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Trends in Childhood Cancer Incidence in Wisconsin, 1980-1999

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ABSTRACT

Objectives: Characterizing the burden of childhood cancer in Wisconsin is the first step to assessing the impact of prevention efforts, identifying especially vulnerable subgroups, and directing etiologic research. To support these goals, population-level data were used to examine trends in childhood cancer incidence among children aged 0-14 years in Wisconsin from 1980 to 1999.

Methods: Data for Wisconsin was provided by the Wisconsin Cancer Reporting System and compared to national data. Annual age-adjusted childhood cancer incidence rates for the entire population and subgroups by age, sex, race, time period, diagnostic code, and geographic region were described. Correlational analysis was conducted to assess the relation between community socioeconomic status and childhood cancer incidence using census data.

Results: Overall, Wisconsin's annual incidence rate for childhood cancers was 14.4 cases per 100,000 children aged 0-14 years during 1980-1999. This rate increased 10.9% (95% confidence interval 1-22%) between 1980 and 1999. Children in the 0-4 age group (20.9 per 100,000 per year) had the highest incidence rates as compared to 5-9 year olds (10.4 per 100,000 per year) and 10-14 year olds (12.0 per 100,000 per year). In males, the age-adjusted incidence of childhood cancers between 1980 and 1999 was 15.5 cases per 100,000 per year, whereas females had an incidence rate of 13.1 per 100,000 per year. Rates for whites were similar to the rates for all other racial groups combined. Leukemia had the highest age-adjusted incidence rate among childhood cancer diagnostic subtypes (4.3 cases per 100,000 per year); leukemia incidence increased by 32% between 1980 and 1999. Among the 13 hospital referral regions in Wisconsin with reported cancer cases, the Dubuque region had the highest annual age-adjusted incidence rate of 24.6 cases per 100,000, followed by Madison with 15.6 per 100,000, and Milwaukee with 15.5 per 100,000. In general, higher socioeconomic status as reflected by census indicators was positively correlated with higher rates of childhood cancer.

Summary: Wisconsin experienced childhood cancer incidence rates and trends similar to those throughout the United States between 1980 and 1999. Analysis of Wisconsin data, which is subject to small numbers in absolute terms (3138 cases during 1980-1999), suggests that not all children have similar risk—infants and younger children (<5 years of age) as well as children living in areas with higher socioeconomic status may be especially vulnerable.

INTRODUCTION

Cancer is a leading cause of mortality and morbidity in children. After unintentional injuries, malignant neoplasms are the second leading cause of death in people 1-14 years of age and consist of 11.6% of all deaths in 2000 for that age group in the United States.[1] In Wisconsin, 23 deaths caused by cancer occurred in 1999 in children <15 years of age, with 14 deaths among males and 9 deaths among females.[2] For Wisconsin children that same year, 69 males and 64 females were newly diagnosed with an invasive neoplasm.[2]

In Wisconsin, cancer is a reportable disease as mandated by section 255.04, Wisconsin Statutes. The Wisconsin Cancer Reporting System (Department of Health and Family Services) was created in 1976 to fulfill that mandate. Therefore, it is the mission of the

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Cancer Reporting System to collect incidence data on all newly diagnosed cases in the state. Data addressing cancer type, stage at diagnosis, and treatment, as well as demographic data, are collected for all incident (not recurrent) cases of invasive and noninvasive malignant tumors, except basal and squamous cell carcinomas of the skin.

No analysis has been conducted in recent years to assess trends in childhood cancer incidence throughout Wisconsin. Tracking cancer trends over time allows for identification of successes and failures in cancer prevention and treatment, and provides the potential for identifying etiologic factors that might otherwise not be indicated.[3] The purpose of this paper is to describe trends in childhood cancer in Wisconsin from 1980-1999 by age, sex, race, and geographic location.

