Exp Oncol 2022
44, 4, 314–319

Experimental ONCOLOGY

MALIGNANT TUMORS IN PEDIATRIC POPULATION OF UKRAINE: TRENDS AND STRUCTURAL FEATURES

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The creation of a central bank of personalized information of cancer patients, including children, allowed to obtain objective data and establish continuous cancer surveillance in the child population in Ukraine. *The aim* of the study was to analyze the dynamics of cancer incidence (1989–2019) and mortality (1999–2019) based on the 3rd revision of International Classification of Childhood Cancer (ICCC-3). *Materials and Methods*: A study cohort includes 31,537 patients aged 0–19 years at the time of diagnosis in 1989–2019, registered in Ukrainian population. *Results*: The major groups of malignancies in the child population are presented by leukemia, lymphomas, central nervous system (CNS) tumors, epithelial neoplasms, bone cancer and soft tissues sarcomas. There were observed no gender differences in cancer incidence, except germ cell tumors and trophoblastic tumors, gonadal malignancies, as well as some other malignant epithelial neoplasms, with their proportion being twice higher in the female population. Our analysis showed a trend towards increase in the incidence of leukemia, CNS neoplasms, neuroblastoma, trophoblastic tumors and epithelial malignancies; decrease in the incidence of lymphomas and bone neoplasms; stabilization in the incidence of malignancies of liver and kidneys. The dynamic changes in cancer mortality in the studied cohort were observed, namely, the decrease of mortality from leukemias and lymphomas in males (but not in females), along with the increase of mortality from CNS neoplasms, neuroblastoma, soft tissues sarcomas and germ cell tumors, regardless of gender. *Conclusions*: The analysis and presentation of the epidemiological data on children's malignancies implementing ICCC-3 classification for all relevant records in the National Cancer Registry of Ukraine allows for evaluating the major trends of cancer incidence and mortality in Ukrainian pediatric population, taking into account tumor morphology, topography, gender and age.

Key Words: **child population malignancies, ICCC-3 classification, cancer epidemiology, cancer registry.**

DOI: 10.32471/exp-oncology.2312-8852.vol-44-no-4.19109

The morbidity due to malignant neoplasms (MN) in the pediatric population remains one of the most topical and least researched aspects in cancer epidemiology in Ukraine. Officially reported statistics about occurrence of MN in children and adolescents aged 0–19 years appeared in Ukraine since 1989 and on deaths from MN — since 1999, which determined the periods of our studies. Organizational measures aimed at reducing cancer morbidity and mortality in children, improving the quality of life in this age group are possible only if all MN cases are adequately registered. The development and implementation of the information technology of the National Cancer Registry of Ukraine (NCRU), currently covering all cancer cases diagnosed in all regions of Ukraine, is of special importance. Personalized NCRU database allows obtaining objective data and conducting countrywide cancer surveillance both in general and particularly in the pediatric population [1].

Cancer morbidity structure in the pediatric population has its own peculiarities. Most pediatric tumors have embryonic origin. This makes analysis of MN in the pediatric population based on the nosology principle (using 10th revision of International Classification of Disease (ICD-10)) uninformative. Instead, in 1996 International Classification of Childhood Cancer (ICCC) was developed, which is currently used worldwide, focusing more on the tumor morphology rather than topography. ICCC consists of 12 main groups of cancers, divided into 47 subgroups, most typical for the pediatric population. Today, the third revision (ICCC-3) is valid [2]. Majority of scientific studies and international comparisons use ICCC-3 for presenting information about cancer burden in the child population, while in Ukraine until now ICD-10 was traditionally used to present statistical cancer information and comparisons, including pediatric oncology and oncohematology.

