Association of European Union funding for pediatric cancer research on pediatric cancer burden in the European Union

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ASSOCIATION OF EUROPEAN UNION FUNDING FOR PEDIATRIC CANCER RESEARCH ON PEDIATRIC CANCER BURDEN IN THE EUROPEAN UNION

Diploma Thesis

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Assist. Prof. Shelly Pranić

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ABBREVIATIONS

ALCL – anaplastic large cell lymphoma

AJCC – American Joint Committee on Cancer

CCSS – Childhood Cancer Survivor Study

CT – computerized tomography

DALYs – disability adjusted life years

EMA – European Medicines Agency

ERN PaedCan - European Reference Network for Pediatric Oncology

ESCP - European Standard Clinical Practice

EU – European Union

FDA – Food and Drug Administration

GNI – gross national income

HDI – human development index

HIC – high-income country

IAES - International Atomic Energy Agency

IHDI – inequality-adjusted human development index

JARC - Joint Action on Rare Cancers

LMIC – low-middle-income country

MRI – magnetic resonance imaging

PET – positron emission tomography

PIP – pediatric investigation plan

UNHD - United Network for Human Development

WHO – World Health Organization

1. INTRODUCTION

Survival of children with cancer has greatly improved over the past few decades due to progressing technologies, diagnostic techniques, and treatments resulting in an approximately 80% cure rate (1) and a 65% decline in death rates from 1970 to 2016 in children ages 0-14 (2) despite childhood cancers mostly being caused by non-modifiable risk factors such as genetics and birthweight (3). However, in the European region, mortality rates still range from nine percent to 57% (1) due to shortcomings and inequality in specialized centers, equipment, and personnel specifically dedicated to screening, diagnosis, treatment, and palliation of pediatric cancer patients. Further complexities of pediatric cancer patients include the aftermath of cancer treatment and potential disability later in life as they become adults that may require monitoring, rehabilitation, or further treatment, all of which affects them and their families both financially and psychologically (4). The definitions below have been provided for terms that are necessary for the understanding of the pediatric cancer disease burden and inequality in funding and research.

Definitions

Disability Adjusted Life Years (DALYs)

Disability Adjusted Life Years are the sum of the years of life lost due to premature mortality (YLLs) and the years lived with a disability (YLDs) due to a certain disease in a population. Using DALYs gives a wider picture of disease burden as it includes the amount of time a certain population has spent in disability or "states of less than full health" (World Health Organization), not only mortality (5) and therefore allow researchers and policymakers to better understand which areas require improvement (i.e., research, development, etc.) (6). DALYs tend to be higher in more severe illnesses (7).

Human Development Index (HDI)

The human development index is a multi-faceted measure of a country's development. It takes into consideration life expectancy at birth, education (years of schooling for adults and children), and standard of living (gross national income per capita [GNI]). This measure can be used to assess national policy and decision making. For example, two countries can have the same GNIs per capita, but different HDIs (8).

Inequality-Adjusted Human Development Index (IHDI)

This measure accounts for inequalities within in a country's HDI. For example, when IHDI equals HDI, there is no inequality across the population. However, as inequality rises, the IHDI value will drop below the HDI (9).

High Income Country (HICs)

A high-income country has a gross national income per capita over 12.055 USD (10).

Low Middle-Income Country (LMICs)

A low middle-income country has a gross national income per capita between 1.036 and 4.045 USD (11). Bulgaria is the only European Union member state that falls under this category (12).

Pediatric Investigation Plan (PIP)

The objective of pediatric investigation plans is to regulate and support the research and authorization of medicines for children to ultimately increase the availability of drugs that are specific for the pediatric population (13). A PIP for a drug includes the full age range, disease overview, chemical formulation, all study data (both clinical and non-clinical), strategies for formulation (i.e., route of administration), and planned clinical trials with outcome predictions. The European Medicines Agency (EMA) Pediatric Committee assesses a submitted PIP to determine if it is acceptable. This procedure takes approximately nine to 10 months. Waivers to a PIP can be administered if a drug is deemed unfit for children, the disease that the drug is intended for occurs only in adults, or if there is not enough significant therapeutic benefit of the drug (14).

Orphan Drug

An orphan drug is used to treat a rare disease (less than or equal to five in 10,000 people affected) that is chronically debilitating or life-threatening. Such drugs are "unlikely to generate sufficient profit to justify research and development…" (EMA)(15).

1.1. Etiology of Pediatric Cancers

Cancer, in both children and adults, is a result of uncontrollable cell growth due to various mutations of a cell's DNA. Certain genes play a very important role in oncogenesis, such as oncogenes that have the potential to cause cancer if mutate, tumor suppressor genes

that code for proteins that regulates cell division, growth, repair, and survival and DNA repair genes that fix mistakes in DNA or cause the cell to die otherwise to avoid dysfunction. Essentially, when functioning normally, these genes prevent cells from growing or dividing uncontrollably. Therefore, mutations and subsequent dysfunction can promote uncontrollable cell growth and division and thus form a tumor (16).

Most adult cancers have lifestyle-related risk factors (i.e., smoking, obesity, alcohol intake, etc.) are a result of the aging process or both (17). These factors do not play a significant role in a childhood cancer diagnosis since they take many years to manifest. Mutations can be inherited from a child's parents. These inherited DNA changes can increase their risk for developing cancer or cause a syndrome that is associated with cancer (18). However, only five percent of childhood cancers are caused by inherited mutations (19). Most pediatric cancer cases are a result of acquired mutations that occur early in the child's life or even before birth. The causes of these acquired mutations are not known and are likely randomly occurring. Environmental factors such as radiation exposure and parental smoking exposure are being explored as possible risk factors, but concrete evidence is still needed (18).

1.2. Diagnosis

The path of diagnosing childhood cancer begins with a child displaying non-specific signs and symptoms warranting medical attention (20). Symptoms may include an unusual lump, paleness, fatigue, easy bruising or bleeding, persistent pain in a certain area of their body, unexplained fever, frequent headaches, vomiting, sudden vision changes, enlarged lymph nodes, sudden weight loss, and loss of appetite (21). After a physical exam and going through the child's medical history with the parent, a healthcare professional might order laboratory tests such as a complete blood count, blood chemistry, and urine test, or other tests such as imaging and scans (i.e., X-ray/fluoroscopy, ultrasound, CT scan, PET scan, MRI, etc.), lumbar puncture, or even bone marrow aspiration and biopsy depending on the physician's suspicions based on the patient's presentation and earlier tests.

For most cancers, biopsy is needed to confirm diagnosis. After a tissue sample is taken and sent to be analyzed by pathology, a treatment plan can be made (20).

1.3. Epidemiology and Sociodemographic Data

Childhood cancer affects about 400,000 children and adolescents ages 0-19 years old each year (1) and is the second leading cause of death in children ages 0-14 years old (22). In Europe, one in every 300 children are at risk for developing cancer before the age of 19.

