RESEARCH COMMUNICATION

Incidence and Survival of Childhood Cancer Cases Diagnosed between 1998 and 2000 in Hiroshima City, Japan

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Abstract

There have been few studies on cancer incidence and survival among children in Japan. Childhood cancer cases in Hiroshima City can be ascertained almost perfectly in terms of completeness and validity as both a population-based cancer registry and a tissue registry cover the whole area. We report here recent incidence and survival of childhood cancer in Hiroshima City. Subjects were cancer patients less than 15 years of age in Hiroshima City registered in the Hiroshima City Cancer Registry and/or the Hiroshima Prefecture Tumor Registry (tissue registry) between 1998 and 2000. Cancer incidence in Hiroshima City was calculated for 12 diagnostic groups according to the International Classification of Childhood Cancer, and compared with general incidence in Japan. Five-year survival was calculated by the Kaplan-Meier method. There were 63 children who had a cancer newly diagnosed during 1998-2000, with only one death-certificate-only case (1.6%). Age-standardized incidence rates (per million) was 144.3 for boys and 93.9 for girls. Leukemia was the most frequent (29%) among the 12 diagnostic groups. There were 13 cancer deaths during this period and five-year survival was 79% (95% Confidence Interval: 67%-87%). Childhood cancer incidence was slightly higher than that for all of Japan, but the relative distribution of patients by diagnostic group was compatible with the general pattern. Both of these observations might be due to the high quality of the tumor and tissue registries.

Key Words: Childhood cancer - cancer registry - incidence - mortality - survival

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Introduction

The cancer registries in Hiroshima, which are the Hiroshima City Cancer Registry (HCPR) and the Hiroshima Prefecture Tumor Registry (HPTR), have been carried out by local governments and local medical associations and supported by the Radiation Effects Research Foundation (RERF). Epidemiological studies have been conducted using the cancer registry data to estimate cancer incidence and to examine several risk factors (Preston et al., 2007; 2008). Thus, it is important to know the background information of the cancer incidence and to continue to evaluate the quality of the cancer registry.

Cancer incidence in Hiroshima City is reported annually as part of the routine work of a cancer registry and has been published (Tumor Statistics Committee of Hiroshima City Medical Association, Curado et al., 2007). Cancer incidence rates (1996-2000) were relatively higher than that of other cancer registries in Japan, probably because the proportion of DCO (death-certificate-only) cases is low (3.1%) and the proportion of MV (microscopically verified) is high (84.5%) (Curado et al., 2007). Such good quality of data resulted from having both a population-based cancer registry and tissue registry which cover the whole area.

In spite of the recent high incidence rate of all ages, the childhood cancer incidence rate in Hiroshima City (1980-1989) was relatively at the same level as those among Japan (incidence rates; Hiroshima 117.1, vs. Osaka 133.4, Kanagawa 94.8, Miyagi 121.8, and Nagasaki 130.0) (Parkin et al., 1998). However, it has not been reported based on more recent data.

In this study, we describe the incidence, mortality, patterns of initial treatment, and survival among childhood cancer patients in Hiroshima City who were diagnosed in more recent years (during 1998-2000), compare the results with those in Japan and other countries, and examine various circumstances related to the childhood cancer patients.

Materials and Methods

Study area

Hiroshima City, the capital of Hiroshima Prefecture, is located in the western part of Japan and covers an area

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of 740 km^2. As is widely known, an atomic bomb was dropped on Hiroshima City in 1945. After the war, Hiroshima City has been developed as an administrative and industrial center in the Chugoku and Shikoku areas. The population in 2000 was 1.12 million, with an age distribution of 15.4% 0-14 years old, 70.3% 15-64 years old, and 14.2% 65 or more years old (Statistics Bureau et al., 2001).

Case ascertainment

The Hiroshima City Cancer Registry (HCCR), established in 1957, has adopted an active method to obtain cancer data: namely, the registry staff goes out to 16 major general hospitals around Hiroshima City to abstract cancer information from the medical charts (Nishi et al. 2008). The staff check all of the medical charts in the hospitals and, for subjects found to be diagnosed with cancer, abstract information on the details and history of the patient's cancer, motivation for the first physician visit, and initial treatment.