Automated coding procedure of pediatric cancers according to the ICCC-3 was implemented in the NCRU software in 2015, making it possible to define ICCC-3 codes for all relevant database records. This allowed NCRU to present Ukrainian data in international studies [3]. If necessary, analysis of pediatric cancer morbidity, mortality and survival in Ukraine could be performed in accordance with ICCC-3 codes in terms of region, gender, age group, time interval and other parameters [4–6]. Due to the NCRU software modernization, the data on cancer incidence in Ukrainian pediatric population were included in "International Incidence of Childhood Cancer, Volume III" by the International Agency for Research on Cancer [2]. The age range of patients selected for the analysis was 0–19 years, determined by the International Agency for Research on Cancer and International Association of Cancer Registries approach used in the project "International Incidence

Submitted: October 27, 2022.
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Abbreviations used: CNS – central nervous system; ICCC – International Classification of Childhood Cancer; ICCC-3 – International Classification of Childhood Cancer, third revision; ICD – International Classification of Disease; MN – malignant neoplasms; NCRU – National Cancer Registry of Ukraine.

of Childhood Cancer", motivated by the relative proximity of cancer behavior in adolescents and children as well as the need for a coordinated strategy for these groups of patients.

MATERIALS AND METHODS

We used the database of the NCRU containing personalized information about all diagnosed cases of MN in the Ukrainian population since 2002 and state reporting data on child morbidity for the period 1989-2001 as well. The NCRU database is collected in regional population-based cancer registries (medical statistics offices at the regional oncology institutions), with annual merging into the national database in the National Cancer Institute. The state-reported data on childhood morbidity and mortality for 1989-2001 were manually coded in ICCC-3 based on ICD-10 codes.

Totally, our study covers 31,537 patients (16,897 males and 14,640 females) aged 0–19 years at the time of diagnosis in 1989–2019 and registered in oncological institutions of Ukraine. Crude and age-specific cancer morbidity and mortality rates per 100,000 of population ($^0/_{0000}$) were calculated for the appropriate age groups.

Data analysis was carried out according to the methods of descriptive statistics adopted in scientific studies of cancer epidemiology. Quality datacheck of the primary information in the NCRU database is based on the principles and methods described elsewhere [1, 2]. Datacheck was performed in cohort of patients diagnosed during the period 2002–2019, when the NCRU database became implemented in all regions of Ukraine and reached 100% coverage. Cancer morbidity and mortality were analyzed within gender and age categories.

RESULTS

The specific proportion of children and adolescents (0–19 years) in the Ukrainian cancer patients' cohort ranged from 1.1% in 1989 to 0.9% in 2019. Mortality ranges equaled 0.7% and 0.4%, respectively [7–9]. The number of cancer patients aged 0–19 was 1,798 in 1989; 1,843 in 1999; 1,460 in 2009; and 1,124 in 2019. The number of patients aged 0–19 who died from cancer was 704 in 1999; 443 in 2009 and 255 in 2019 (the data for 1989 are not available).

Over the past 30 years, cancer incidence among children and adolescents (0–19 years) in Ukraine has increased from $12.2^0/_{0000}$ in 1989 to $15.3^0/_{0000}$ in 2019 with minor fluctuations during the study interval (Fig. 1). The MN mortality rate in the pediatric population over the past 20 years decreased from $5.5^0/_{0000}$ in 1999 to $3.5^0/_{0000}$ in 2019, or by 36.5%, which corresponds to the global trends [10].

The age structure of childhood and adolescent cancers in Ukraine has a stable distribution by age groups (Table 1). The highest specific proportion in morbidity structure is observed in the group of adolescents 15–19 year old.

Special attention was paid to the analysis of the changes in the morbidity and mortality rates of children of different age groups (Fig. 2, 3). The highest MN incidence rate was registered in children aged 0–4 years ($12.27–17.47^0/_{0000}$) and adolescents aged 15–19 ($13.40–19.09^0/_{0000}$), with lower incidence rate values in other age groups. The highest MN mortality