In addition, this study addresses the relationship of socioeconomic factors and the incidence of childhood cancers by geographic region in Wisconsin through an ecological analysis. This analysis contributes to knowledge of the distribution of childhood cancers in Wisconsin as well as the association of childhood cancers and socioeconomic status in general. Though socioeconomic factors have frequently been identified as determinants of cancer incidence and survival,[4,5] few studies have analyzed the relationship between socioeconomic determinants of childhood cancers in the United States.

METHODS

Incident cancer cases in children ages 0-14 years old in Wisconsin for the years 1980-1999 were obtained from the Wisconsin Cancer Reporting System. A total of 3138 cases were identified through this registry. Available data for each incident case included age group, grouped year of diagnosis, sex, race group, hospital referral region of residence, and tumor histology and topography. Age and other variables were provided to researchers in grouped categories to protect the confidentiality of the cancer cases. This project was determined to be exempt from institutional review board review by the University of Wisconsin Health Sciences Human Subjects Committee on April 9, 2003 due to the non-identifiability of the cancer cases.

Age was stratified into 3 groups: 0-4 years, 5-9 years, and 10-14 years; age groups were chosen to be consistent with data available from the census and to allow for comparisons with rates in the United States.[6,7] Race groups included only "white, black, others and unknown" due to inconsistencies in reporting of race throughout the study period. Cancer cases were stratified geographically according to their residences at diagnosis by 14 hospital referral regions that represent areas defined according to patterns of locally-delivered health care.[8] For hospital referral regions that crossed state borders (e.g. Dubuque), data was only collected for Wisconsin residents diagnosed or treated within Wisconsin. In addition, no cases were reported by the registry for the Marquette region, therefore it was excluded from our analysis. The classification of childhood cancer in this paper is based on tumor morphology rather than, as for adults, the site of the tumor. The International Classification of Childhood Cancer (ICCC) classified cancer cases into 12 groups established by the definitions presented in the International Agency for Research on Cancer Technical Report No. 29.[9] The ICCC diagnostic codes for this study were obtained from the Surveillance, Epidemiology, and End Results (SEER) Web site.[10] Cases that had histology and topography combinations that were inconsistent with those in the ICCC system were classified through consensus of the study investigators; 2.9% (n=91) of all cases were classified in this way.

Population data used in incidence rate calculations were obtained by ZIP code from the 1980, 1990, and 2000 US Census.[6] Since hospital referral regions are defined based on ZIP code boundaries, population counts for each age group, year of diagnosis period, sex, race, and hospital referral region were calculated by summing the population in the ZIP codes within each hospital referral region. Population estimates for inter-decade incidence rate calculations were obtained by straight-line interpolation between decade end-points. Population counts for ZIP codes took into account the changes in the ZIP code boundaries between each census as well as the more recent use of ZIP code tabulation areas by the US Census Bureau; ZIP codes that were eliminated or arose during 1980-2000 were also accounted for in the population count estimation. For regions that crossed state borders, population counts of children were obtained for ZIP codes only within Wisconsin.

Annual incidence rates per 100,000 children aged 0-14 years in Wisconsin were calculated for the time period 1980-1999. Annual rates were also calculated for subgroups defined by sex, race, hospital referral region, cancer site, and 4 time periods (1980-1984, 1985-1989, 1990-1994, and 1995-1999). All incidence rates were adjusted to reflect the age distribution of children ages 0-14 using the 2000 US standard million population.[11]

Percent change in incidence rates over the course of the 4 study periods was calculated, along with corresponding 95% confidence intervals. First, we esti-

Table 1. Average Annual Incidence Rates of Childhood Cancer According to Age and Year of Diagnosis, Sex, and Race, Wisconsin, 1980-1999*