European statistics in 2020 estimated that childhood cancer affected 16,000 children per population and was the cause of 2,000 deaths per population that year (23). The average (standard deviation) age of cancer diagnosis is six years for children (ages 0 to 14) and 17 years for adolescents (ages 15 to 19) with an overall average of 10 years old (24).

Disability adjusted life years (DALYs) further quantify the burden of childhood cancer, as 11.5 million DALYs were estimated globally due to childhood cancer in 2017, 97.3% of which are attributed to death whereas 2.7% attributed to years lived with disability (25). Despite improving survival rates, incidence is still on the increase – 0.8% per year since 1975 (24).

The most common pediatric cancers in decreasing order of prevalence are leukemia, brain and central nervous system tumors, lymphoma (Hodgkin and non-Hodgkin), neuroblastoma, nephroblastoma, rhabdomyosarcoma, retinoblastoma, and bone cancer (26).

1.3.1. Gender

The risk for developing cancer is genetically similar in both boys and girls. Sex chromosomes are responsible for cancers such as breast or prostate – both of which are extremely rare in children. However, discrepancies can still be seen among genders. The International Agency for Research on Cancer estimated a global ratio of boys to girls being diagnosed with cancer is 1.37, meaning that four boys are diagnosed for every three girls diagnosed (27). Boys with cancer in HICs, tend to have poorer outcomes than girls, whereas data from low- and middle-income countries (LMICs) suggests that boys are registered more frequently than girls, implying that there is a higher population of girls with cancer remaining underdiagnosed. Detection of cancer is a crucial initial step when determining survival in terms of timely staging and treatment thereafter. Due to potential under-recording by cancer registries, the yearly incidence of childhood cancer could be as much as 60% higher because of the lack of initial "capturing" of the cancer (WHO) (4).

1.3.2. Financial Burden

High-quality health care is oftentimes difficult to access in countries with lower incomes (4). The Joint Action of Rare Cancers (JARC) defines "access" as being able to secure prescriptions on time and with out-of-pocket costs within an affordable budget in patient (28). A 2016 study found that a higher percentage of the population paid for health care services out of pocket in low- and upper-middle income countries than in higher income countries. Inefficiency and general burden thus prompt individuals to neglect health issues that need

proper care, and in the case of children, leads families to abandon treatment as they fail to make ends meet (4).

According to a survey conducted by the JARC in 2020, financial accessibility to newer and more expensive medicines and appropriate pricing and reimbursement strategies sensitive to the pediatric population are greatly needed (28).

A study by Merrill et. Al, found that childhood cancer treatment costs an average of 700 USD higher than that of adults. Furthermore, the study calculated the costs of hospitalization for leukemia in children and in adults, which resulted in pediatric leukemia costing 15.500 USD higher. Caregivers of pediatric cancer patients are often faced with difficulties in their day-to-day employment which ultimately impacts the household incomes. Combined with high medical costs, families experience great financial burden which has the potential to influence treatment decisions (29).

Childhood cancer survivors are oftentimes at risk of secondary health conditions and complication related to their disease or the treatment thereof that can last through their lives. This also adds to the financial burden as their medical needs do not stop after their primary cancer diagnosis (29).

1.3.3. Factors contributing to inequality in cancer management

Throughout Europe, there is about a 20% difference in children's survival rates (30). From 2005 to 2007, the estimated five-year survival from rhabdomyosarcoma was almost approximately 30% higher in northern Europe compared to eastern Europe (4). Factors that contribute to potential avoidable death in regions with such insufficiencies include errors in diagnosis, inaccessibility to care, neglect of treatment, toxicity to treatment, and relapse of disease (1). Despite higher survival rates, countries with higher human development index (HDI) scores showed greater incidence rates than countries with lower HDI scores. This can be attributed to insufficient diagnosis and under-recording of possible cancer cases in lower-scoring countries and, therefore, providing an under-estimate of the general childhood cancer disease burden (4).

In 2017, 82.2% of childhood cancer DALYs occurred in countries with low, low-middle, or middle socio-demographic indexes (25). The JARC found that in central and Eastern Europe, "there are substantial inequalities in access to the best standard treatment, care, and research," (30). In the EU, it has been shown that countries with the highest childhood cancer rates tended to be Bulgaria, Portugal, Hungary, Czech Republic, Slovakia, and Poland, and those with the lowest mortality rates include Austria, the UK, Germany, the Netherlands, and

Finland, all of which have higher GNIs and HDIs than the former (3). Furthermore, declines in mortality have been shown to a greater extent in northern countries that have higher GNIs compared to countries in southern and eastern Europe with lower GNIs (31).

To depict the overall shortage of essential cancer medicines for children and adolescents compared to GNI per capita of each European country, Figure 1 below shows shortages existing to a greater extent in countries with lower GNIs. However, they still exist in wealthier countries as well.