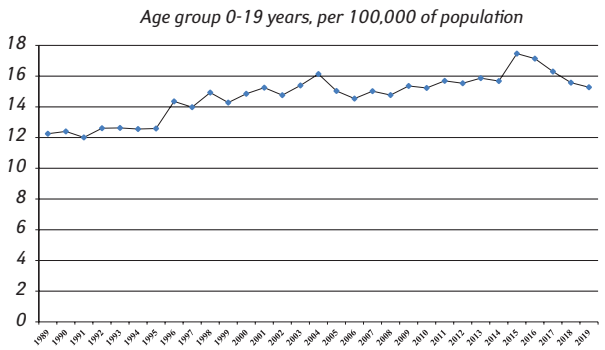

Fig. 1. Cancer incidence in Ukraine, age group 0–19 years, 1989 –2019

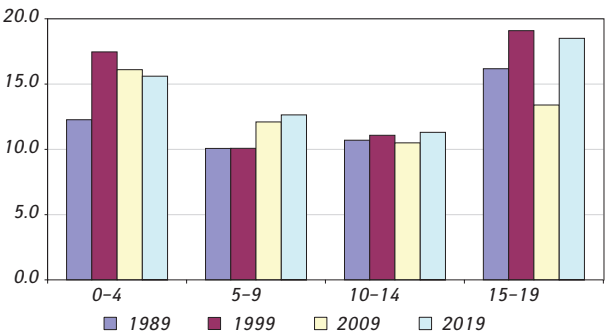

Fig. 2. Age-specific cancer incidence in children and adolescents, Ukraine (per 100,000 of population)

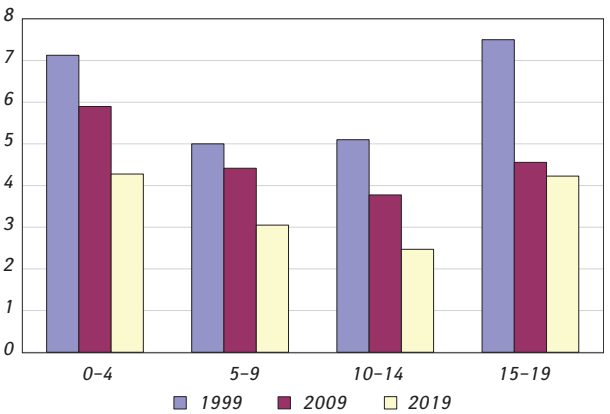

Fig. 3. Age-specific cancer mortality in children and adolescents, Ukraine (per 100,000 of population)

Table 1. Age structure of cancer incidence in children and adolescents

Years	Percentage by age groups				
	< 1 year	1–4 years	5–9 years	10–14 years	15–19 years
1989	4	22	21	22	31
1999	4	18	17	23	38
2009	7	25	15	19	34
2019	5	23	23	20	29

rates as well as the highest morbidity rates were registered in children aged 0–4 years (4.28–7.13$^0/_{0000}$) and adolescents of 15–19 years old (4.23–7.50$^0/_{0000}$).

The structural peculiarities of MN morbidity in children and adolescents are presented in Fig. 4. We found that in the structure of male morbidity (0–19 years old), MN of lymphatic and hematopoietic tissues prevail (53.7% in 1989 and 44.9% in 2019), and brain MN occupy the second place. The top mostly widespread MN in males also include bone tumors, epithelial MN and malignant melanomas. In females (0–19 years old) MN of lymphatic and hematopoietic tissue rank first in the morbidity structure (49.3% in 1989 and 40.1% in 2019), with brain MN, and bone MN being among the top mostly widespread cancers as well. The germ cell tumors, trophoblastic tumors, genital MN as well as soft tissue sarcomas and other extraosseous sarcomas should also be noted as the structurally forming element of morbidity in females (0–19 years old). Epithelial MN and malignant melanomas also significantly contribute to morbidity structure.

Analysis of the MN distribution in the morbidity structure was also provided within different age categories in males and females 0–19 years old (Fig. 5, 6).

In boys below one year, a significant proportion of MN morbidity falls on neuroblastomas and other peripheral nerve cell tumors, central nervous system (CNS) neoplasms and other intracranial and intraspinal neoplasms as well as germ cell tumors, trophoblastic tumors and gonadal neoplasms — in total 38.5% in 2009 and 61.9% in 2019.

In boys aged 1–4 years, leukemias are structurally significant as well as CNS neoplasms and kidney MN. Cancer morbidity in the age group of 5–9 years is mainly formed by leukemias and lymphomas as well as CNS neoplasms. The structure of MN morbidity in males aged 10–14 was characterized by 5.7% increase of lymphoma and leukemia proportion. The proportion of bone MN was also high as compared to that in other age groups (20.8% in 2009 and 20.2% in 2019). In MN morbidity in male adolescents (15–19 years) proportion of leukemia and lymphoma somewhat decreased. In addition, we registered a significant increase of CNS MN (1.7-fold from 2009 to 2019) and germ cell tumors (1.4-fold from 2009 to 2019) morbidity. The categories of "other epithelial MN and malignant melanoma" also occupy a significant place in the morbidity structure in this cohort.

