

EDITORIAL

PEDIATRIC CANCER AND THE ENVIRONMENT: A FIFTY-YEAR PERSPECTIVE

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In 1970, when I was the final months of my pediatric residency at Boston Children's Hospital, I spent four weeks on the children's cancer ward. This was a service staffed by some of the most dedicated physicians and nurses in that storied institution, and the care they provided the children was superb. However, the ward was a sad place, because in 1970 a diagnosis of childhood cancer was a death sentence. Chemotherapy was in its infancy. The chemicals were harsh and painful. The best outcome for which we could hope was a remission of a few months' duration. In that era, virtually every child with cancer died.

Since that time, progress in the treatment of childhood cancer has been spectacular. This progress has been the fruit of remarkable advances in medicine, surgery and basic biology. The first five-year survival of a child with pediatric leukemia was reported in the 1970s (1). Today, more than 85% of children with leukemia are cured, and the mortality rate for all forms of pediatric malignancy in the United States

has fallen by 70% (2, **figure 1**). This is one of the great triumphs of modern medicine. Unfortunately, this success in the treatment of pediatric cancer is not the entire story. In the same years as childhood cancer deaths were falling because of better treatments, the incidence of childhood cancer – the number of new cases per 1,000 children – was increasing. Leukemia incidence in the United States has increased by 21% since 1976 (3), brain cancer incidence by 45% (3), and testicular cancer incidence by 51% (2). Cancer is now the leading cause of death by disease among American children under the age of 15 years.

The causes of these increases in cancer incidence are only partially understood. They are far too rapid to be of genetic origin. It has been suggested that they may reflect improved access to medical care or the increasingly widespread availability of newer diagnostic technologies such as MRI and CAT scan. That explanation might have accounted for a one-time "bump" in cancer incidence when Medicaid was introduced

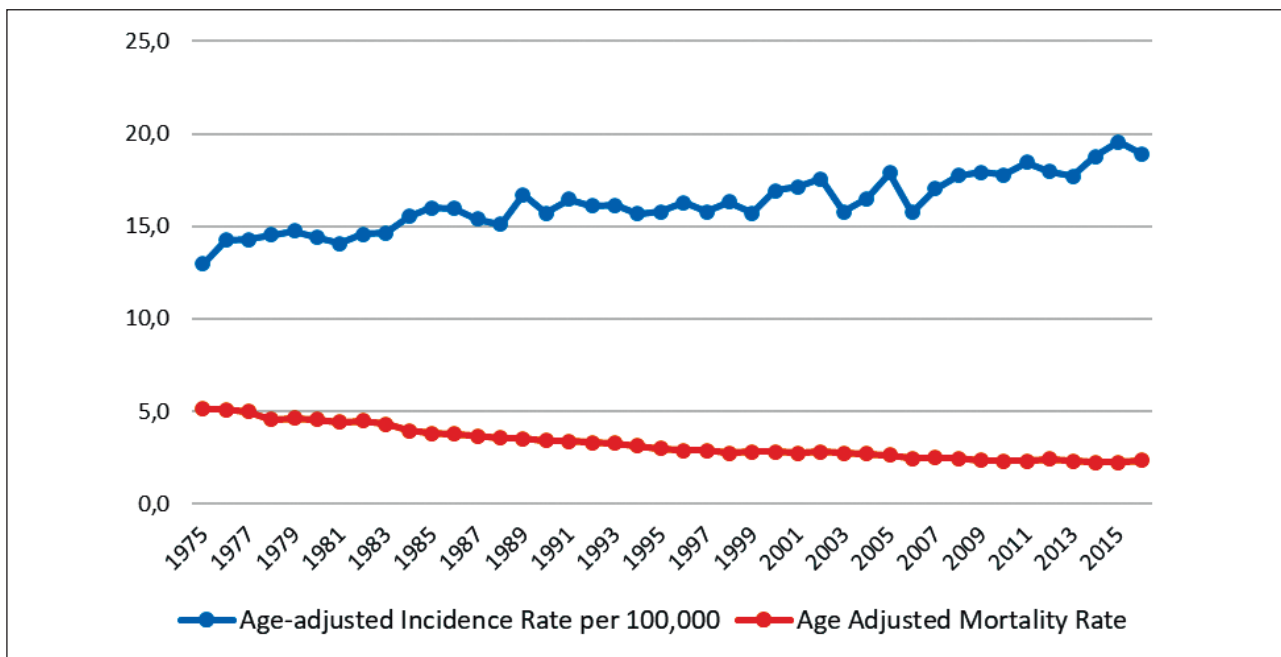


Figure 1. Childhood cancer, United States - Age-adjusted incidence and mortality, 1974-2016. This figure comes from the National Cancer Institute SEER Program (2).