The Hiroshima Prefecture Tumor Registry (HPTR), initiated in 1973, collects tumor tissues on prepared slides, including both benign and malignant tissue, as well as pathology reports. The pathologists of the registry working committee summarize and code those data, based on the pathology report and the tissue slides, using the International Classification of Disease for Oncology 3rd revision (ICD-O-3) (WHO 2000). Diagnoses based on both the tissue slide and the pathology report enhances the quantitative and qualitative caliber of the cancer registry. Moreover, the HPTR has had legal authority to obtain death certificates since 1998. We used HCCR, HPTR, and death certificate data, so that we could ascertain the entire course of cancer from the first physician visit to diagnosis, treatment, and ultimate prognosis in terms of survival.

The number of study subjects was 63 cases who were living in Hiroshima City and who were diagnosed as having a first primary cancer between 1998 and 2000 at ages of 0-14 years. Only one case (1.6% of diagnoses) was identified through death-certificate-only (DCO).

Classification of Childhood Cancer

Childhood cancer needs a special classification system other than ICD-O (Ajiki et al., 2004). We adopted the International Classification of Childhood Cancer 3rd revision (ICCC-3) (Steliarova-Foucher et al. 2005) to assign incident childhood cancer cases to 12 diagnostic groups, based on the Main Classification table of SEER (Surveillance Epidemiology and End Results) Data Reporting tools (Surveillance Epidemiology and End Results).

Analyses

We calculated the age-standardized cancer incidence rate per million (standard population: the Japanese standard population in 1985) (ASR) among children aged 0-14 in Hiroshima City and examined the distribution of patients according to 12 diagnostic groups. The proportions of patients who underwent surgery, radiotherapy, and/or chemotherapy were also calculated according to the same diagnostic groups.

The HPTR has obtained the underlying cause of death among people who died and whose address was in Hiroshima Prefecture since 1998. The number of childhood cancer deaths was calculated according to underlying cause of death (ICD-10) (WHO 1992) for each year from 1998 to 2000.

Five-year cumulative survival was calculated using the Kaplan-Meier method. Five-year relative survival was also calculated by the Ederer II method using the Japanese cohort survival table downloaded from the National Cancer Center in Tokyo, Japan (Center for Cancer Control and Information Services). The single DCO case was excluded. Patients were followed for vital status until the end of July 2006 using death certificates, so all patients were followed for at least five years.

Ethical Consideration

Approval to use the data of HCCR and HPTR was obtained from each review committee. The data do not include identifying information such as the patient name and address.

Results

There were 63 children (0-14 years of age) with malignancies diagnosed between 1998 and 2000 in Hiroshima City. The cases comprised 24 in 1998, 21 in 1999, and 18 in 2000. Twenty-three cases (36%) had cancer information from both HCCR and HPTR, 33 (52%) had information from only HCCR, 6 (10%) had information from only HPTR, and one case (1.6%) was DCO.

The ASR of all types of childhood cancer was 144.3 per million for boys and 93.9 per million for girls (Table 1). The distribution of patients by diagnostic group is shown in the same table. Among childhood cancers for boys, leukemia was the most prevalent (30.8%), followed

Table 1. Number of Incident Cases and Age Standardized Incidence Rate among Childhood Cancer Patients in Hiroshima City, 1998-2000

Cancer site/type	Boys		Girls	
	N (%)	Rate/10^5	N (%)	Rate/10^5
I. Leukemia	12 (31)	44.5	6 (25)	23.5
II. Lymphoma and reticuloendothelial system	5 (13)	18.6	2 (8)	7.8
III. Central nervous system and intracranial and intraspinal	4 (10)	14.8	5 (21)	19.7
IV. Sympathetic nervous system (neuroblastoma)	4 (10)	14.9	4 (17)	15.6
V. Retinoblastoma	1 (3)	3.6	2 (8)	7.8
VI. Kidney	2 (5)	7.4	1 (4)	3.8
VII. Liver	3 (8)	11.1	1 (4)	4.0
VIII. Bone	0 (0)	0.0	1 (4)	3.8
IX. Soft tissue sarcoma	3 (8)	11.1	1 (4)	3.9
X. Embryonal/gonadal	4 (10)	14.7	1 (4)	3.8
XI. Carcinoma and other malignant epithelial tumor	1 (3)	3.7	0 (0)	0.0
XII. Others/unclassified	0 (0)	0.0	0 (0)	0.0
Total	39 (100)	144.3	24 (100)	93.9

