Cancer Incidence and Survival Trends among Infants in the United States from 1975 to 2014

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Abstract

Background: Cancer among infants (<1 year old) has unique epidemiologic, clinical and genetic characteristics compared with cancer in older children. Nonetheless, data on secular trends in infant cancer incidence and survival in the US is sparse. Methods: Population-based data from Surveillance Epidemiology and End Results (SEER 9) was used to estimate the incidence, average annual percentage change (APC) for trends and survival of malignant neoplasm among infants from 1975-2014. Data were stratified by gender, race, registry and cancer type. Results: There were 3,437 new infant cancer cases with an overall incidence of 23.6/100,000. Neuroblastoma was the most common infant malignancy (6.5/100,000), followed by leukemia (3.8/100,000), and brain and central nervous system tumors (3.3/100,000). The incidence rate increased significantly over the observational period (APC 0.68; 95%CI 0.30-1.06; p<0.05). Variations in overall incidence rates were uneven across SEER registry geographic areas, with the lowest rates among both males and females in New Mexico. Relative to other racial distribution, rates were highest among whites. The relative survival rates improved over time for all tumors except for renal, sarcomas and germ cell and were not significantly different by gender or race. Conclusions: Cancer incidence among infants increased over time largely driven by leukemia, germ cell and sarcoma mainly among male infants. The overall survival for infant cancer has improved over the years especially since 1990 for hepatic tumors, lymphoma and leukemia. Further research is needed to explore the potential impacts of genetic, environmental, and perinatal factors for possible explanations for these increased cancer incidence trends.

Abbreviations	Abbreviations
SEER	The Surveillance, Epidemiology, and End Results
APC	Annual percentage change
ICCC-3	The International Classification Childhood Cancer (ICCC-3)
RR	Relative risk

Introduction :

Cancer among infants younger than one year of age represents a unique problem with distinct epidemiological, clinical and genetic characteristics compared with cancer in older age groups.(1) Cancers occurring in infants differ substantially from those in older children in terms of anatomic site, histological features and behaviors.(2) The prognosis for infants is often worse than for older children, even if the pathologic diagnosis is the same(3). In addition, those under the age of 1 have been shown to have a higher mortality from childhood cancer.(4)

Infant cancer incidences and trends in the United States (U.S.) were reported in 1997(5) and 1998(6) covering the periods from 1973-1992 and 1979-1991 but these data did not include survival rates. To the best of our knowledge, there is no comprehensive updated report that specifically focuses on cancer incidence trends and survival among infants in the U.S.(7-9) Because infants continue to be at a disproportionately higher risk of early cancer mortality, notwithstanding pediatric oncology treatment advances in the last two decades,(4, 10) it is critical to examine what happened in this cancer cohort in order to explore how survival rates can be improved.

Therefore, the aims of this study were to describe the cancer incidence, temporal trends, and survival among infants (<1 year old) over the 40-year period from 1975 to 2014 in the U.S. using SEER data to identify demographic and geographic variations.

Materials and Methods :

Study design, Database and Case Identification

We conducted a retrospective cohort study using population-based data. Incidence of malignant neoplasms among infants (age <365 days) diagnosed between January 1, 1975 and December 31, 2014 were extracted from the SEER registry using the *International Classification Childhood Cancer (ICCC-3)(11), 3rd Edition* . Infant cancer cases were collected from 9 population-based cancer incidence registries (SEER 9) that provided continuing data for the 40-year observation period and represent approximately 10% of the U.S. population.(12) The registries include broad geographic and racial distributions of persons in the states of Connecticut, Hawaii, Iowa, New Mexico, and Utah and the metropolitan areas of Atlanta, Georgia; Detroit, Michigan; San Francisco-Oakland, California; and Seattle-Puget Sound, Washington. The raw data in our study were downloaded from the SEER website via SEER*Stat in client-server mode after we submitted a request for access and signed the SEER research data agreement.(12) This study was classified as exempt by the Institutional Review Board at the Baylor College of Medicine in Houston, Texas.

Numerators for incidence rates comprise the total number of cancer cases occurring among infants from 1975 to 2014. Denominators for calculation of incidence rates were population counts for infants aged <1 year in each of the 9 SEER programs included in this report. Since the number of cancers diagnosed per year among infants was often quite small, some trends were calculated after combining cases diagnosed in two-year. Race was grouped as white, black, and other. Approximately 96% of all cases were confirmed microscopically. Only infants diagnosed with malignant tumors were included in the analyses. Diagnoses were classified into 12 main tumor groups and 47 subgroups according to the ICCC version 3 (ICCC-3). These 12 groups were described as follows: (1) leukemia: leukemias, myeloproliferative and myelodysplastic diseases; (2) lymphoma: lymphomas and reticuloendothelial neoplasms; (3) CNS neoplasms: CNS and miscellaneous intracranial and intraspinal neoplasms; (4) neuroblastomas: neuroblastoma and ganglioneuroblastoma; (5) Sarcomas: soft tissue and other extraosseous sarcomas; (6) germ cell: germ cell tumors (GCTs), trophoblastic tumors, and neoplasms of the gonads; (7) Retinoblastoma: Retinoblastoma; (8) Hepatic tumor: Hepatic; (9) Renal tumors: Renal; (10) Bone: Malignant bone tumors; (11) Other and unspecified malignant neoplasms; and (12) other: other malignant epithelial neoplasms and malignant melanomas. Bone (10), other and unspecified (11) and other (12) tumors were excluded from analysis due to the small number of cases (<50).