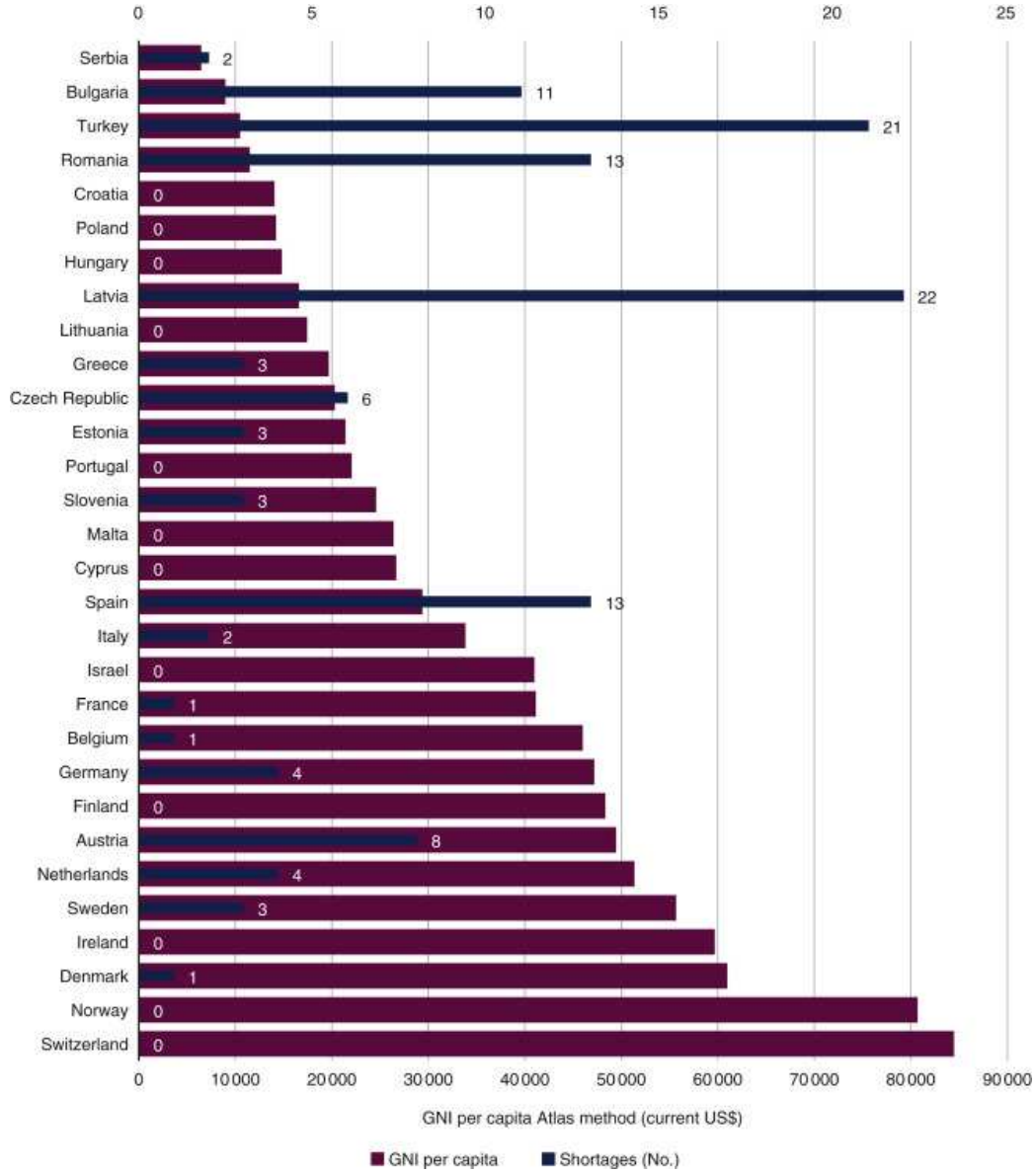

Figure 1. The shortage of essential medicines for all types of cancer for children and adolescents compared to the GNI per capita of each European country (28).

For example, as seen above, Spain and Romania differ greatly in their GNI values and according to the United Network for Human Development (UNHD) reports, they also have differing HDI values of 0.901 and 0.808, respectively (32). However, both countries experience

the same amount of medicine shortage. The UNHD reported that their Inequality-adjusted Development Index (IHDI) values as of 2010 are similar, with Spain scoring 0.782 and Romania 0.726, suggesting that healthcare inequality, as seen in figure one, can contribute to overall inequality in high-income countries (HICs) (9).

Deficiencies in laboratory, imaging, and pathology services in these countries also attribute to incorrect staging and/or diagnosis and, therefore, leading to mismanagement of a given child's disease. Currently, the IAEA recommends "approximately one megavoltage external beam radiotherapy machine per 180 000 people", a criterion which only 20 of the 53 WHO European Region Member States meet (4). A 2016 survey on standards of care in European pediatric oncology centers found that 18 out of 35 countries that provided responses claimed that they have "full diagnostic services, all necessary drugs, and supportive care" (34).

Even in high-income countries, rural areas still experience inequality in care due to decreased access to resources, education around the health of their children, and ability to "navigate" through health services that are potentially generally insufficient in their countries. Studies in Denmark, Norway, and Hungary showed an increase in incidence in cancer among children from higher income families and likewise a higher survival rate than children of lower income families due to better education and involvement of the parents that cannot only influence the initial care, but also guide proper compliance to the therapy. Fragmentation and rejection of new treatments that are too expensive also contribute to inequalities in these countries where a portion of the population still cannot access the care that they need.

According to surveys conducted by the International Atomic Energy Agency (IAES) from 2010-2013, "multidisciplinary treatment decision making became less common as economic resources fell and, in some countries, coordination with pediatric oncology seemed poor". The IAES also stated that services such as radiotherapy patient hostels and free transportation was significantly lacking in those areas as well as rates of follow-up of adults who are childhood cancer survivors to monitor and treat late effects of treatment or disease (4).

Palliative care inequalities are also seen across areas of varying incomes. LMICs have a higher population of children needing palliative care services, however, they are less available to them (35).

The European Reference Network for Pediatric Oncology (ERN PaedCan) was developed in 2017 as an initiative to facilitate cross-border healthcare for all pediatric cancer patients. ERN PaedCan aims to improve survival and quality of life by means of knowledge exchange amongst specialists throughout Europe via "virtual tumor boards". The network advocates for high-quality and cost-effective care for all pediatric cancer patients in the EU no

matter which country they come from by providing them and their parents a “roadmap” of specialist healthcare centers throughout the EU and proper education all about their treatment abroad (36). As of 2023, ERN PaedCan has organized several educational programs for oncology professionals as well as developed the European Standard Clinical Practice (ESCP) Guidelines. The ESCP Project brings together experts in each field to endorse recommendations for standard treatments to be available for all pediatric cancer patients in Europe, especially if there are none existing on the national level or no clinical trials are available (37). The ERN PaedCan sets an example that there is potential for the childhood cancer inequality gap to be closed through proper multi-disciplinary cooperation and education.

1.4. Treatment

Several different treatment modalities are considered after a cancer diagnosis, and they include surgery, chemotherapy, radiotherapy, immunotherapy, and stem cell transplantation. Most of the time, a combination of these therapies is necessary. The goal of treating cancer with these options is to make tumors smaller for more successful surgical removal (neoadjuvant), kill cancer cells directly and prevent recurrence (adjuvant), and to alleviate symptoms in cases of incurable disease (palliative) (38).

1.4.1. Side Effects

Chemotherapy is a group of drugs that disrupt the cell division process that takes place in cancer cells and essentially kills them (39). These cytotoxic drugs are an essential part of evidence-based practice in the treatment of pediatric cancer and attribute to the 80% disease-free survival at 5 years in childhood cancer patients (28). Side effects are a result of the drug damaging normal cells along with the cancer cells. Cells with high division rates such as those of the lining of the mouth and gut, bone marrow, and hair follicles are affected the most and therefore produce the most common side effects of fatigue, nausea, hair-loss, anemia, and infections. Organs such as the kidney, liver, heart, testicles/ovaries can also be affected by chemotherapeutic drugs and can result in long-term damage and manifest as late side effects appearing later in life (39).

Like chemotherapy, radiotherapy can also affect healthy cells and the patient may experience symptoms depending on the area of the body that is irradiated. There are several different types according to the location of the tumor.

External beam radiation therapy is the most common modality that uses a linear accelerator to direct electrons to a target tissue. The electrons damage tumor cell DNA and therefore induce

cell death (40). Side effects are similar to chemotherapy with the addition of skin reactions and developmental problems if the brain is the target of therapy (41).

Both chemotherapy and radiotherapy carry a small chance of the patient developing a secondary cancer later in their lives (44).