or newer imaging techniques first became available. However, it fails to explain the continuing increase in incidence of three different types of childhood cancer over a span of five decades (4). The conclusion becomes inescapable that external, environmental factors must be responsible for at some of the increase.

MANUFACTURED CHEMICALS AND PEDIATRIC CANCER

Evidence is great and growing that environmental exposures, and especially exposures to manufactured chemicals, are in fact important contributors to childhood cancer. Children today are surrounded by an estimated 350,000 manufactured chemicals and chemical mixtures (5). These are novel materials, nearly all of them invented since 1950. They are produced in enormous quantities. Global production volume is on track to double by 2030. Manufactured chemicals now pollute every corner of the planet from the deepest ocean trenches to the high Himalayas. Several hundred are found in measurable quantities in the bodies of almost all persons on earth, including nursing mothers, infants and children (7). Some will persist for centuries. Chemical pollution has become so widespread and complex that an expert body recently concluded that it exceeds societies' abilities to monitor and contain it and thus threatens the safe operating space for humanity (8).

Manufactured chemicals cause disease, disability and death in children. Exposures in the first 1,000 days of life are especially dangerous. Polychlorinated biphenyls (PCBs), organophosphate insecticides, brominated flame retardants and phthalates are all linked to cognitive impairment, reduced intelligence, and behavioral problems (9). Prenatal exposures to phthalates are linked to abnormalities of the reproductive organs in baby boys (10). Early-life exposures to toxic chemicals appear linked to increased risk in later life of cardiovascular and renal disease (11, 12). Manufactured chemicals also cause cancer. The International Agency for Research on Cancer (IARC) has determined through meticulous independent review of the published epidemiological and toxicological data on over 1,000 manufactured chemicals and other environmental hazards that 120 agents are proven causes of cancer in humans (13). The majority of these proven human carcinogens remain in commerce today. Chemicals known to cause cancer in children include benzene, 1, 3-butadiene, and prenatal pesticide exposures (14). Prenatal exposure to DDT is linked to increased risk of female breast cancer in adult life (15).

FAILURE OF CHEMICAL POLICY

The root causes of this chemical crisis are the failure of the chemical industry to take responsibility

for the materials they produce, regulatory failure within countries, and shortcomings in global chemical governance. In most countries, manufactured chemicals are presumed to be harmless until they are proven to cause disease or environmental damage (16). They are brought to market with great enthusiasm but with little or no assessment of their potential dangers. Fewer than 50% of the most widely used manufactured chemicals have been tested for toxicity, and fewer than 20% have been examined for potential developmental toxicity (16). In consequence of this regulatory failure, new chemicals are incorporated into consumer products with no consideration of the hazards they may pose to human health or the environment. Early warnings of danger are ignored or even suppressed (17). The result is that time and again manufactured chemicals have been found – sometimes after years or even decades of use – to have caused great harm to children’s health and the environment. Historical examples include tetraethyl lead added to gasoline, DDT, thalidomide, polychlorinated biphenyls (PCBs), diethylstilbestrol (DES) and the chlorofluorocarbons that almost destroyed the earth’s stratospheric ozone layer. Newer chemicals that threaten to repeat this sorry history include the phthalates, bisphenols, neonicotinoid insecticides, brominated flame retardants, and perfluorinated substances (PFAS).

A further impediment to the control of hazardous chemicals has been the “risk assessment/risk management” paradigm, introduced in the 1970s (18). With its basis in the presumption that chemicals are harmless until proven to cause harm and its insistence on subjecting each chemical one at a time to exhaustive, multi-year analysis prior to any regulatory action, the “risk assessment/risk management” paradigm has paralyzed chemical control and impeded the protection of public health.