Among girls below 1 year neuroblastoma (20.4% in 2009 and 33.3% in 2019), leukemia and lymphoma (26.5% in 2009 and 27.8% in 2019), kidney tumors, and soft tissue sarcomas dominated in the MN morbidity structure. The proportion of germ cell tumors increased significantly from 2.0% in 2009 to 16.7% in 2019.

In girls aged 1–4 and 5–9 years, the structure of MN morbidity is mainly formed by leukemias, lymphomas and CNS neoplasms — 49.7% and 68.3% in 2009 and 52.7% and 69.1% in 2019, respectively. Soft tissue sarcomas and kidney tumors also significantly contribute — above 20% in each subgroup. MN morbidity in girls aged 10–14 years only slightly differed from the previous age group. Females of the age group 15–19 years showed an increase of lymphoma occurrence (by 8.4% from 2009 to 2019) and decrease in leukemia incidence (by 5.3% from 2009 to 2019). A category "other epithelial MN and malignant melanomas", mainly formed by thyroid cancer played

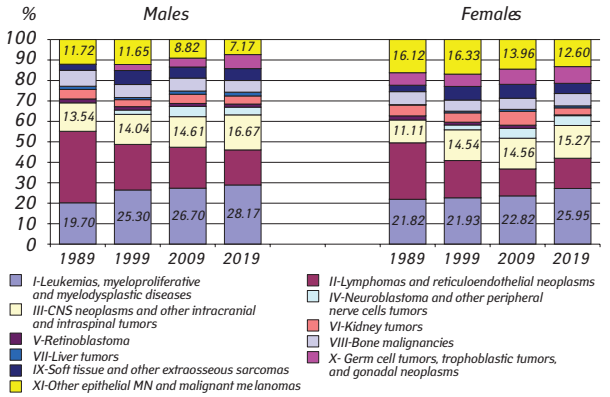

Fig. 4. MN morbidity structure by ICCC-3 codes in childhood population aged 0–19

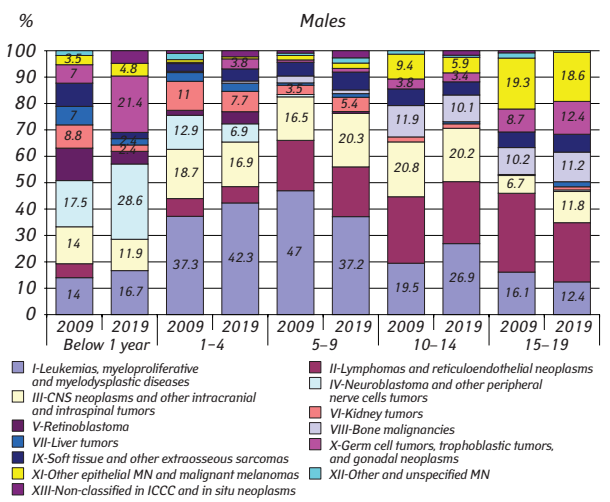

Fig. 5. MN morbidity structure by ICCC-3 codes in age subgroups of male child population

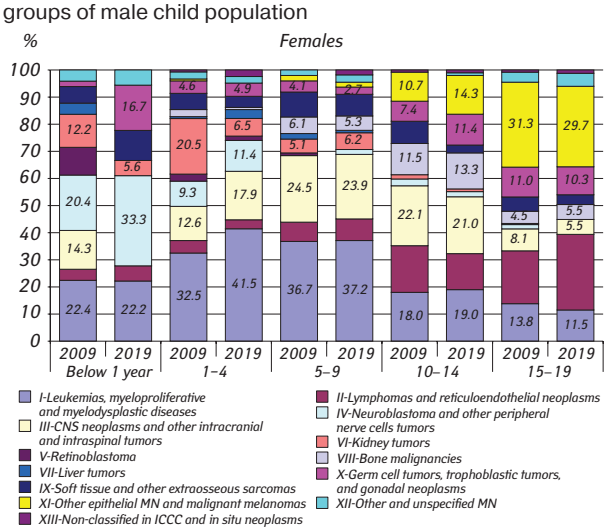

Fig. 6. MN morbidity structure by ICCC-3 codes in age subgroups of female child population

a significant role in the structure of MN morbidity in this age group.