Table 2. Numbers of Patients (%) Treated with Surgery, Radiotherapy, or Chemotherapy

Cancer site/type	Surgery			Radiotherapy			Chemotherapy			Total
	Yes	No	Unknown	Yes	No	Unknown	Yes	No	Unknown	
I. Leukemia	0 (0)	17 (94)	1 (6)	0 (0)	17 (94)	1 (6)	17 (94)	0 (0)	1 (6)	18 (100)
II. Lymphoma and reticuloendothelial system	5 (71)	1 (14)	1(14)	0 (0)	6 (86)	1 (14)	4 (57)	2 (29)	1 (14)	7 (100)
III. Central nervous system tumor and intracranial and intraspinal	9(100)	0 (0)	0 (0)	4 (44)	4 (44)	1 (11)	3 (33)	5 (56)	1 (11)	9 (100)
IV. Sympathetic nervous system tumor (neuroblastoma)	8(100)	0 (0)	0 (0)	0 (0)	8(100)	0 (0)	2 (25)	6 (75)	0 (0)	8 (100)
V. Retinoblastoma	2 (67)	1 (33)	0 (0)	0 (0)	3(100)	0 (0)	2 (67)	1 (33)	0 (0)	3 (100)
VI. Kidney	3(100)	0 (0)	0 (0)	1 (33)	2 (67)	0 (0)	2 (67)	1 (33)	0 (0)	3 (100)
VII. Liver	1 (25)	2 (50)	1(25)	0 (0)	3 (75)	1 (25)	3 (75)	0 (0)	1 (25)	4 (100)
VIII. Malignant bone	1(100)	0 (0)	0 (0)	0 (0)	1(100)	0 (0)	1(100)	0 (0)	0 (0)	1 (100)
IX. Soft tissue sarcoma	4(100)	0 (0)	0 (0)	0 (0)	3 (75)	1 (25)	2 (50)	1 (25)	1 (25)	4 (100)
X. Embryonal and gonadal	3 (60)	2(40)	0 (0)	3 (60)	1 (20)	1 (20)	3 (60)	1 (20)	1 (20)	5 (100)
XI. Carcinoma/other epithelial	1(100)	0 (0)	0 (0)	0 (0)	0 (0)	1(100)	0 (0)	0 (0)	1(100)	1 (100)
Total	37 (59)	23 (37)	3 (5)	8 (13)	48 (76)	7 (11)	39 (62)	17 (27)	7 (11)	63 (100)

Table 3. Number of Childhood Cancer Deaths in Hiroshima City (1998-2000)

ICD-10	1998			1999			2000			Total		
	B	G	T	B	G	T`	B	G	T	B	G	T
C22 Malignant neoplasms of liver and intrahepatic bile ducts	0	0	0	1	0	1	1	0	1	2	0	2
C56 Malignant neoplasms of ovary	0	0	0	0	0	0	0	1	1	0	1	1
C74 Malignant neoplasms of adrenal gland	0	0	0	1	0	1	1	0	1	2	0	2
C91 Lymphoid leukemia	2	1	3	0	1	1	1	0	1	3	2	5
C92 Myeloid leukemia	0	0	0	1	1	2	0	0	0	1	1	2
C95 Leukemia of unspecified cell type	0	0	0	1	0	1	0	0	0	1	0	1
C00-C97	2	1	3	4	2	6	3	1	4	9	4	13

by lymphoma and reticuloendothelial system neoplasm (12.8%). Central nervous system and intracranial and intraspinal neoplasm, sympathetic nervous system tumor (neuroblastoma), and embryonal and gonadal tumor were the third most common cancers (10.3%). As for girls, leukemia was the most common (28.6%), followed by central nervous system and intracranial and intraspinal neoplasm (14.3%), and lymphoma and reticuloendothelial system neoplasm (11.1%).

The age distribution of the patients at the time of diagnosis is shown Figure1. Out of 12 patients, less than one year old (infants), seven were diagnosed as having neuroblastoma. Among patients aged 1-4 years, the most frequent cancers were lymphomas (five cases).