Statistical Analysis

The SEER*Stat 8.3.5 is a statistical software designed specifically for the analysis of SEER and other cancer-related databases. The software was used to analyze incidence rates (1/100,000), 95% confidence intervals for incidence rates, relative risk (RR), 95% confidence interval for RR and annual percentage change (APC) of incidence rate. The male-female incidence rate ratios (M/F) were also calculated. SPSS (version 25; Chicago, IL, USA) was used for survival data analysis, including relative survival (RS), a net survival measure that estimates the probability of avoiding death due to a particular cancer relative to the general population. RS is defined as the ratio of the proportion of observed survivors in a cohort of cancer patients to the proportion of expected survivors in a comparable set of cancer free individuals. The Kaplan-Meier method was used to calculate the overall survival rate. The log-rank rest was used to formally test the differences for survival.

A p value <0.05 was considered statistically significant for incidence rate, APC and survival.

Results :

Cancer Incidence

There were 3,437 infants with newly diagnosed cancer (1,740 cases in males and 1,689 cases in females) from 1975 to 2014. Incidence by 10-year time frame, gender, race, registry, and ICCC-3 groups are shown in Table 1. The overall annual incidence rate of malignant neoplasms in infants was 23.6 cases per 100,000 population. Males and females had similar incidence rates (male 23.3/100,000 and female 23.8/100,000).

Infant cancer incidence rates among whites was about 20 percent higher ($p<0.05$) than black and other races (American Indian/Alaska Natives, and Asian/Pacific Islanders) .There were no significant differences in cancer incidences between blacks (19.9/100,000) and other racial groups(19.4/100,000). New Mexico had the lowest incidence rate (19.5/100,000). Incidence rates in Seattle, Connecticut, Utah, Detroit and San Francisco were significantly higher than those in New Mexico. Among males, only San Francisco had a significantly higher incidence rate than New Mexico. Among females, Iowa, Seattle, Connecticut, Utah, and Detroit had significantly higher rates than New Mexico. Connecticut was the only registry in which the incidence ratio between genders was significantly different. The incidence rates increased more than 20 percent from 20.5/100,000 in 1975-1984 to 26.5/100,000 in 2005-2014. For males, the incidence rates in 1985-1994, 1995-2004 and 2005-2014 were all significantly higher than 1975-1984. In contrast, for females, only the incidence rate in 2005-2014 was significantly higher than in 1975-1984. The three most frequently diagnosed cancers among infants were neuroblastoma, leukemias and CNS tumors. These three cancers accounted for 21 percent, 18 percent, and 8 percent, respectively, of all cancers diagnosed among infants. There were large variations in incidence rates between different ICCC-3 groups ranging from 0.05/100,000 (lymphomas) to 6.3/100,000 (neuroblastoma). The incidence ratio between male and female among different ICCC-3 groups ranged from 0.82 (retinoblastoma) to 1.17 (hepatic tumors), but no significant differences in the incidence of infant cancers by sex were observed.

Temporal Trends in Cancer Incidence

Figure 1 shows the infant cancer incidence trends by gender and races from 1975 to 2014. Infant cancer incidence rates experienced a significant increase from 1975 (17.24/100,000) to 2014 (23.8/100,000) with APC 0.68 (CI 0.30-1.06, $p<0.05$). The cancer incidence rate rose by 38.1% during this period. There were large variations (SD 3.65) during the 40-year period ranging from 17.24/100,000 in 1975 to 34.62/100,000 in 2005. Both males and females had increasing trends with APC 0.77 ($p<0.05$) and 0.55 ($p<0.05$) respectively. The increasing trend was not observed in black infants, but significant increasing trends were found in white (APC 0.63, $p<0.05$) and other races (APC 1.03, $p<0.05$). The incidence trends in different SEER areas are shown in Figure 2. Among all 9 registries, New Mexico (APC 1.65) had the highest incidence increase over the 40 years period, followed by Utah (APC 0.90 $p<0.05$) and Detroit (APC 0.85 $p<0.05$). No increasing trends were noted in other SEER areas. From Figure 3, the increasing incidence trends were only found in Germ cell (APC 2.95, $p<0.05$), leukemias (APC 1.33, $p<0.05$) and sarcomas (APC 1.79, $p <0.05$) . Renal and lymphomas showed a decreasing incidence trend (APC<0), but not significant($p>0.05$).