Study of mortality structure showed that among males aged 0–19 years the main mortality causes in 1999 and 2009 were leukemia and lymphoma. In 2019, the corresponding share decreased by 1.4-fold as compared to 1999 (Fig. 7). From 1999 to 2019 in this group of patients mortality from brain tumors increased by 7.9%, from bone MN — by 2.5%, from soft tissues MN — by 3.3%. Proportion of neuroblastoma as a cause of death in children and adolescents almost doubled — from 3.5% in 1999 to 8.8% in 2019.

The mortality structure in females aged 0–19 was mainly formed by leukemia and lymphoma. In 2019, its occurrence was similar, but the proportion of leukemia prevailed (31.6%). Proportion of mortality due to brain tumors in this group of patients increased by 9.5% from 1999 to 2009, but somewhat decreased in 2019. Bone and soft tissue MN in mortality structure in 1999 ranked 4th place with shares of 8.4% and 6.2%, respectively; in 2009 the proportion of bone MN decreased 2.2-fold, while mortality from soft tissue MN increased by 1.4 times. In 2019, these indices slightly decreased. A significant place in mortality structure in this cohort is occupied by germ cell, trophoblastic and gonadal MN — from 4.4% in 1999 to 7.9% in 2019.

The peculiarities of mortality structure from MN within gender and age categories were also studied (Fig. 8, 9). It was found that in 2009 the most common causes of death from MN in boys under one year were leukemia, liver tumors, neuroblastoma, and CNS MN — 84.7% in total. In 2019, redistribution of mortality causes in this subgroup was registered due to decreased proportion of leukemias with simultaneous increase in neuroblastoma and germ cell MN. In boys aged 1–4 years, 69.8% of deaths in 2009 were caused by leukemias, CNS tumors, and neuroblastomas, while in 2019 the main cause of death were CNS tumors, leukemia, soft tissue sarcomas, liver cancer, and germ cell tumors — 80.0% in total. Mortality structure in boys aged 5–9 and 10–14 in 2009 was mainly constituted by leukemias, lymphomas, MN of CNS and soft tissues sarcomas, In 2019 the general scape mainly did not change. Mortality from cancer among males aged 15–19 in 2009 was caused by leukemias, lymphomas, MN of bones, soft tissues and CNS in 82.2% of cases, and 86.7% — in 2019.

In 2009 and 2019, leukemia, neuroblastoma, and CNS MN were the most common causes of cancer-related death in girls under 1 year of age (72.8% *vs.* 50.1%, respectively). Among girls aged 1–4 years, 72.0% of deaths in 2009 were caused by leukemias and lymphomas, CNS tumors and neuroblastomas. In 2019, 95.4% of girls with MN died from CNS tumors, leukemias, lymphomas, liver cancer, and germ cell MN. Mortality structure in the subgroup of girls aged 5–9 and 10–14 years in 2009 was mainly formed by leukemias and lymphomas and CNS MN and soft tissues sarcomas. In 2019, there was an increase in the proportion of neuroblastoma and bones MN in these age categories. Mortality from cancer in female subgroup aged 15–19 in 2009 was caused by leukemias, lymphomas, bones, soft tissue, CNS and germ cell MN — 85.2% of cases. In 2019, 88.8% of female adolescents of this age died from leukemias, cancers of CNS, bone, soft tissue sarcomas, germ cell and other epithelial MN.