Another type of radiation therapy is proton beam radiation therapy that has the advantage of adequate delivery at a reduced dosage and with higher precision, thus reducing damage to healthy tissue (42). However, secondary radiation-induced malignancy rates are only slightly lower with this modality making the benefit for a child to travel distances to a proton facility questionable as it can impose social and financial hardships on them and their families (43).

1.4.2. Transition into Adulthood

With increasing survival rates comes a greater number of individuals living long enough to experience late side effects of their childhood cancer disease course (45). Two-thirds of childhood cancer survivors have late-occurring side effects due to their treatments, half of which are considered severe (46). Pulmonary, cardiac, endocrine, and nervous system morbidity make up most of the conditions that contribute to the 95.5% prevalence of chronic conditions amongst cancer survivors 35 years after original diagnosis (47).

As of 2016, over 83% of childhood cancer patients have become five-year survivors, 20-80% of which are left with disabling or life-threatening conditions that negatively impact their quality of life. An analysis of the Childhood Cancer Survivor Study (CCSS) showed that younger survivors "report a quality of life comparable with general population individuals who are approximately two decades older," (48). A questionnaire sent to survivors within the Swiss Childhood Cancer Survivor Study and their siblings in 2013 found that survivors "scores significantly lower than their siblings in physical function, role limitation, and general health," (49).

These chronic conditions have been associated with neurocognitive deficits that can therefore negatively impact the quality of life of these adults in terms of education and employment (50). The strongest predictor for long-term neurocognitive deficits is cranial external beam radiation therapy (51), which is an extremely important treatment option as one-third of childhood malignancies are brain tumors. Long-term brain function deficits can present as confusion and poor memory. Sensorineural hearing loss (SNHL) has also been associated with cranial radiation therapy. A 2016 study found that 14% of patients developed SNHL after their therapy, 65.5% of which reported with a continued decline in hearing sensitivity on

follow-ups. Ototoxicity risk is further elevated when combining radiotherapy with platinum-based chemotherapy such as cisplatin (52), which is “an important component of pediatric chemotherapy regimens” used to treat several types of tumors (53).

Patients receiving radiotherapy are also at risk of radiation necrosis, secondary tumor development, and endocrinopathies due to damage to the hypothalamus, pituitary gland, and other endocrine organs in case of total body, thoracic, or abdominal radiation. Endocrine disorders affect up to 50% of childhood cancer survivors more than 5 years after treatment (54). The St. Jude Lifetime cohort study compared the prevalence of endocrine deficiency between children with brain tumors who underwent cranial radiation and those who did not. The results showed a significant increase in prevalence amongst the irradiated group (47). Endocrinopathies can manifest as short stature, dwarfism, hypothyroidism, low bone mineral density, reproductive disorders, and metabolic syndrome. These conditions can predispose patients to various complications such a reduced exercise tolerance, hypertension, dyslipidemia, obesity, osteoporosis, infertility, and diabetes – all of which can chronically impact their qualities of life (54). Furthermore, brain surgery, along with irradiation, also could lead to irreversible damage to healthy and developing brain tissue and can result in CNS dysfunction, seizures, and cognitive impairment (55).

Chemotherapy is also associated with endocrine disturbances by causing direct damage to endocrine organs, mainly the gonads, manifesting as Leydig and germ cell dysfunction in boys and ovarian failure and premature menopause in girls (56).

As survival rates have increased, light has been shed on long-term psycho-social outcomes on surviving the experience of cancer as a child. Pediatric cancer patients experience not only physical pain, but also low mood, anxiety, fear, and low self-esteem throughout their disease course (84). Symptoms of post-traumatic stress (PTS) are common among survivors and can reduce their quality of life and limit their educational and occupational potential (57). They include irritability, unable to think clearly, sleeping problems, isolation, loss of interest, and negative feelings such as fear and guilt (58).

Frequent hospital visits, painful treatments, health scares, physical limitations, and disruption of day-to-day life, and the constant fear of re-occurrence are factors making a child vulnerable to PTS (57).

A 2021 Nordic cohort study found that the odds for healthcare-related unemployment at age 30 were significant in childhood cancer survivors with the most prominent factors being diagnosed with cancer younger than 15 years old and surviving a CNS tumor, a history of

cranial irradiation, and hospital contacts at ages 25-29. The risk of unemployment was two times higher than the general population or sibling comparisons (59).

Palliative care is still of importance as children transitioning into young adulthood could still be battling life-threatening conditions as well as the aftermath of their battles. Therefore referrals, transferring of care, and altering therapeutic plans is often needed throughout the child's future (60).

Under the EU4Health Programme 2021-2027, the EU co-funded the SmartCare project which proposes a Cancer Survivor Smart Card. As part of Europe's Beating Cancer Plan, this mobile application will facilitate improvement in the quality of life of cancer survivors by allowing easy access to treatment summaries and sharing with healthcare professionals. Such tools would provide a personalized experience that allows patients to better communicate with their physicians or nurse to get the care they need (61).

1.4.3. The Drug Industry and Regulation

Less than two-thirds of drugs on the WHO Model List of Essential Medicines for Children were "always available" in at least 90% of countries surveyed in 2017. Only five of those medicines essential for treating the most common childhood cancer-acute lymphoblastic leukemia- were described as "always available" in only 60% of the countries (28). Due to the rarity of pediatric cancers, traditional research methods such as population-based randomized clinical trials are not always suitable as sample sizes are limited. Thus, important information cannot be provided to stakeholders such as regulatory authorities responsible for drug approval (62). Furthermore the "lack of market initiative" for pharmaceutical companies further blocks progress in drug development as pediatric cancer is not considered profitable due to its rarity and complexity (63). In 2007, Europe became included in the Pediatric Medicine Regulation and began to work towards bringing better medicines for children, including new anticancer drugs (64). However, to be deemed suitable for children in terms of efficacy and safety, such drugs must undergo studies and comply with pediatric investigation plans (PIPs). Despite 45 oncological PIPs being approved after five years of implementation in Europe, the death rate of children with cancer in Europe still suggests a deficiency of new drugs, especially since none of the PIPs included malignancies that occur exclusively in children (65).

Drugs in early-phase clinical trials could potentially save children with relapsed or aggressive malignancies, and only 10% of the patients who need them can currently receive them as they are only available in special centers in a few countries and often require the patients' families to pay out-of-pocket (4).

