under the assumption that the number of second malignant neoplasms is distributed according to the Poisson distribution [18]. The Kaplan–Meier method and Greenwood's formula [19] were used to compute cumulative risk estimates and corresponding confidence limits.

RESULTS

A total of 127 second malignancies were observed in the registry population consisting of 20 388 cases of first malignancies in children less than 15 years of age. In 7 children the time between the detection of both neoplasms was less than 1 month. An underlying diagnosis of the first and second malignancies in two of these cases was neurofibromatosis, in two other cases a genetic disorder was suspected. In two cases, three malignant neoplasms were diagnosed within the observation period.

Table 1 shows the distribution of these 127 second malignancies by the type of first malignancy classified by the

Table 1. *Observed number of second malignancies before the age of* 15 *years by first malignancy*

	Second malignancy												
First malignancy	Leukaemia	Lymphoma	CNS	Sympathetic nervous system	Retinoblastoma	Kidney tumour	Hepatic tumour	Bone tumour	Soft tissue tumour	Germ cell tumour	Carcinoma	Other	Total *n* (%)
Leukaemia	13	9	16	0	1	1	0	0	1	0	5	1	47 (37)
Lymphoma	7	2	0	0	0	1	0	0	0	1	0	1	12 (9)
CNS tumour	4	0	12	3	0	0	0	0	6	0	1	0	26 (20)
Sympathetic nervous system	6	1	1	0	0	0	0	0	1	0	0	0	9 (7)
Retinoblastoma	1	0	0	0	0	0	0	2	0	0	0	1	4 (3)
Kidney tumour	0	0	3	1	0	0	0	0	1	0	0	0	5 (4)
Hepatic tumour	1	0	0	0	0	0	0	0	0	0	0	0	1 (1)
Bone tumour	2	1	1	0	0	0	0	0	0	0	0	0	4 (3)
Soft tissue tumour	6	1	2	0	1	0	0	2	1	0	0	0	13 (10)
Germ cell tumour	1	0	0	1	0	0	0	0	1	0	0	0	3 (2)
Carcinoma	0	0	0	0	0	0	0	0	0	0	0	0	0 (0)
Other	1	0	0	0	0	1	0	0	1	0	0	0	3 (2)
Total (*n*)	42	14	35	5	2	3	0	4	12	1	6	3	127
%	33	11	28	4	2	2	0	3	9	1	5	2	

scheme of Birch and Marsden [21]. The most frequent second cancers were, in decreasing order, leukaemias (33%), CNS tumours (28%), lymphomas (11%) and soft tissue tumours (9%). Except for the latter diagnosis, this ranking corresponds to that of first malignancies in the registry population [2]. However, the frequency distribution of leukaemia subtypes was different, i.e. the proportion of acute non-lymphoblastic leukaemias was 71% of all second leukaemias and only 14% of all first leukaemias. Likewise, the ranking of first malignancies after which the most second malignancies occurred is similar to the ranking of first malignancies in the registry population. The most frequent combinations of malignancies are CNS tumours after leukaemias, leukaemias after leukaemias, CNS tumours after CNS tumours, and lymphomas after leukaemias.

The distribution of the time intervals between both malignancies is depicted in Table 2. With prolongation of the observation period beyond the age of 15 years, these figures are likely to alter. In particular, the proportion of solid tumours which are associated with longer latency periods is expected to increase.

In Table 3, observed and expected numbers of specific types and the total of second malignancies are shown together with the SIR and corresponding 95% confidence limits. The overall SIR for a second malignancy was 12.5 (95% CI: 10.4–14.9) i.e. the risk of a child with cancer developing a second malignancy before the age of 15 years is estimated to be approximately 12-fold that of a child in the general population. The SIR of 12.5 together with the incidence of first malignancies of 13.4 implies an absolute excess risk of 141.5

Table 2. Observation time between first and second malignancies occurring before the age of 15 *years*