DISCUSSION

It has been shown that the incidence of MN in the pediatric population has a constant upward trend with a moderate decrease in the mortality rate. Childhood

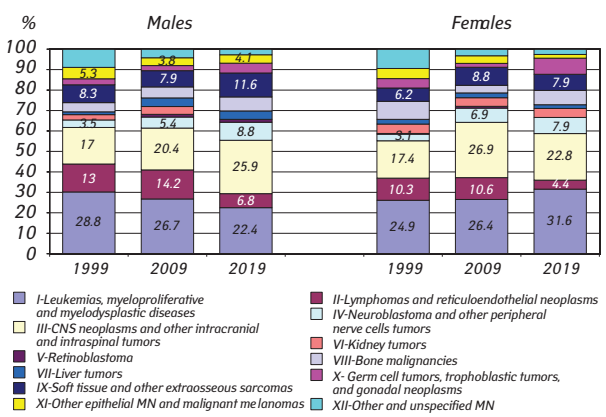

Fig. 7. Cancer mortality structure by ICCC-3 codes in childhood population aged 0–19

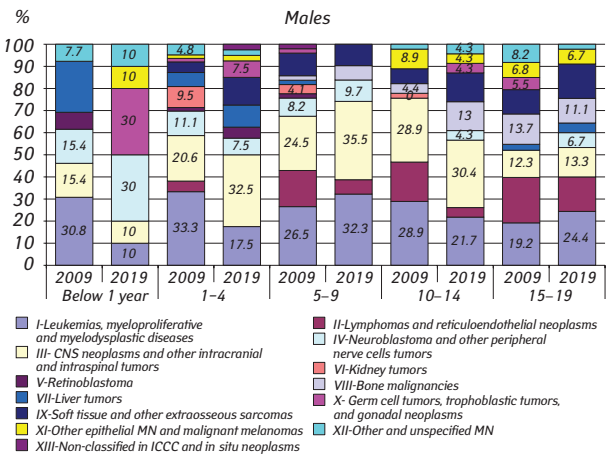

Fig. 8. Cancer mortality structure by ICCC-3 codes in age subgroups of male child population

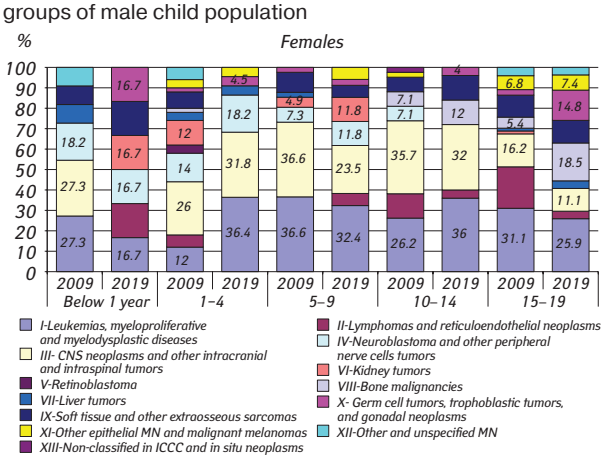

Fig. 9. Cancer mortality structure by ICCC-3 codes in age subgroups of female child population

incidence of MN is characterized by peak values in the first 5 years of life with the highest age-specific child mortality from MN in this age group. The highest MN morbidity rate is registered in children of the first year of life with further insignificant decrease in morbidity rates within 1 to 14 years. At the age of 15–19, morbidity rates begin to increase. Although the absolute number of new MN cases among children and adolescents in Ukraine gradually decreased, as well as registered mortality value, MN incidence rate per 100,000 of Ukrainian children and adolescents (0–19 years) over 30 years has increased by 1.25 fold.

In general, over the last 30 years, there were no noticeable fluctuations in the age structure of the MN morbidity in children and adolescents. Adolescents of 15–19 years consistently hold the highest proportion in age structure of morbidity — from 29.0% to 38.4% while other age subgroups show an even distribution — from 15% to 24%.

The MN morbidity in the pediatric population is formed mainly by leukemias, lymphomas, CNS tumors, epithelial MN, bone MN, and soft tissue sarcomas. It should be noted that no significant gender difference was found in childhood morbidity structure, except for embryonal cell tumors, trophoblastic and gonadal MN, as well as a group of "other epithelial MN", which is twice more frequent in the female population.