	Average Annual Incidence Rate per 100,000 (Number of Cases)					Percent Change† (95% CI)
	Entire Period 1980-1999	1980-1984	1985-1989	1990-1994	1995-1999	
Overall						
0-4 years	20.9 (1485)	19.6 (351)	21.9 (396)	20.6 (370)	21.7 (368)	7.7% (-6.3%, 23.6%)
5-9 years	10.4 (761)	9.7 (163)	9.7 (173)	11.5 (219)	10.7 (206)	15.0% (-5.3%, 39.7%)
10-14 years	12.0 (892)	11.0 (205)	11.8 (198)	12.9 (243)	12.3 (246)	12.8% (-5.4%, 34.6%)
Total	14.4 (3,138)	13.3 (719)	14.3 (767)	14.9 (832)	14.8 (820)	10.9% (0.9%, 21.9%)
Males						
0-4 years	23.2 (843)	21.3 (196)	25.2 (233)	21.9 (201)	24.6 (213)	8.8% (-9.4%, 30.8%)
5-9 years	11.5 (429)	11.5 (99)	9.9 (91)	12.7 (124)	11.7 (115)	9.1% (-15.4%, 40.8%)
10-14 years	12.3 (468)	11.5 (110)	11.4 (98)	13.6 (132)	12.4 (128)	12.7% (-11.6%, 43.6%)
Total	15.5 (1,740)	14.7 (405)	15.3 (422)	16.0 (457)	16.1 (456)	9.8% (-3.3%, 24.7%)
Females						
0-4 years	18.6 (642)	17.8 (155)	18.5 (163)	19.3 (169)	18.7 (155)	6.2% (-14.0%, 31.0%)
5-9 years	9.3 (332)	7.9 (64)	9.4 (82)	10.2 (95)	9.7 (91)	24.4% (-7.9%, 68.2%)
10-14 years	11.7 (424)	10.5 (95)	12.3 (100)	12.1 (111)	12.1 (118)	13.1% (-12.5%, 46.2%)
Total	13.1 (1,398)	11.9 (314)	13.3 (345)	13.8 (375)	13.4 (364)	12.3% (-2.6%, 29.6%)
Race						
White	14.3 (2,793)	13.3 (656)	14.2 (683)	15.0 (740)	14.8 (714)	12.4% (1.6%, 24.3%)
Others	14.5 (345)	14.4 (63)	15.5 (84)	14.0 (92)	14.3 (106)	-3.2% (-27.9%, 30%)

* Incidence rates for the "Total" categories are age-adjusted to the 2000 US standard population.
† Percent change estimated from the slope of a regression line through the log of the age-adjusted incidence rates of the 4 time periods.

mated the slope of the regression line through the log of the age-adjusted incidence rates of the 4 time periods. Using the variance for the log of the age-adjusted incidence rates, we calculated the 95% confidence intervals for the slope. Then, we transformed the slope and confidence intervals to the original scale by taking the exponent of these estimates. Wisconsin and US childhood cancers incidence rates were compared for the period 1980-1999.[12] The population-based incidence rates for the United States are from the SEER Program's 9 areas, which comprise about 10% of the US population. To obtain rates for the United States, the SEER*Stat software from the Surveillance Research Program at the National Cancer Institute was utilized.[13,14]

Information regarding socioeconomic conditions within each hospital referral region was obtained from the 1990 census to allow for ecologic analysis of the association between childhood cancer incidence and community socioeconomic factors in Wisconsin. Variables of interest were: educational attainment of persons ≥25 years in 1989, poverty status in 1989 by age, and residence in rural or urban areas. Data were obtained for every category of these variables that were available from the US Census. Categories were then grouped to form the following variables in each hospital referral region: the percent of persons ≥25 years with a bachelor's degree, the percent of persons who are at or above poverty status, and the percent of persons living in urban areas. Pearson product-moment correlations weighted by the population counts of 0-14 year olds in each hospital referral region were calculated between each socioeconomic variable and the incidence of cancer according to each hospital referral region.

All data analysis and calculations were conducted using SAS statistical software (SAS Institute Inc., Cary, NC) and Excel (Microsoft Corporation, Redmond, WA).