		Time in years since first malignancy				
Second malignancy	Number	Min	25th percentile	Median	75th percentile	Max
Leukaemias	42	0.0	1.6	2.6	4.6	8.5
Lymphomas	14	0.6	2.7	3.7	5.3	7.7
CNS tumours	35	0.0	3.3	6.1	8.0	12.4
Sympathetic nervous system	5	0.0	0.5	0.6	4.2	8.4
Retinoblastoma	2	0.8	–	1.1	–	1.4
Kidney tumours	3	0.0	–	0.2	–	1.6
Hepatic tumours	0	–	–	–	–	–
Bone tumours	4	3.8	5.7	8.7	9.8	9.9
Soft tissue tumours	12	0.0	0.1	3.0	5.1	9.4
Germ cell tumours	1	–	–	2.8	–	–
Carcinomas	6	2.2	6.6	7.3	8.2	8.5
Other	3	1.0	–	1.5	–	1.8
All malignancies	127	0.0	1.6	3.8	6.3	12.4

Table 3. Observed and expected second malignancies which occurred before the age of 15 *years with corresponding SIR and absolute excess risk per* 10^5 *based on* 85 591 *person-years at risk*

Second malignancy	Observed	Expected	SIR (95% confidence interval)	Absolute excess risk per 10^5
Leukaemias	42	3.6	11.8 (8.5–15.9)	46.5
Acute lymphoblastic	10	3.0	3.3 (1.6–6.1)	8.4
Acute non-lymphoblastic	30	0.5	62.7 (42.3–89.5)	35.7
Lymphomas	14	1.6	8.8 (4.8–14.7)	15.0
Hodgkin's disease	6	0.6	9.7 (3.6–21.1)	6.5
Non-Hodgkin's lymphoma	6	0.9	6.8 (2.5–14.9)	6.2
CNS tumours	35	1.9	18.4 (12.8–25.6)	40.1
Sympathetic nervous system	5	0.5	9.7 (3.1–22.6)	5.4
Neuroblastoma	3	0.5	6.6 (1.4–19.4)	3.1
Retinoblastoma	2	0.1	13.6 (1.6–49.1)	2.2
Kidney tumours	3	0.6	5.3 (1.1–15.6)	3.0
Nephroblastoma	3	0.5	5.5 (1.1–16.2)	3.0
Hepatic tumours	0	0.1	–	–
Bone tumours	4	0.6	7.0 (1.9–17.9)	4.2
Osteosarcoma	4	0.3	12.9 (3.5–33.1)	4.5
Ewing's sarcoma	0	0.2	–	–
Soft tissue tumours	12	0.7	18.3 (9.5–32.0)	13.7
Rhabdomyosarcomas	3	0.4	7.6 (1.6–22.2)	3.2
Germ cell tumours	1	0.4	2.8 (0.1–15.6)	0.8
Carcinomas	6	0.1	57.3 (21.0–124.8)	7.1
Other	3	< 0.1	93.1 (19.2–272.0)	3.6
All malignancies	127	10.1	12.5 (10.4–14.9)	141.5

per 10^5. Except for germ cell tumours, the SIRs for specific cancers were significantly increased. The SIRs were exceedingly high in acute non-lymphoblastic leukaemias (62.7) and carcinomas (57.3). Additionally, CNS tumours (18.4) and soft tissue tumours (18.3) had increased incidence ratios.

The impact of the type of first malignancy on the occurrence of second malignancies is displayed in Table 4. Because of the small number of specific second malignancies, the calculation of SIRs was based on all types together. Rhabdomyosarcoma as first cancer yielded the highest SIR of 24.4, followed by Ewing's sarcoma (18.4) and CNS tumours (18.3).

To investigate whether SIRs were constant in time after diagnosis of the first malignancy, we calculated SIRs for different time periods thereafter (Table 5). SIRs steadily increased up to 10 years after diagnosis. The following decrease may be due to the small number of person-years at risk.

Figure 1 shows the estimated cumulative risk of developing a second malignancy. The cumulative risk within 10 years after diagnosis of the first malignancy was estimated to be 1.9% (95% CI: 1.5–2.3).