The European Medicine Agency (EMA) is greatly responsible for decisions regarding PIPs and waivers or changes thereof. Factors taken into consideration include indications of drug use, age ranges and long-term follow-ups of patients. A drug PIP may be waived on several grounds including being ineffective or unsafe for children, only indicated for adult conditions, or being not more beneficial than existing therapies (13). In 2012, 45 PIPS have been approved for 43 different oncological drugs, 15 of which are for leukemias/lymphomas, 13 for solid tumors, and six for brain tumors. Nine PIPs were concerning supportive care for side effects of treatment such as nausea, vomiting, thrombocytopenia/anemia, hyperuricemia, etc. A number of these PIPs have been approved for children, but only for extremely rare conditions such as chronic myeloid leukemia, melanoma, gastrointestinal stromal tumors, and thyroid cancers. From 2007-2012, the EMA approved 28 new oncological drugs, 26 of which are potentially useful for pediatric cancers. However, 14 were waived on grounds of adult indication and only four were approved at the end (66). Further studies have found that the development, application, and approval process for PIPs has "resulted in the unintended delay in the initiation of early-phase clinical trials" (67).

The United States offers more drugs to be available for early-phase clinical trials through the Cancer Therapy Evaluation Program that develops drugs that are "provided free by pharmaceutical industries". "Many parents are tempted to go to the United States to have their child participate in a clinical trial with innovative drugs that may represent a 'last hope' for many families" (28). One notable example is the drug crizotinib, which is an inhibitor of the MET-ALK oncogene pathway that is used to treat lung cancer with EML4-ALK translocation, a malignancy that is not found in the pediatric population. However, ALK mutations are also found in in over 60% of anaplastic large cell lymphoma (ALCL) and in eight to 10% of sporadic neuroblastoma. Because of its adult indications, crizotinib was waived in both the EU and the US. However, in 2010, the Best Pharmaceuticals for Children Act was passed, and the US Food and Drug Administration (FDA) requested a phase 1 trial of crizotinib which showed responses and prolonged complete remissions in ALK-mutated ALCL and neuroblastoma patients. This shows that regulation driven by adult indication overlooks potential for drugs to be available for the pediatric population. Furthermore, looking at current anticancer drugs, 90% are already used in both children and adults. For example, anthracyclines, cyclophosphamide, cisplatin, and carboplatin are used to treat neuroblastoma, a childhood malignancy, as well as breast, ovarian, and lung cancers which are mainly adult malignancies. If the pediatric regulation was introduced earlier, when these older drugs were

still being approved, a waver would have been obtained on the grounds of adult indication and none of them would be available for pediatric use (60).

Seventy-five percent of rare diseases affect children as most of them start in childhood (68). Considering that only five percent of rare diseases have official treatment options, physicians often resort to using off-label medicines that do not have direct indications in children (69, 70). In 2004, an investigation performed by the EMA highlighted that adverse reactions are more frequent and more severe in pediatric off-label drug use (70). Incentives such as fee exemption and grants are rewarded to companies in the European Union for the development of orphan medicines for such conditions based on the opinions of the EMA, and then must get further authorization such as marketing and maintenance of orphan status, both of which depended on the individual companies. Since the implementation of the Orphan Regulation in 2000, 57% of the 2121 orphan-designated drugs were approved for both adult and pediatric use, and only 12% exclusively for pediatric use. In 2018, 164 of the medications were granted marketing authorization where only six percent were authorized for children only, suggesting orphan products targeting pediatric diseases had a lower success rate (71). Parents participating in a 2017 survey reported having to adjust the dose and formulation of their child's orally-administered medicine (i.e., crushing, dissolving, or mixing pills in food or liquids) for it to be consumed, consequentially leading to potentially risky and high-stress situations (28).

Pediatric and orphan drug regulations are separate entities that operate successfully on their own, however, when combined in rare pediatric diseases such as childhood cancer, a lack of integration is seen to further facilitate development of drugs for rare pediatric diseases. Strategy and decision-making communicated amongst stakeholders such as the drug industry, government regulators, epidemiologists, the scientific community, patients and their parents, and pediatricians can bring scientific and regulation processes together for a more efficient and targeted drug development process (71).

1.5. Further Discrepancies in Childhood Cancer Management

Children encompass only 1% of total cancer patients (72), making them a subspecialty that allows a very narrow area for growth as the cancers themselves are not necessarily linked to known lifestyle factors and other comorbidities that are seen in adult cancers. However, cancer in the pediatric population addresses different complications such as long-term consequences of the children and their families both in health and socioeconomic sectors. Survivors often live with chronic conditions such as diabetes, secondary cancer, declining lung function, and infertility after the course of the disease and treatment that require an increased

amount of hospital and outpatient visits. Furthermore, childhood cancer is in most cases not preventable, making it difficult for screening and primary prevention initiatives to be developed. Therefore, early diagnosis is imperative as well as adequate therapy and supportive care (4).

1.5.1. Adult Cancer

For every child diagnosed with cancer, 200 adults are diagnosed. Given that pediatric cancers are rare entities, it necessitates the need for more precise research, organization, and decision making. “Pediatric oncologists are overall either pediatricians or medical oncologists. Some radiation oncologists and surgeons may specialize in treating some or all childhood cancers, in both cases without dedicated training pathways” (30). A study conducted in Spain analyzed the treatments of children and adolescents diagnosed with cancer from 2007 to 2010 and concluded that specialized centers and specific tumor boards are indeed needed (73). “Children are not just smaller adults – it must be taken into account that there are well-established physiological and developmental differences…” (71). According to pediatric pan-cancer analyses, 45% of driver genes in pediatric cancers matched those in adult pan-cancer studies. Therefore, findings in drug trials of adult caners can potentially be used to “guide” pediatric studies (74).

Since childhood cancers are mainly a matter of genetics, oncology is one field that exemplifies the need for extra attention in terms of research and counseling. Over 100 genetic syndromes carry a cancer risk, however, only 10% of genetic predispositions are identified. With intense sequencing and the potential help of modern tools such as artificial intelligence, genetic profiling can increase the percentage of known genetic defects and become more precise, giving way for opportunities for targeted therapy development (30). Due to its rarity, fewer patients and therefore fewer tissue samples available for studying hinders research and precise “molecular characterization” needed in order to discuss potential therapeutic options. Smaller patient numbers also make it difficult to conduct trials as they are unable to produce statistically significant data due to the small sample size. Some trials stay open for years in hopes of recruiting enough patients.

A majority of the genetic drivers in pediatric cancer still do not overlap with those of adults, exemplifying the need for more targeted and specific pediatric therapy (74). A 2015 study analyzed the EMA’s pediatric decision committee and PIPs for leukemia drugs. It was found that adult leukemias are being prioritized since it is more common than pediatric leukemia (75), despite it being the most common malignancy in children.

Parental education is also a crucial point as children are dependent on them to notice symptoms and take them to their physicians. A study in Germany conducted during the COVID-19 pandemic revealed an increase in pediatric cancer diagnoses possibly due to parents spending more time around their children at home during the lockdown period to notice early signs of disease (4).