RESULTS

Trends by Patient Characteristics

Overall, Wisconsin's average annual incidence rate for childhood cancers was 14.4 cases per 100,000 children ages 0-14 during 1980-1999 (n=3138). This rate increased 10.9% (95% confidence interval 0.9-21.9%) during 1980-1999. Cancer incidence for younger children (20.9 per 100,000 per year; ages 0-4 during 1980-1999) was almost twice as high as for older age groups, peaking at 21.9 per 100,000 per year during 1985-1989.

Table 2. Average Annual Incidence Rates of Childhood Cancer (Ages 0-14 Years) According to ICCC Diagnostic Code and Year of Diagnosis for Wisconsin and the United States, 1980-1999*

ICCC Diagnostic Code	US Incidence Rates (No. of cases) 1980-1999	Wisconsin Annual Incidence Rates (Number of cases) 1980-1999	1980-1984	1985-1989	1990-1994	1995-1999	Percent Change† (95% CI)
Leukemia	4.3 (4,527)	4.3 (942)	3.8 (203)	4.0 (217)	4.5 (250)	5.0 (272)	32.3% (11.3%, 57.2%)
CNS and Miscellaneous Intracranial and Intraspinal Neoplasms	3.0 (3,117)	3.0 (653)	2.3 (122)	3.6 (189)	3.2 (180)	2.9 (162)	19.9% (-3.8%, 49.5%)
Lymphomas and Reticuloendothelial Neoplasms	1.4 (1,468)	1.7 (380)	2.0 (105)	1.5 (76)	2.1 (117)	1.4 (82)	-15.7% (-35.9%, 10.9%)
Sympathetic Nervous System Tumors	1.1 (1,182)	1.0 (223)	1.0 (56)	1.1 (61)	1.0 (57)	0.9 (49)	-10.5% (-37.7%, 28.5%)
Soft-Tissue Sarcomas	1.0 (1,024)	1.0 (224)	0.9 (48)	1.0 (51)	1.0 (56)	1.2 (69)	35.8% (-4.4%, 92.8%)
Renal Tumors	0.9 (938)	0.9 (199)	1.0(53)	1.0 (54)	0.8 (45)	0.9 (47)	-15.3% (-41.7%, 23.1%)
Malignant Bone Tumors	0.7 (674)	0.7 (155)	0.7 (35)	0.7 (34)	0.9 (48)	0.7 (38)	7.5% (-30.4%, 66.0%)
Carcinomas and Other Malignant Epithelial Neoplasms	0.5 (535)	0.6 (125)	0.6 (30)	0.6 (30)	0.6 (32)	0.6 (33)	0.6% (-37.1%, 60.9%)
Germ-Cell, Trophoblastic and Other Gonadal Neoplasms	0.5 (524)	0.5 (105)	0.5 (29)	0.4 (23)	0.4 (21)	0.6 (32)	2.8% (-36.8%, 67.2%)
Retinoblastoma	0.4 (454)	0.3 (74)	0.4 (24)	0.3 (17)	0.2 (13)	0.4(20)	-19.1% (-54.6%, 43.9%)
Hepatic Tumors	0.2 (211)	0.1 (31)	0.1 (6)	0.1 (8)	0.1 (8)	0.2 (9)	45.0% (-45.3%, 284.9%)
Other and Unspecified Malignant Neoplasms	0.1 (55)	0.1 (27)	0.1 (8)	0.1 (7)	0.1 (5)	0.1 (7)	-22.5% (-70.8%, 105.9%)

*Rates per 100,000 per year and age-adjusted to the 2000 US standard population taken from the SEER 9 areas.
† Percent change estimated from the slope of a regression line through the log of the age-adjusted average annual incidence rates of the 4 time periods.

Incidence during the entire time period increased most for children ages 5-9 (15%) although this increase was not substantially different from the increase for the 2 other age groups. For children 5-9 and 10-14, incidence was highest during 1990-1994, at 11.5 and 12.9 per 100,000 per year, respectively.