Among those aged 5-9 years, there were six leukemia cases and four soft tissue sarcoma cases.

Among those aged 10-14, there were six cases of leukemia and three cases each of central nervous system and intracranial and intraspinal neoplass, and embryonal and gonadal tumors.

Treatments received by the patients are shown in Table 2. Thirty-seven children (58.7%) underwent surgery, eight children (12.7%) received radiotherapy, and thirty-nine children (61.9%) received chemotherapy. In particular, 94% of leukemia patients received chemotherapy. All eight patients (100%) with neuloblastoma underwent surgery.

Table 3 shows the number of childhood cancer deaths from 1998 to 2000: three in 1998, six in 1999, and four in 2000 for both sexes combined. During this period, lymphoid leukemia deaths were most frequent (38%).

Figure 2 shows the five-year cumulative survival among the childhood cancer patients diagnosed during 1998-2000. The five-year survival was 79% (95% confidence interval, CI: 67% - 87%) and the relative five-year survival rate was also 79%.

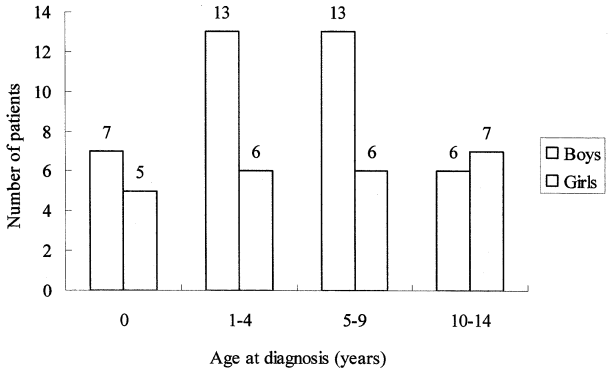

Figure 1. Distribution of Patients by Age at Diagnosis

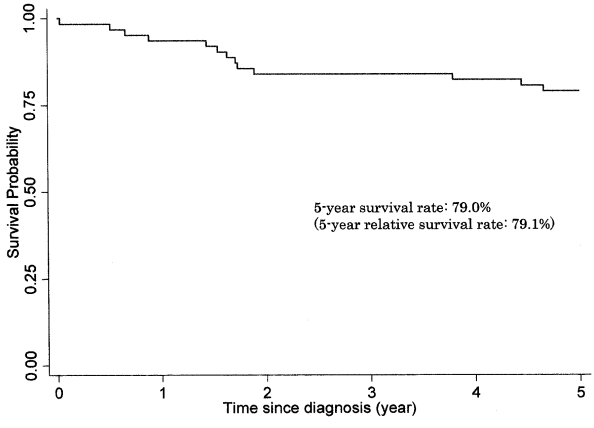

Figure 2. Kaplan-Meier Survival Probability

Discussion

This is the first report on incidence and survival among childhood cancer patients in Hiroshima City. Proportions of type-specific cancers in Hiroshima City were similar to those in Japan overall, which were (in order, beginning with the most frequent): leukemia (boys, 34%; girls, 34%), central nervous system (CNS) and miscellaneous intracranial and intraspinal neoplasma (brain and CNS) (boys, 15%; girls, 11%), and neuroblastoma and other peripheral nervous cell tumors (neuroblastoma) (boys, 13%; girls, 11%). However, the total childhood cancer ASR was higher than those which were 103.7 per million for boys and 80.1 per million for girls in 2000 estimated overall in Japan (Marugame et al., 2007). The percentage of DCO cases in Hiroshima City was much lower (1.6%) than that in Japan overall (7.1%). Moreover, comparing with the childhood cancer incidence rate (1980 - 1989) among other cancer registries in Japan, those of Hiroshima City (117.1 per million), Osaka (133.4), Miyagi (121.8), and Nagasaki (130.0) were almost the same level, while that of Kanagawa Prefecture was only low (94.8). It is considered that the percentage of DCO cases in Kanagawa Prefecture was 30 %, in spite of other cancer registries the percentage of DCO cases were less than 1% (Parkin et al., 1998). Thus, the apparently higher incidence in Hiroshima (1998-2000) may be due to the quality of its cancer registry resulting in a greater number of acceptable diagnoses.