Study of the dynamics of cancer epidemiological indices according to ICCC-3 revealed a clear trend towards increase in share of leukemia, CNS MN, neuroblastomas, trophoblastic and epithelial MN cases, the decrease of lymphomas and bone tumors, and stabilization of share of liver and kidney MN. In addition, significant dynamic changes in mortality from MN in the studied cohort are observed, namely, decrease of mortality from leukemias and lymphomas in males (unchanged in females), along with increase in share of CNS MN, neuroblastoma, soft tissues sarcomas and germ line tumors, regardless of gender.

Our study analyzes the trends of cancer dynamics in the Ukrainian pediatric population, taking into account tumor site and morphology, gender and age. Today, we have all the prerequisites and technical capabilities for detailed analysis of the child cancer morbidity, mortality and prevalence, which allows comparison with the international data based on ICCC-3.

In conclusion, it should be said that implementation of cancer control measures and epidemiological studies would not be possible without appropriate population-based cancer registry based on the international standards and recommendations [1]. Sustainable functioning of the NCRU is a prerequisite for the complete and comparable cancer morbidity and mortality surveillance in a pediatric population of Ukraine, providing a much better opportunity to retrieve the most objective information about oncological care for the child population.

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ЗЛОЯКІСНІ НОВОУТВОРЕННЯ В ДИТЯЧІЙ ПОПУЛЯЦІЇ УКРАЇНИ — ТРЕНДОВІ ТА СТРУКТУРНІ ОСОБЛИВОСТІ

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Створення центрального банку персоніфікованої інформації про онкологічних хворих, у тому числі й дітей, дозволило отримувати об'єктивні дані та здійснювати постійний контроль за розвитком онкологічної ситуації в дитячій популяції України. ***Мета***: Проаналізувати динаміку захворюваності на рак (1989–2019 рр.) та смертності (1999–2019 рр.) дитячого населення України за міжнародною класифікацією дитячих злоякісних новоутворень 3-го перегляду (International Classification of Childhood Cancer — ICCC-3). ***Матеріали та методи***: Когорта дослідження становила 31 537 хворих віком від 0 до 19 років на момент встановлення діагнозу в 1989–2019 рр., що перебували на обліку в онкологічних закладах України. ***Результати***: Захворюваність на злоякісні новоутворення (ЗН) дитячого населення формується перш за все за рахунок лейкемій, лімфом, пухлин центральної нервової системи (ЦНС), епітеліальних новоутворень, злоякісних пухлин кісток та сарком м'яких

тканин. Не виявлено виражених гендерних відмінностей у структурі дитячої захворюваності, окрім пухлин із зародкових клітин, трофобластичних пухлин та гонадних ЗН, а також інших епітеліальних ЗН, питома вага яких у структурі ЗН дівчаток є удвічі більшою, ніж у хлопчиків. Вивчення динаміки онкоепідеміологічних показників за ICCC-3 виявило тенденцію до зростання захворюваності на лейкемії, новоутворення ЦНС, нейробластоми, трофобластичні пухлини та епітеліальні ЗН; до зниження рівня захворюваності на лімфоми та пухлини кісток та стабілізацію захворюваності на ЗН печінки та нирки. Прослідковуються виражені динамічні зміни у смертності від ЗН в досліджуваній когорті — зменшення кількості лейкемій та лімфом у хлопців за незмінної величини показника у дівчат; зростання питомої ваги новоутворень ЦНС, нейробластом, сарком м'яких тканин та пухлин із зародкових клітин незалежно від статі. ***Висновки***: Ретельний аналіз даних став можливим завдяки впровадженню інформаційної технології Національного канцер-реєстру (НКР) на всій території України. Як міжнародний стандарт аналізу й представлення епідеміологічних даних про ЗН дитячого віку в роботу НКР було імплементовано нову версію ICCC-3, що дозволяє формувати коди ICCC-3 для всіх записів, наявних в НКР, представляти дані України для міжнародних досліджень, а також проводити аналіз дитячої захворюваності, смертності та виживаності за класифікацією ICCC-3 в розрізі регіонів, статево-вікових груп, часових інтервалів та інших параметрів.

***Ключові слова*:** злоякісні новоутворення дитячого населення, класифікація ICCC-3, епідеміологія раку, канцер-реєстр.