In males, the age-adjusted average annual incidence of childhood cancers between 1980 and 1999 was 15.5 cases per 100,000 per year, whereas females had an incidence rate of 13.1 per 100,000 per year. In each 5-year time interval, and in the 20 years combined, childhood cancer incidence was greater in males than females. Females showed a greater increase in incidence rates (12.3%) than males (9.8%) in the 20-year combined period. Over the 20-year time period, incidence in males increased the greatest in the oldest age group (12.7%, 10-14 year olds), while incidence rates increased the least in the youngest age group (8.8%). In contrast, females in the same time period showed the greatest increase in the 5-9 year olds (24.4%) and the least increase was seen in the 0-4 year olds (6.2%).

Whites had an overall incidence rate of 14.3 cases per 100,000 per year for the 20-year combined period between 1980 and 1999. "Others" (Blacks, other and unknown categories) had a similar overall incidence rate of 14.5 cases per 100,000 per year. The incidence rate in whites increased across the 4 time periods by 12.4% (95% confidence interval; 1.6%-24.3%), while there was essentially no increase (3.2%, 95% confidence interval; 27.9%-30%) in the "Other" race category.

Trends by ICCC Diagnostic Classification

Incidence rates according to diagnostic classifications for Wisconsin were similar to rates for the country. For both Wisconsin and the United States, leukemia had the highest age-adjusted incidence rate at 4.3 cases per 100,000 per year, followed by central nervous system (CNS) neoplasms at 3.0 cases per 100,000 per year. Across the 4 time periods, incidence rates for both of these 2 classifications increased: leukemia rates increased 32.3% (95% confidence interval; 11.3%-57.2%), and rates of CNS and miscellaneous intracranial and intraspinal neoplasms increased 19.9% (95% confidence interval; 3.8%-49.5%).

Table 3. Average Annual Incidence Rates of Childhood Cancer, Ages 0-14 Years, According to Hospital Referral Region and Year of Diagnosis for Wisconsin, 1980-1999*

Hospital Referral Region	Average Annual Incidence Rate per 100,000 (Number of Cases)					Percent Change† (95% CI)
	1980-1999	1980-1984	1985-1989	1990-1994	1995-1999	
Dubuque	24.6 (32)	24.0 (9)	23.4 (8)	35.8 (11)	14.6 (4)	-27.4% (-75.8%, 117.6%)
Madison	15.6 (543)	19.3 (116)	14.8 (138)	14.2 (132)	16.6 (157)	-13.4% (-31.4%, 9.3%)
Milwaukee	15.5 (1,417)	15.0 (339)	15.7 (357)	15.5 (356)	15.8 (365)	4.2% (-9.5%, 19.8%)
Neenah	14.8 (123)	11.1 (23)	13.0 (27)	17.2 (36)	17.5 (37)	63.4% (-0.1%, 167.3%)
Green Bay	14.7 (269)	14.7 (67)	16.7 (76)	16.3 (74)	11.4 (52)	-21.0% (-43.8%, 11.0%)
Appleton	14.7 (188)	12.9 (40)	16.1 (51)	14.3 (46)	15.4 (51)	13.3% (-23.4%, 67.6%)
La Crosse	14.4 (129)	13.6 (30)	13.3 (30)	14.6 (33)	16.0 (36)	19.0% (-24.9%, 88.7%)
Marshfield	12.6 (199)	9.1 (37)	6.3 (25)	20.6 (80)	15.0 (57)	124.2% (50.8%, 233.3%)
Wausau	12.5 (93)	11.6 (22)	11.3 (21)	15.9 (29)	11.5 (21)	9.4% (-37.8%, 92.4%)
Minneapolis	10.1 (86)	11.4 (24)	9.4 (20)	7.9 (17)	11.6 (25)	-3.6% (-43.9%, 65.5%)
Rochester	8.5 (7)	13.4 (3)	8.9 (2)	10.1 (2)	0 (0)	— ‡
Duluth	7.1 (26)	4.2 (4)	3.2 (3)	9.9 (9)	11.1 (10)	239.0% (11.1%, 934.2%)
St. Paul	4.7 (23)	2.6 (3)	6.7 (8)	7.1 (9)	2.3 (3)	-9.1% (-79.1%, 295.1%)