Survival

The overall 5-year relative survival rates for infant cancer from 1975 to 2014 was 73.4%. There was no statistically significant difference in overall survival by gender and race; however, there were significant differences in overall survival by ICCC cancer types and over the years. The 5-year relative survival was only 65.1% in 1975-1984, but increased to 78.0% in 1995-2004 and to 80.5% in 2005-2014. The 5-year overall relative survival rates for retinoblastoma, neuroblastoma, renal tumors and germ cell were over 80%. The 5-year overall relative survival for both leukemia and CNS were under 50% [Fig. 4]. We analyzed the survival rate changes for different ICCC types by 10-year period. Significant relative survival increases occurred for all the ICCC types except renal and sarcomas[Fig 5]. The largest 5-year relative survival rate increase from 1975-1984 to 2005-2014 occurred in hepatic tumor (57.7%, from 39.7% to 97.4%), lymphoma (52.4%, from

31.0% to 83.4%) and leukemia (38.0%, from 26.9% to 64.9%). For CNS and neuroblastoma, the 5-year overall relative survival increases from 1975-1984 to 2005-2014 were 23.9% (35.5%-59.4%) and 10.5% (84.0%-94.5%) respectively. Survival for infants having retinoblastoma since 1995 has approached the survival rate for infants without this cancer. Leukemia and CNS were two infant cancers whose survival improved continuously over four decades. The significant survival improvement for Heptic tumor, germ, and Neuroblastoma occurred only during 1995-2004 and 2005-2014. For retinoblastoma, the survival improvement was only in 1995-2004, for lymphoma survival increase only happened in 2005-2014.

Discussion

SEER 9 registries database used in this study allows us to study infant cancer incidence and survival over 40 years from 1975 to 2014. The SEER 11 and SEER 18 registries database have more geographic coverage, but only cover 23 years and 15 years respectively. This study assessed the incidence, temporal trends, and survival of cancer among infants (age younger than 1 year) and found the important secular trends in infant cancer incidence and survival over a 40-year period of observation in the U.S., using the International Classification of Childhood Cancer (ICCC-3)(11) – the standard classification of child tumors.

In this study, we found a 30% increase in incidence rates of cancer among infants from 20.5/100,000 in 1975-1984 to 26.5/100,000 in 2005-2014. The 40 years of data from 9 SEER registries support the increasing incidence trend and geographic variation in infant cancer incidence rates by sex, type, and race/ethnicity consistent with earlier reports.(5, 6, 13) Although the reason for infant cancer incidence increase is largely unknown, but some believe that genetic, environmental factors and infectious agents play a significant role in cancer development(14). A study spearheaded by the Environmental Working Group (EWG) found an average of 200 industrial chemicals and pollutants in umbilical cord blood from babies. Tests found as many as 287 chemicals in umbilical cord blood, 180 of which are known to cause cancer in human or aminals.(15) Infectious agents are associated with cancer development and it is reported that about 20% of the world's cancer burden is attributed to infectious agents(16).New Mexico had the lowest incidence rate compared with other registries, but experienced the largest temporal increase in four decades. New Mexico's population is 46.4% Hispanic and 41.4% white in 2014 compared with 12.9% Hispanic and 63.9% white nationally(17). New Mexico has the largest Hispanic statewide population share nationally(18). The racial/ethnic composition might play a role. Since SEER9 does not have ethnicity data, further study are needed.

Significant increase trends were found for germ cell, sarcomas, and leukemia over the 40-year period.. It was reported that exposure to post-natal diagnostic x-rays is associated with the risk of childhood acute lymphoid leukemia (ALL), especially B-cell ALL.(19) For sarcomas, although the etiology remains unknown in most cases, environmental factors that increase sarcomas risk include exposure to radiation, chemical carcinogens, and viruses.(20) The heritable aspects of sarcoma have not extensively been studied, but genetic predisposition to sarcoma has been well characterized in some familial cancer syndromes.(21) Germ cell tumors are rare tumors contributing 2.9% to the cancer registry(22) and infancy is one of two peaks in age distribution for germ cell tumors, the other occurring during puberty. The potential influence of in utero exposure to maternal endogenous hormones, parental environmental exposures, and maternal disease during pregnancy relative to the development of childhood germ cell tumors has also been reported.(23) However, the mechanism of how these risk factors have contributed to the increasing trends for these cancers is not clear. For example, a recent study found that exposure to an intrauterine hyperglycemic environment due to maternal gestational diabetes does not increase the risk for pediatric cancer.(24)