Pediatric cancers oftentimes require disease-specific staging systems or multiple different systems for one cancer as the TNM Classification of Malignant Tumors staging system is not "adequate" enough (76). The most common pediatric cancers are blood cancers and brain tumors, both of which do not follow the traditional cancer staging systems, such as the American Joint Committee on Cancer (AJCC) system (77, 78). Furthermore, many pediatric cancers fall under adult "tumor families" such as hematologic malignancies, sarcomas, etc., despite their unique clinical pictures and prognosis due to having a different biological makeup (30).

Most of the pediatric cancer research has been focused on improving cure rates. However, supportive care has been neglected as patients' quality of life was not prioritized. One study found that one in four deaths of children with acute lymphoblastic leukemia was due to treatment-related toxicity. Furthermore, standardization of supportive care is suboptimal. A 2015 systematic review found that only four out of 17 evidence-based supportive care guidelines were specifically focusing on children with cancer, most of which were not adequate to be used clinically (79).

Even though children encompass only seven percent of the global palliative care need, pediatric palliative care varies greatly from that of adults (80). Most of the pediatric palliative care population are cancer patients receiving therapy, therefore communication between pediatric oncologists and palliative care specialists is of utmost importance (83). Since children have the capacity of growth and further development, a child with a life-threatening or life-limiting disease needs a longer period of care and often has an unclear prognosis since his or her body is potentially changing rapidly and the disease itself is rare or of unclear pathology (81, 82). Pediatric cancer patients qualify for palliative care when current available treatments are not successful and when the child needs specific therapy that is not intended to be curative (of their current disease) whether for physical or mental distress. Pediatric oncological palliative care is not a synonym for "end-of-life care" as it approaches the entire disease course regardless of current cancer therapy (83). For example, according to a survey conducted by the JARC, the lack of safe, age-appropriate, and inexpensive pain medication for children is significant (30). Considering the complexity of child anatomy and physiology and the

limitations of pediatric cancer treatment in the first place, the need for proper components of palliative care is only growing.

2. OBJECTIVES

2.1. Aims of the study

1. To assess the correlation of the amount of EU funding for research allocated to pediatric cancers and the burden of the diseases (measured as disability-adjusted life years) from 2011 to 2019.
2. To determine the relationship of the EU finding amount between the types of pediatric cancers from 2011 to 2019.
3. To determine the relationship of the burden of the pediatric cancers (measured as disability-adjusted life years) between the types of pediatric cancers from 2011 to 2019.

2.2. Hypotheses

1. There will be a positive correlation between the amount of EU funding for research allocated to pediatric cancers and the burden of the diseases (measured as disability-adjusted life years) from 2011 to 2019.
2. There will be a difference in the EU funding amount between the types of pediatric cancers from 2011 to 2019.
3. There will be a difference in the burden of the pediatric cancers (measured as disability-adjusted life years) between the types of pediatric cancers from 2011 to 2019.

3. METHODS

This cross-sectional study analyses EU grants awarded to study the treatment of childhood cancers from the 1st of January 2011 to the 31st of December 2019. We excluded projects that exclusively track disease occurrence or surveillance projects, any grants that do not describe specific cancers, grants for research focused on diseases outside of the EU, and grants from institutions outside of the EU. Projects will be included that fund an intervention or follow the treatment course of the cancers.

3.1. Disease Categories

Data from CORDIS (https://cordis.europa.eu/en) was used to identify all pediatric grants that studied a type of cancer and the amount of funding for each. For projects that had grant periods beyond the search dates, we included the amount awarded for only the search period.

3.2. Disease Burden

The Institute and Health Metrics (IHME) online database (https://ghdx.healthdata.org/gbd-results-tool) was used to obtain data on disease burden in annual numbers for the disability adjusted-life years (DALYs) for children from birth to 17 years of age for 2011 to 2019 for the specified cancers. DALYs summarize the years of life lost due to a disability because of acute or chronic disease (5). The IHME describes data according to the following age groups: birth to 1 year, 1 to 4 years, 5 to 9 years, 10 to 14 years, and 15 to 19 years. As performed in the study by Rees at el. (87), we summed the values for children aged 0 to 14 and three-fifths of values for youth aged 15 to 19 to retrieve data for children aged 0 to 17 years (87). We chose and included the specific level category for the cancers that are mapped to diagnoses in the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) coding system. The use of DALYs is intended to measure the impact of the cancers on children, although may not sufficiently capture the full impact that chronic disease burden and health care use may address. No EU-wide in-patient database for children exists, so data on hospitalization or comorbid conditions were unavailable to compliment the data in this study.

3.3. Searching for Grants

The search terms pediatric, children, and cancer was searched for in the CORDIS grants database. The search terms were MeSH derived search terms. Using the search terms, one investigator searched the CORDIS database for “pediatric” and “childhood” along with

"cancer" joined by the Boolean operator "AND." The CORDIS database describes the titles, abstracts, results, and funding award information for each grant or project.

3.4. Selection of Grants and Characterization

One investigator searched for grant titles and abstracts available on CORDIS, select, and include them according to the eligibility criteria. Another investigator reviewed them and any disagreements were resolved through consensus discussion. The two investigators assigned the grants to a cancer category. We included six cancer categories (leukemia, brain/CNS, Hodgkin lymphoma, non-Hodgkin lymphoma, kidney, and other malignancies) for ages 0-14 and 15-17 years. We classified the grants according to the categories available in the IHME database (other malignant tumors, brain and central nervous system cancer, other malignant tumors, and leukemia) on a random selection of 10% of the grants to establish agreement on the selection of eligible grants according to our eligibility criteria. We had good agreement (Cohen's kappa [κ]=0.82, 95% confidence interval [CI] 0.69-0.95) for the selection of eligible grants and achieved complete agreement on assigning IHME cancer categories to each grant. After establishing agreement, one investigator assigned the remaining grants to the cancer categories. We divided the awarded funds equally between grants studying multiple eligible cancers. For grants involving more than one EU country, we totaled the countries' DALYs within the study period to compute the total DALYs for those countries.

3.5. Statistical Analysis

We used the Kolomogorov-Smirnov test to determine the normality of numerical variables. Based on the non-parametric distribution of the numerical variables, we reported median (interquartile range [IQR]) for total funding and DALYs by cancer category. We used Spearman rank correlation (r) to compare the total amounts of cancer-specific EU funding and DALYs for children aged 0-17 years in the 2011-2019 period. Dunn-Bonferroni post-hoc analysis was used for the Kruskal-Wallis H test to determine in which category differences existed. We performed all analyses using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, N.Y., USA) and MedCalc Statistical Software version 17.1 (MedCalc Software bvba, Ostend, Belgium). We considered a two- sided P-value < 0.05 to indicate statistical significance.

4. RESULTS

We selected 36 pediatric grants awarded by the EU from 2011-2019 out of 42 grants (5 were excluded for studying non-eligible cancers and one was excluded for non-EU-based research). In total, the EU funding provided for these grants during 2011-2019 was €87,717,655 or €8,771,765 per year.