*Incidence rates per 100,000 per year and age-adjusted to the 2000 US standard population; cases included from Wisconsin areas of the hospital referral regions only.
† Percent change estimated from the slope of a regression line through the log of the age-adjusted average annual incidence rates of the four time periods.
‡Not calculated due to small numbers.

Trends by Geographic Location

Among the 13 hospital referral regions in Wisconsin with reported cancer cases, the Dubuque region had the highest age-adjusted incidence rate of 24.6 cases per 100,000 per year (n=32 cases) followed by the 2 regions with the highest numbers of reported cases: Madison with 15.6 per 100,000 per year (n=543 cases), and Milwaukee with 15.5 per 100,000 per year (n=1417 cases). Only 2 regions—Marshfield and Duluth—had rates that changed significantly across the 4 time periods. Cancer incidence in the Marshfield region increased 124% (95% confidence interval; 50.8%-233.3%; 199 cases). The Duluth hospital referral region also experienced a significant increase in childhood cancer rates, from 4.2 to 11.1 cases per 100,000, although these rates are based on only 26 cases during 1980-1999.

Correlations between rates for each hospital referral region with census indicators of socioeconomic status were calculated based on rates for the entire time period 1980-1999. In general, higher socioeconomic status was positively correlated with higher rates of childhood cancer. The percent of each region defined as urban was positively correlated with childhood cancer incidence (r=0.61, *P*=0.03; see Figure 1), suggesting that regions with more urban areas had higher rates of childhood cancer. The correlation between the percent of people in each region with a college degree and childhood cancer incidence was 0.42 (*P*=0.15); similarly, the percent of people in each region living above the poverty level was modestly correlated with childhood cancer incidence (r=0.30, *P*=0.32).

To evaluate the influence of the relatively lower rates of childhood cancer in the northwest corner of the state on these correlation coefficients, cases for the Duluth, St. Paul, Rochester, and Minneapolis hospital referral regions were combined. Using this combined region along with the other 9 hospital referral regions, the correlation between childhood cancer incidence rates and urban areas (r=0.63, *P*=0.05) and adults with college educations (r=0.47, *P*=0.17) did not change substantially, although the correlation with the percent of the population living above poverty was slightly stronger (r=0.54, *P*=0.11). Correlation coefficients increased slightly when cancer cases were limited to leukemia (urban area: r=0.67, *P*=0.03; college education: r=0.47, *P*=0.17; above poverty level: r=0.54, *P*=0.11).

DISCUSSION

Trends of childhood cancer incidence in Wisconsin were consistent with trends in the United States between 1980 and 1999.[12] The US data indicate that overall childhood cancer incidence rates and rates in 5-year age groups have increased since the mid-1970s, but rates began to stabilize around the first half of the decade between 1990 and 1999, and have shown a slight decline between 1995 and 1999. Similar trends were observed in Wisconsin with incidence rates peaking for most subgroups during 1990-1994. The finding that males had higher incidence rates than females in Wisconsin was consistent with what was observed in the United States.[12]

Rates in the United States indicate a lower rate of

childhood cancers for older children compared to children <5 years of age, and for blacks and others compared to whites in general.[14] Wisconsin rates according to these age groupings are consistent with the US rates, along with the observation that the 3 highest incidence rates by ICCC diagnosis groups in Wisconsin were for leukemia, CNS neoplasms, and lymphoma.[12,14] Childhood cancer rates in Wisconsin for whites and "others" were similar, however this may be a result of the relatively small number of diagnoses in minority populations.