The top three infant cancer incidence rates in the U.S., neuroblastomas, leukemia and CNS neoplasms, have also been reported by other countries including France(25) (16.7/100,000 in 2000-2004) and England(26) (16.7/100,000 in 1968-1995). On the contrary, the incidence rate of hepatic tumors was 2 to 5 times higher in China (Beijing and Taiwan) than other countries, which might be strongly related to the high infection rate of Hepatitis B and C among mothers(27) and suggests that genetic variations be considered as a risk factor for infant cancer in China.(28)

Previous epidemiological data reported the impact of cancer genetics and its implication for treatment,

prognosis, and improving overall survival rates.(10, 29) However, only few causal factors have been identified for childhood cancer.(30, 31) Given the current surge of molecular biologic technology and DNA sequencing, the study of inherited factors, environmental and epigenetics have become fields of interest to identify predisposing factors for pediatric cancers(31). Although leukemia, sarcomas, and germ cell malignancies have experienced significant incidence increases in the past four decades, the risk factors associated with these changes are unknown.

Enhanced early detection likely contributed to the increased infant cancer incidence in the past four decades, but cannot fully explain the increasing incidence only for leukemia and sarcomas in males while not in females in some registries (such as New Mexico, Detroit and Utah). This suggests that a true increase exists, but it is possible that this difference could be explained by confounding factors such as poorer access and utilization of care by some populations.(32) Efforts should be made to identify the causes of these differences.

Several hypotheses, including maternal and early infancy dietary factors (i.e., determinants of high birth weight), paternal pre-conception occupational exposures and smoking, pre-natal and post-natal exposure to pesticides, and the interplay of maternal or early postnatal immune system response to common infections have been formulated.(33-35) However, causation warrants investigation not only with epidemiologic data but with prospective pregnancy - birth cohorts to minimize potential temporal-relationship or recall bias.(36)

Although survival rates for most infant cancers have improved in past four decades, the improvement has been especially dramatic for only a few cancers. The 5-year relative survival for hepatic tumors, lymphoma and leukemia have greatly improved. The advent of successful transplants using umbilical cord blood since in 1989 and Arsenic trioxide and Imatinib approved by FDA in 2000 and 2001 might have contributed to the dramatic survival improvement for leukemia.(37) Nearly all lymphoma diagnoses among infants younger than 1 year of age are miscellaneous lymphoreticular neoplasms.(38) Treatment advances and effective management of toxicities of treatment over time might have resulted in a significantly longer survival rate for lymphoma patients.(39, 40) Improved survival in brain and CNS tumors might be due to advanced imaging technology, enhanced surgical procedures and better postoperative surveillance with early diagnosis of recurrence and routine use of more effective chemotherapy.(41) The treatment changes of hepatic cancer over the past few decades with curative options such as liver transplantation, hepatic resection and radiofrequency ablation can explain the survival improvement for hepatic cancer.(42, 43)

This study has several strengths. The SEER 9 registries represent approximately 10% of the US population and contain data on more than 3 million cases of cancer.(44) Furthermore, SEER data are well validated, including consistency of histologic diagnosis.(45) This study also has several limitations. First, the change in morphology classification and diagnostic technology over time might have affected the tumor detection and incidence reporting, so that comparisons in this study with previous studies require caution. Second, because the rarity of infant cancers, small numbers of patients in some types were more likely to fluctuate yearly and lead to unstable statistics. Third, it should be recognized that the SEER only collects data about malignant neoplasms, so that the total frequency of tumors in infants in our study is likely underestimated. This limitation is particularly important for brain tumors. Finally SEER 9 does not have ethnicity variable which prevented us from investigating ethnic differences in cancer.

Conclusions : Our analysis suggests that cancer incidence among infants increased over time in U.S. The increasing trends were largely driven by three cancers - leukemia, germ cell and sarcoma and were present mainly among male infants. The overall survival for infant cancer has improved over the years especially since 1990 for hepatic tumors, lymphoma and leukemia. Further research is needed to explore the potential impacts of genetic, environmental, and perinatal factors for possible explanations for these increased cancer incidence trends.

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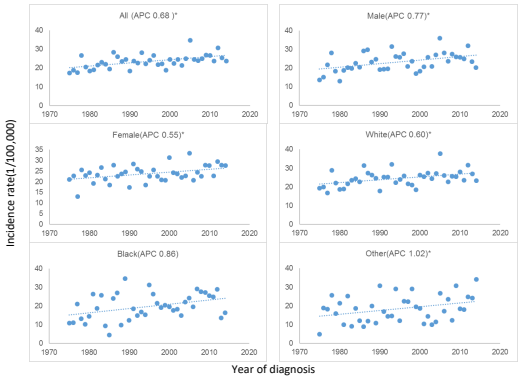

Figure 1 Infant cancer incidence (1/100,000) trend by gender and race in US from 1975 to 2014
(* indicates p<0.05)