Of great concern to those who care for children is the likelihood that the chemical carcinogens that have been identified to date may account for only a small fraction of the cancers that are caused in children by manufactured chemicals. Almost certainly, there are additional carcinogenic chemicals in the modern environment. They are hidden among the many thousands of manufactured chemicals to which children are exposed every day. However, because most of these chemicals have never been tested for safety or toxicity, we do not know which of them may cause cancer, or which may be driving increases in cancer incidence. We are flying without radar.

The time has come for the oncology and the public health communities to come together to jointly confront the rising incidence of childhood cancer. We can no longer focus almost exclusively on cancer treatments. We can no longer dismiss rising trends in cancer incidence as diagnostic artifacts or the consequence of better reporting. We must instead deploy prevention-oriented research programs designed to discover the environmental causes of pediatric malignancy and implement science-based policies that focus on cancer prevention.

NEED FOR INCREASED RESEARCH INTO PEDIATRIC CANCER

The greatest impediment to discovery of the environmental causes of childhood cancer is lack of funding. In the United States, the National Institutes of Health awards only 3% to 7% of its total funding for childhood leukemia to studies evaluating environmental etiologies, including dietary factors, infections and chemicals (14). The majority of this funding comes from the National Institute for Environmental Health Sciences (NIEHS). The National Cancer Institute directs approximately 1% of its funding for childhood cancer toward research into environmental causes (14).

Increased funding into the environmental causes of childhood cancer has potential to yield a high return on investment. Large, prospective, multi-year birth cohort studies that incorporate assessments of prenatal environmental exposures are especially powerful engines of scientific discovery because they permit unbiased assessment of exposures as they occur before the onset of disease. To bring together data on the preventable, environmental causes of childhood cancer from multiple prospective birth cohort studies in countries around the world, the World Health Organization has organized the International Childhood Cancer Cohort Consortium (I4C) (19). The launching of additional prospective studies would increase this database and further enhance global capacity for discovery of the preventable causes of childhood cancer.

NEED FOR FUNDAMENTAL REVISION OF CHEMICAL POLICY

Chemical policies in all countries need to pivot away from the failed risk assessment/risk management paradigm (18) and its presumption that chemicals

are harmless until proven to cause disease or environmental damage. Chemical management policies must instead be based on the Precautionary Principle, (17) which assumes that all manufactured chemicals are hazardous until they are proven to be safe, and on the Essential Use Doctrine, which states that new chemicals cannot be brought to market unless their use is deemed essential (20).

In short, a new health-protective approach to chemical management must embody the “No Data, No Market” Principle, already articulated in the European Union in its REACH legislation (21) which requires that all new manufactured chemicals be tested for safety and toxicity before they are allowed to enter markets, and that all existing chemicals must be tested – beginning with the worst first – if they are to remain on markets. National chemical policies must require that all manufactured chemicals be subjected to the same degree of scrutiny before they enter markets as chemicals that are intended to be used as pharmaceuticals.

Additional key components of health-protective chemical management policies will be the adoption of strict procedures for full disclosure and elimination of all conflicts of interest and an insistence that testing of chemicals for safety and toxicity be conducted in independent laboratories rather than in laboratories controlled by the chemical industry (22). The current system in which chemical manufacturers generate virtually all data on the potential hazards of new chemicals is broken and must be replaced. New procedures for assessment of the risks of chemicals need also to embody a clearly articulated emphasis on human rights, equity and protection of vulnerable populations, including infants and children against the hazards of manufactured chemicals (23). Lastly, they need to incorporate an explicitly articulated intent to reduce unnecessary use of manufactured chemicals and to transition to a more circular economy that emphasizes planetary stewardship (24) and care for the earth, our Common Home (25).

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CONCLUSIONS

Need for a new paradigm

The rising incidence of childhood cancer poses a major challenge to our society and to the oncology and public health communities. The time has come for our communities to come together to jointly

confront this growing problem. Going forward, we need to insist that all new chemicals and all widely used existing chemicals be tested for safety and toxicity. We can no longer allow our children to be exposed to thousands of manufactured chemicals of unknown hazard. We need to support strong research programs that include epidemiological and toxicological studies. We need to strengthen legislation in all countries to better protect our children and we need to enforce these laws. We need to work with chemical researchers and the business community to develop new green chemicals that will sustain our society without harming future generations. We must act together as wise guardians of our children and of our planet.

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