Geographic variation in childhood cancer incidence was evident with incidence rates in Wisconsin hospital referral regions ranging from 24.6 cases per 100,000 per year in Dubuque to 4.7 cases per 100,000 per year in St. Paul. However, these regions cross state borders and therefore the number of actual cases diagnosed and reported from Wisconsin are small, giving rise to unstable incidence rates. Among those hospital referral regions that did not cross state borders, the highest incidence rates were seen in the Madison region, followed by the Milwaukee region, and the lowest incidence rates were observed in Marshfield and Wausau.

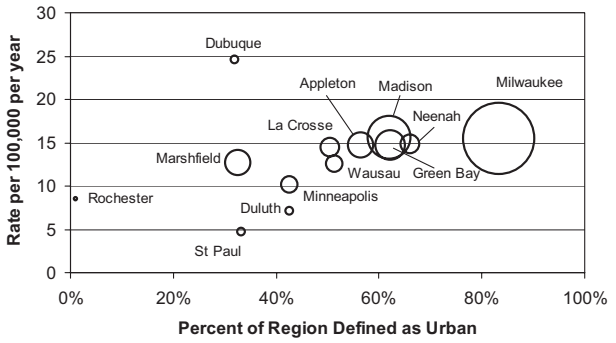

Figure 1. Percent of each hospital referral region defined as urban according to the incidence rate (per 100,000 per year) of cancer in children 0-14 years of age, Wisconsin, 1980-1999. Sizes of the circles are proportional to the number of cases diagnosed in each region. Pearson correlation=0.61, *P*=0.03.

Our analysis exploring the relation of community socioeconomic characteristics with childhood cancer incidence indicated that, in general, higher socioeconomic status was positively correlated with higher rates of childhood cancer. Other studies that have explored the relation between community-level socioeconomic characteristics and childhood cancer incidence have reported mixed findings.[15] Some studies conducted at the ecologic and individual level outside of the United States suggest a higher likelihood of childhood cancers with higher socioeconomic status,[16-19] while others suggest the opposite effect.[15,20] Of the socioeconomic status characteristics we examined, urbanicity of a hospital referral region was most highly correlated with greater childhood cancer incidence in Wisconsin, especially when analysis was limited to leukemia cases. One study of Canadian cases of childhood leukemia noted that the positive correlation between incidence rates and neighborhood-based measures of income was strengthened slightly by restriction to urban areas,[19] whereas another study conducted in northwest England reported higher childhood soft-tissue sarcoma rates in areas with greater unemployment and more rural districts.[16] Whereas many studies demonstrate links between cancer in children and socioeconomic indicators, more work is needed to define the specific mechanisms that underlie these relationships.

There are limitations that need to be considered in this study. Certain sub-group analyses were based on small counts of case reports. Incidence rates by age, sex, and race subgroups, rates for regions that cross state borders, and rates for some rare cancer sites were unstable because of the small number of cases. Rates may also have been affected by the estimated counts of the children living in each ZIP code in years when a census was not conducted. Rates of urban and rural areas may have been differentially influenced by this estimation process since new ZIP codes containing growing cities were more likely to appear and change in size rapidly; these rapid population changes may not have been reflected accurately using the straight-line interpolation estimation procedure. In addition, due to the limited number of time points in the analysis (4), we estimated percent change in incidence rates from the slope of a linear regression line through the log of the age-adjusted incidence rates. We assumed that the trend in the log-rate was linear. However, any departure in the data from this assumption would make the percent change in the incidence rate less meaningful.