All patients who were suspected of having neuroblastoma by mass screening at ages less than one year survived at least five years after diagnosis. Five-year survival for all neuroblastoma patients was 88%, which is high compared with that of the ACCIS study in the EU (59%, 1988-1997) (Spix et al., 2006) and US SEER (66.0%, 1985-1999) (Desandes et al., 2008; Surveillance Epidemiology and End Results, 2008). A higher rate of diagnosis of neuroblastoma due to mass screening has been thought to greatly affect an apparent increase in its incidence and survival (Ajiki et al., 1998; Honjo et al. 2003). Mass screening for neuroblastoma was performed for infants through six months of age until 2003 in Japan, and the seven infants who were diagnosed as having neuroblastoma were all initially identified through mass screening. In this study, among eight patients with neuroblastoma, one had a localized tumor, one had a tumor that had advanced into the regional lymph node, one had a tumor that had advanced into the regional organs, three had metastasis, and two had unknown stage; all underwent surgery. Because it is well known that a localized neuroblastoma diagnosed before the age of one has a good prognosis (Hiyama et al., 2008), surgery may be unnecessary for patients with localized tumors. Due to the fact that mass screening for neuroblastoma in Japan ceased in 2003, effects on the subsequent epidemiology of childhood neuroblastoma, such as incidence, mortality, survival, and method of treatment (surgery, chemotherapy, and radiotherapy), clearly need to be evaluated periodically.

There were about five childhood cancer deaths in Hiroshima City each year. Although it is a fact that some cancer deaths are unavoidable, from the standpoint of public health, it is necessary to continue evaluating and improving the medical management of childhood cancer patients. Issues to be evaluated include patterns of diagnosis, treatment, and reference to larger hospitals that, unlike local clinics, have the resources to provide and combine many specialties in the treatment of childhood cancer. We will also continue to gather information on children who died from cancer causes to facilitate ongoing evaluation of childhood cancer mortality (Tsutsui et al., 2009).

Five-year relative survival among Hiroshima City children was 79%, which is slightly high compared with that in Osaka (71.7%, 1990-94) (Ajiki et al., 2004), France (75.2%, 1990-1999) (Goubin et al., 2006), the ACCIS study in the EU (72%, 1988-1997), and SEER (74.0%, 1990-1999), but may not be statistically significant because the confidence interval overlapped the five-year survival of other countries. After excluding patients diagnosed with neuroblastoma, the five-year relative survival was 78%. Survival from childhood cancer has improved recently, particularly due to improvements in chemotherapy, which is used in 61% of childhood cancer cases. Therefore, because the period of diagnoses reported for Hiroshima City is later than those referenced above for other registries, increased survival due to improvements in treatment could explain some of the difference. In Hiroshima City, the reference system—whereby children suspected of having cancer are referred to a hospital specializing in cancer care or to a large general hospital to be diagnosed and undergo treatment—works quite well: 81% of the patients were treated in designated cancer-care hospitals (Sugiyama et al., 2008). It is plausible that the better survival may be due to this concentration of childhood cancer treatment in cancer-care hospitals.

Incidence of childhood cancer is substantially lower than that of adult cancer. In this study, based on a relatively small population and short follow-up period, it was difficult to evaluate the childhood cancer statistics from many traditional epidemiologic viewpoints (e.g., trends in age-specific incidence, relative proportions according to stage, and survival by diagnostic category). Furthermore, there are many important issues to be evaluated using cancer registry data, such as neuroblastoma mass screening (Ajiki et al., 1998; Hiyama et al., 2008) and childhood cancer survival as an indicator of improvements in treatment (Honjo et al., 2003; Pession et al. 2008; Swaminathan et al., 2008). Thus, it is important to report descriptive statistics on childhood cancer, and we hope to update such reports periodically.

In conclusion, the ASR (per million) was 144.3 for boys and 93.9 for girls and five year survival rate was 79% in Hiroshima City during 1998-2000. Based on childhood cancer statistics in Hiroshima City in 1998-2000 that suggest a higher incidence than in Japan overall, we infer that the high quality of the tumor and tissue registries leads to better ascertainment - thus a lower frequency of DCO diagnoses - and therefore only the appearance of higher incidence. We will continue the follow-up and

report updated childhood cancer statistics in the near future.

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