DISCUSSION

To date, the GCCR has documented childhood malignancies for approximately 16 years. The level of cancer ascertainment up to the age of 15 years is nearly complete. In contrast to other studies on second malignancies, this analysis comprises mainly children who underwent modern therapy

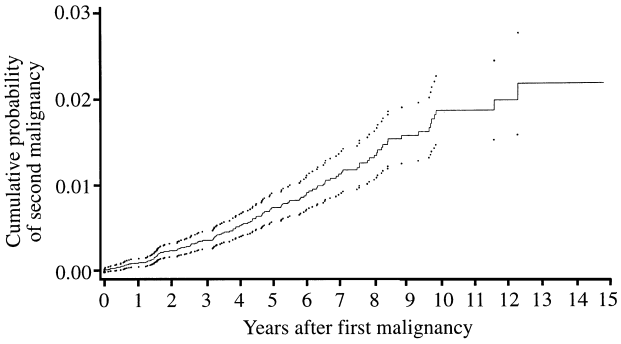

Figure 1. Kaplan–Meier cumulative risk estimates of developing a second malignancy before the age of 15 years with corresponding pointwise 95% confidence intervals.

Table 4. *Observed and expected second malignancies which occurred before the age of* 15 *years with corresponding SIR and absolute excess risk per* 10^5 *for different types of first malignancy*

First malignancy	Person-years	Observed	Expected	SIR (95% confidence interval)	Absolute excess risk per 10^5
Leukaemia	31520	47	3.8	12.5 (9.2–16.6)	137.2
Acute lymphoblastic	27930	42	3.3	12.7 (9.2–17.2)	138.5
Acute non-lymphoblastic	3005	4	0.4	10.6 (2.9–27.1)	120.6
Lymphoma	8045	12	0.9	13.6 (7.0–23.7)	138.2
Hodgkin's disease	2988	4	0.3	12.5 (3.4–32.0)	123.2
Non-Hodgkin's lymphoma	4856	6	0.5	11.1 (4.1–24.1)	112.4
CNS tumour	12046	26	1.4	18.3 (12.0–26.8)	204.1
Sympathetic nervous system	6954	9	1.0	8.9 (4.1–17.0)	115.0
Neuroblastoma	6521	8	1.0	8.4 (3.6–16.5)	108.0
Retinoblastoma	3186	4	0.4	8.9 (2.4–22.8)	111.5
Kidney tumour	7502	5	1.0	5.2 (1.7–12.2)	53.9
Nephroblastoma	7162	4	0.9	4.4 (1.2–11.3)	43.2
Hepatic tumour	789	1	0.1	8.6 (0.2–47.8)	111.9
Bone tumour	2715	4	0.3	14.3 (3.9–36.6)	137.0
Osteosarcoma	1365	1	0.1	7.2 (0.2–40.2)	63.1
Ewing's sarcoma	1051	2	0.1	18.4 (2.2–66.6)	180.0
Soft tissue tumour	5232	13	0.6	20.0 (10.7–34.3)	236.1
Rhabdomyosarcoma	3337	10	0.4	24.4 (11.7–44.8)	287.4
Germ cell tumour	3792	3	0.5	5.8 (1.2–16.9)	65.4
Carcinoma	495	0	0.1	–	–
Other	315	3	< 0.1	75.4 (15.5–220.3)	940.6
All malignancies	82591	127	10.1	12.5 (10.4–14.9)	141.5

Table 5. *Observed and expected second malignancies which occurred before the age of* 15 *years with corresponding SIR and* 95% *confidence limits for varying time periods after diagnosis of the first malignancy*