Another concern in this study was the issue of incomplete reporting of cancer cases from border states. Wisconsin children who were diagnosed and treated in Illinois, Iowa, Michigan, and Minnesota may not be fully represented in these analyses, especially during the 1980s before data sharing agreements were established with several states and over 20 individual Minnesota hospitals. Prior to 1995, the estimated completeness for the statewide tumor registry was 92%-93%. Since 1995, the average annual completeness estimate has exceeded 95%. Improvements in registry completeness clearly may have influenced the estimates of percent change

in childhood cancer rates between 1980 and 2000. For example, many cancer cases living in the Duluth hospital referral region may not have been reported to the Wisconsin tumor registry during the 1980s if they were diagnosed and treated solely in Minnesota facilities (percent increase in childhood cancer incidence is 239% since 1980). However, completeness of cancer reporting in the Marshfield hospital referral region most likely was consistently high throughout the time period of this analysis (percent increase 124%).

As with this Wisconsin data, analysis of temporal cancer registry data in the United States and in Europe has documented increases in childhood cancer rates.[21,22] Some reports conclude that increased childhood cancer rates were due to improved diagnostic technology and changes in classification, particularly during the 1980s when magnetic resonance imaging and prenatal ultrasound testing disseminated.[23] Others argue that improvements in registry completeness explain the observed, but artifactual, increases in childhood cancer rates.[24,25] The small numbers in absolute terms of childhood cancer cases make the detection of statistically significant changes in rates challenging, especially when even a single additional case carries social importance.

Assuming an increase is true and not artifact, biological mechanisms to support an increase because of emergent risk factors have been suggested. Reasons include decreased infant mortality, older parental age, greater proportion of children who were first-born, and heavier birth weight, all of which have been associated with selected childhood cancers.[26] Environmental pollutants have also been evaluated, although no firm conclusions can be drawn from the evidence.[27]

The role of infectious disease in the etiology of childhood cancers, in particular acute lymphoblastic leukemia, is frequently argued. While it has been proposed that common childhood infections such as varicella, infectious mononucleosis, and Epstein-Barr virus play a role, the specific causal agents have not been confirmed. Two leading hypotheses regarding infections have been tested using registry and cancer cluster data. Kinlen proposed the population mixing hypothesis that childhood cancer is associated with large in-migration and the introduction of an infectious disease to a susceptible, isolated population in a short period of time.[28] Alternatively, Greaves suggested that ALL develops after a delayed exposure to infections that produces proliferative stress in B cell precursors belonging to a clone expanded as a consequence of spontaneous mutation.[29] These 2 similar hypotheses may be supported by evidence that childhood cancer rates are lower in population groups with lower socioeconomic status, assuming that children living in households with lower income and poorer living conditions tend to encounter infectious agents earlier and more commonly than their affluent counterparts.[19] Since several studies using various measures of socioeconomic status have reported contrary results, Raaschou-Nielsen et al[15] suggest that these differences may be explained by the possibility that community behavior is more strongly associated with childhood cancer risk than individual socioeconomic position. Community or neighborhood characteristics putatively associated with childhood cancer may include infectious disease as well as other factors that could influence the immune system and cancer susceptibility, such as psychosocial stress.

Although incidence of childhood cancer has increased over the past several decades, mortality rates have decreased. US mortality rates for all cancers in males and females ages 0-14 decreased from 4.9 per 100,000 in 1975 to 2.5 per 100,000 in 2001.[30] Decreasing mortality rates concurrent with increases in incidence are due to improved survival rates. Five-year relative survival rates dramatically improved in the United States from 55.9% in 1974-1976 to 78.5% in 1995-2000.[30] While improvements in therapy have been primarily responsible for delaying or preventing children's death from cancer, effective primary prevention efforts must be developed so that cancer can be avoided entirely.

In conclusion, incidence of cancer in children appears to occur in Wisconsin with similar frequency as in the United States as a whole. Infants and young children, as well as children living in areas with higher socioeconomic status, may disproportionately be diagnosed with this spectrum of diseases—a spectrum of diseases that is more common now than 25 years ago. Further work should focus on exploring whether the trends described here are due to an artifact of small numbers and incomplete reporting, or whether geographic variation in rates offers clues to the causes of cancer in children.

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