The amount of funding allocated to each cancer category had a wide range (Table 1). Funding for a wide variety of cancers including neuroblastoma, medulloblastoma, and Ewing sarcoma family tumors received the most (75%) funding of €6,537,385 per year and brain and central nervous system cancer received the least (4%) funding of €353,138 per year from 2011 to 2019.

Table 1. EU pediatric funding and disease burden by cancer category. 2011-2019

Disease Categories	Total Funding Amount (€)	DALYs for children aged 0-17 years
Brain and central nervous system cancer	3.531.377	809.200
Leukemia	18.812.429	1.278.606
Other types of cancer or malignant tumors	65.373.849	4.868.639

Abbreviations: DALYs, Disability-adjusted life years

Table 2 shows that the difference in funding between the cancer categories were significant.

Table 2. Comparisons in the total EU grant funding amount according to the different cancer types.

Disease categories	Total Funding Amount (€), median (IQR)	P-value
Brain and central nervous system cancer	3.513.377	
Leukemia	18.812.429	0,012
Other types of cancer or malignant tumors	65.373.849	

Abbreviations: IQR, interquartile range

*Kruskal-Wallis H test with a significance set at P<005

†Post-hoc pairwise comparisons showed differences between brain and central nervous system cancer vs. other types of cancer or malignant tumors, P=0.022

4.1. EU funding and pediatric disease burden

The DALYs for 0-17year old children varied for the various pediatric cancers (Table 1). The median (IQR) DALYs for brain cancer, leukemia, and other malignancies are shown in Table 3. There was so no significant difference in the DALYs according to cancer type.

Table 3. Comparisons of DALYs for children aged 0-17 years according to the different cancer types.

Disease categories	DALYs for children aged 0-17 years, median (IQR)	P-value
Brain and central nervous system cancer	47.900 (47.900 – 75.782)	
Leukemia	79.690 (62.893 – 33.784)	0,760
Other types of cancer or malignant tumors	239.197 (91.320 – 383.369)	

Abbreviations: IQR, interquartile range; DALYs, disability-adjusted life years

*Kruskal-Wallis H test with a significance set at P<0.05

Figure 2 shows the correlation between funding amounts and DALYs during the 2011-2019 period. There was a significant positive correlation between EU funding and DALYs for children aged 0-17 years (r=0.76, 95% CI 0.57-0.87; P<0.001).

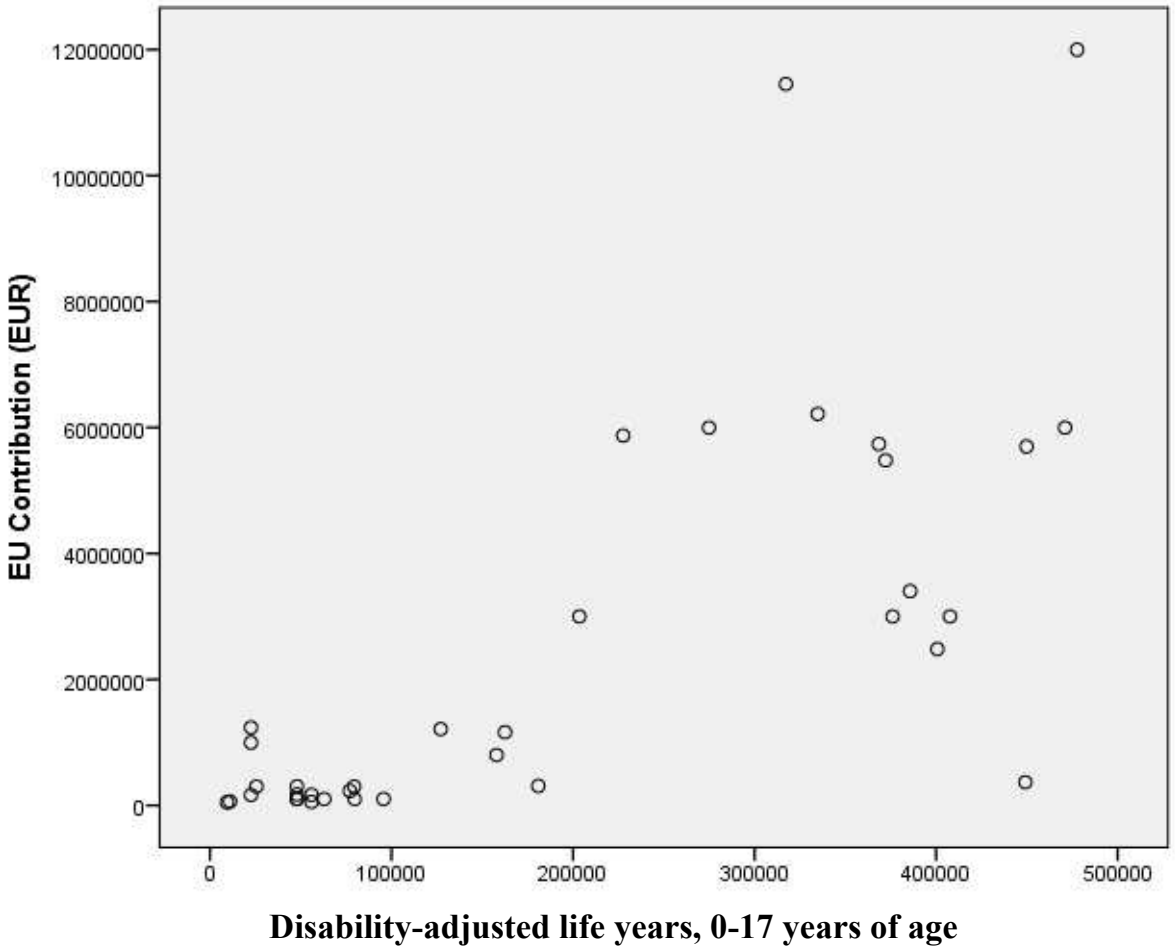

Figure 2. Correlation between the pediatric cancer burden measured as disability-adjusted life years and European Union funding, 2011-2019

5. DISCUSSION

5.1. Results Summary

This study examined 36 pediatric grants awarded by the EU between 2011 and 2019, totaling 87,717,655 in funding. These grants were allocated across different pediatric cancer categories, with notable variations in funding levels. Neuroblastoma, medulloblastoma, and Ewing sarcoma tumor families received the highest funding (75%) at 6,537,385 per year, while brain and central nervous system cancer received the least (4%) at 353,138 per year. We also analyzed the burden of disease in terms of DALYs for children aged 0-17 years during the 2011-2019 period, which resulted in findings that suggested higher EU funding is associated with higher DALYs.

5.2. Interpretation

Despite the positive correlation that we found between EU funding and disease burden childhood cancer is still the first leading cause of death by disease in children over one year old in Europe (30). Our findings showed that no relationship was found between funding and types of cancer, suggesting that inequalities still lie amongst various aspects of childhood cancer due to the complexity of cancer management. Most of the grants studied were directly related to developing new therapy and very little concerned other aspects of the disease burden such as side-effects, late outcomes, palliative care needs, and access to proper healthcare.