Time period in years after first malignancy	Person-years	Observed	Expected	SIR (95% confidence interval)
[0–2]	31993	41	4.5	9.1 (6.5–12.3)
[2–4]	20405	27	2.5	10.7 (7.0–15.5)
[4–6]	13233	23	1.4	16.2 (10.3–24.3)
[6–8]	8570	20	0.8	23.9 (14.6–36.9)
[8–10]	5180	14	0.5	28.0 (15.3–47.0)
[10–12]	2507	1	0.3	4.0 (0.1–22.3)
[12–15]	704	1	0.1	13.7 (0.3–76.4)
0–15	82591	127	10.1	12.5 (10.4–14.9)

schemes. This fact may in part account for the striking differences between our risk estimates (overall SIR 12.5) and that of the Nordic countries (3.6) and the United Kingdom (5.8). The observation period of the latter studies comprises a time span of approximately 40 years and dates back to the early 1940s, i.e. a time when the chance of cure was very poor. Therefore, most of the children might not have been at risk of developing a second malignancy because of their short survival time. Children who, in spite of lacking therapy modalities, became long-term survivors are selected and might have a lower risk of developing a second malignancy. Moreover, former therapies were generally less aggressive, and a lack of potent chemotherapeutic agents lessened the carcinogenic hazard.

Furthermore, the data allow only risk estimation up to the age of 15 years, as follow-up data of older patients are less complete and were excluded from analysis. Cancers with a long latency period, especially some solid tumours such as bone, thyroid or breast cancer, might not become apparent before the age of 15 years [21]. Therefore, it is suspected that the frequency order of specific first and second malignancies will alter with prolongation of follow-up. Additionally, the observation period varied between specific cancer types, with longer time periods for cancers with frequency peaks early in childhood, such as leukaemias and embryonal tumours, and shorter time periods for cancers with peaks in late childhood and early adolescence, such as bone tumours or Hodgkin's disease. Thus, the contribution of specific cancer types to the risk estimation is different, and the risk estimates might be biased.

Comparison of different studies is made difficult because of different inclusion criteria for cases. Beginning observation one or more years after the initial diagnosis [7, 9] excludes those cases whose second malignancy developed shortly after the first one. In our study, all children with multiple primary neoplasms were included, irrespective of the time lag between the cancers. 20 (16%) of the second cancers occurred within the first year after the initial diagnosis. As shown in Table 5, the relative risk of developing a second neoplasm increased with time after diagnosis of the first malignancy. Thus, excluding the first follow-up year from the analysis increases the overall SIR from 12.5 to 14.2.

With regard to short time intervals between both malignancies, it cannot be ruled out that their natural development differed from the order of the diagnosis. This means that the right sequence could not be determined in each case. The question is whether early cases of second malignancies in which a genetic predisposition to multiple cancers may play a major causative role should be neglected in statistics and the starting point of observation redefined. However, the choice of a new starting point would be rather arbitrary because we do not know exactly the shortest duration of latency for specific cancer types. This aspect has to be taken into consideration when studying the relationship between primary therapy and subsequent cancers.

To estimate the relative risk of developing second malignant neoplasms, we regarded the registry population as a cohort which has been observed since the inception of the registry. Children lost to follow-up (4.1%) were considered as if they were observed until the age of 15 years, but at most to the end of 1995. Since some of these children might have moved to other countries or have died before the age of 15 years, the number of person-years at risk might be overstated which in turn leads to biased relative risk estimates. Alternatively, we could consider children to be at risk of developing a second malignant neoplasm only before they were lost to follow-up. However, since we feel that children lost to follow-up will, in all likelihood, be reported to the registry in case of a second malignant neoplasm, this also would result in biased relative risk estimates. Either way, comparing the results of both approaches, we found only minor differences with regard to the relative risk estimates.

Cancer registries are being established in the 16 federal states of Germany, so that incidence rates for adolescents and adults as well as information on second malignancies beyond childhood will be available in the future. Simultaneously, the GCCR continues its efforts at completing the follow-up data of registered patients beyond childhood. 90% of all children known to the registry are participants of clinical trials where therapy information is recorded in detail. This information will be used in a planned nested case–control study of second malignant neoplasms with regard to potential therapeutic risk factors. Therefore, this paper may be regarded as an interim report on the current data on multiple primary neoplasms in the GCCR.

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