Furthermore, we found that brain and CNS tumors were not being prioritized. Not only are they the second most common childhood cancers, but the treatment of said tumors (cranial irradiation) lead to the most serious late effects as mentioned previously and thus contributing greatly to the disease burden.

5.4. Limitations

Our study focused solely on funding by the EU for childhood cancer research. However, organizations such as charities and independent non-profit organizations exist which contribute to funding. Cancer charities provide aid for research and clinical trial as well as advocacy for research and influence on policy. These charities are also known to create online forums, blogs, and informative sites for the scientific community and for patients as well (84). Private companies, such as the European Organization for Research and Treatment of Cancer (EORTC), can receive funds from institutions, corporations, and private donors as well as use fees from various private ventures to fund their studies (85). Even though our results showed no relationship between funding and disease burden, these other sources of funds could

contribute to different aspects of the disease burden and funding of specific cancer categories that EU grants did not prioritize (such as brain and CNS tumors).

The IHME database only provides disease burden data up to 2019. Newer data from the past three years could reflect a change in trends of disease burden and funding as some of grants that we studied were for time periods that exceeded past 2023. For example, the ESCP and the EU4Health Programme mentioned previously are tools that tackle aspects of the childhood cancer disease burden such as access to healthcare and communication within the healthcare community. Thus, the impact of programs like these that have been developed or that are in development, on the disease burden has not been studied, as they came into action after 2019.

As described previously, under-reporting of childhood cancer and disabilities thereof (most notably in lower-income countries) could impact DALY values. A study conducted in Estonia in 2017 claimed that childhood cancer survival rates are lower than the European cancer average despite a decrease in incidence. This investigation evaluated the Estonian Cancer Registry's reporting on nonfatal childhood cancer cases and found a significant amount of missing cases and thus an increase in overall incidence rates (86). Under-recording and under-diagnosis may be due to the rarity of childhood cancer and a complicated diagnosis process that includes non-specific symptoms, unknown risk factors, a potential lack of access to advanced diagnostic tools in certain lower-income areas, and a lengthy treatment process which requires long-term care that is difficult to follow-up on.

6. CONCLUSION

After conducting our study, we concluded that disease burden of childhood cancer is remains significant despite EU funding and that the funding is not being allocated equally amongst the different groups of cancers. Re-assessment of the various factors that contribute to the complicated disease burden of childhood cancer and reform of policy concerning these factors in the healthcare and governmental sectors is needed in order to close the gaps in childhood cancer management in the EU. These factors include drug development, access to healthcare, diagnostic innovations, education, communication, supportive care, financing, and palliation.

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8. SUMMARY

Objectives: To analyze the association of European Union funding for pediatric cancer research on pediatric cancer burden in the European Union.

Methods: EU grants awarded for childhood cancer research between January 1, 2011 and December 31, 2019 were selected from CORDIS using MeSH-derived terms and then categorized based on the six cancer categories (leukemia, brain/CNS, Hodgkin lymphoma, non-Hodgkin lymphoma, kidney, and other malignancies). The IHME database was used to derive data on disease burden through disability-adjusted life-years (DALYs) in children ages 0 to 17 years for each category of cancer during the same time period (2011-2019). Non-parametric statistical analysis was performed using Spearman rank correlation and the Kruskal-Wallis H test with Dun-Bonferroni post-hoc tests.

Results: From 2011 to 2019, 36 EU grants were selected for pediatric research with a total funding of €87.717.655. The amount of funding allocated to each cancer category had a wide range and a significant difference, with brain and CNS cancer receiving the least (4% of funding). No significant difference was found in DALYs according to cancer type, however, a positive correlation was found between DALYs and EU funding. EU funding not having a relationship with DALYs for childhood cancer suggests gaps in cancer management and a need for re-assessment and reform in the healthcare sector regarding childhood cancer.

Conclusion: Despite a positive correlation between EU funding and childhood cancer burden, childhood cancer remains the leading cause of disease-related death in children of the EU over one year old. The lack of a relationship between funding and disease burden indicates persistent inequalities in childhood cancer aspects due to its complex management. Important burdens such as side effects, late outcomes, palliative care, and healthcare access might not be prioritized in the EU's fight against childhood cancer.

9. CROATIAN SUMMARY

Ciljevi: Analizirati povezanost novčane potpore Europske unije za istraživanja karcinoma kod djece i utjecaj karcninoma kod djece u Europi.

Metode: dodijeljena EU sredstva za istraživanja karcinoma kod djece između 01. siječnja 2011 i 31. prosinca 2019. Izbrana su iz CORDISA uporabom pojmova s MESH stranice. Zatim su kategorizirana prema 6 tipova karcinoma (leukemija, mozak/središnji živčani sustav, hodginov limfom i ne hodginov limfom, bubreg, i drugi maligniteti). IHME baza podataka je upotrijebljena za izvadak podataka o utjecaju bolesti kroz "godine života prilagođene invaliditetu" (DALYs) u rasponu godina od 0 do 17 za svaki tip karcinomatijekom istog perioda (2011-2019). Za neparametarsku statističku analizu korištena je Spaerman vrsta korelacije i Kruskal Wallis H test s Dun- Bonferroni post hoc testom.

Rezultati: Od 2011 do 2019, 36 EU novčnih sredstava potpore su izabrani za istraživanje karcninoma kod djece s ukupnim financiranjem od 87,717.655 eura. Svaki iznos financiranja koji je dodijeljen pojedinom tipu karcinoma imao je široki opseg i značajnu statističku razliku. Karcinomi mozga i centralnog živčanog sustava najmanje su financirani (4%). Nije pronađena statistički značajna razlika u DALYs-u s obzirom na tip karcinoma, ali utvđena je pozitivna korelacija između DALYs-a i EU financiranja. Budući da financiranje EU nije imalo povezanosti s DALYs-om za karcinome kod djece, podatak ukazuje na nedostatke u liječenju karcinoma i potrebu za ponovnom procjenom i reformom u sektoru zdravstvene skrbi u svezi s malignim bolestima u dječjoj dobi.

Zaključak: Unatoč pozitivnoj korelaciji između financiranja EU i utjecaja karcinoma kod djece, karcinom kod djece ostaje vodeći uzrok smrti djece kada je bolest u pitanju posebno kod europske djece starije od godinu dana. Nedostatak povezanosti financiranja i utjecaja bolesti upućuje na stalne nejednakosti u aspektima karcinoma kod djece zbog kompleksnog vođenja. Važni utjecaji bolesti kao što su nuspojave, kasniji ishodi, palijativna skrb i pristup zdravstvenoj skrbi možda nisu prioritizirane u borbi EU protiv karcinoma kod djece.