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Concluding Commentary: Children in All Cancer Prevention Policy Decisions.

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This interesting series of articles on Opportunities for Cancer Prevention During Early Life brings many ideas for the primary prevention of cancer in childhood, or in adults due to early life events. The economic burden not only of cancer mortality but also of lifelong morbidity among cancer survivors, as shown by Guy et al,[1] raises the importance of this critical public health issue. The topics of these articles were developed during online seminars with the pioneers in this area, some of whom authored the articles. They reflect the determinants of health diagrammed so eloquently in Healthy People 2020.[2] Broadly, the determinants of health outcomes are biology/genetics, the physical environment, individual behavior, the social environment, and health services. The articles have been grouped according to these categories. For example, the article by Terry and Forman[3] focuses on interventions at the individual level, and the article by Massetti et al,[4] focuses on interventions aimed at social determinants.

Classically, mutagenesis was the first basic mechanism clearly identified for carcinogenesis, and either inherited mutations or the mutagenesis of agents, such as tobacco and radiation, were the focus. Viral infections also have long been recognized to be involved with certain cancers. Our current models for carcinogenicity recognize that, for most cancers, multiple stages are required to not only initiate the cancer but also to elude biological mechanisms for repairing DNA, immune surveillance, and other natural defenses against cancer. One carcinogen, diethylstilbestrol (DES), did not neatly fit either the mutagen or viral hypotheses,[5,6] and we now understand that in addition to inherited or acquired genetic susceptibilities, a basic mechanism for carcinogenesis due to either physical or social exposures is epigenetics. Epigenetics is the study of how the expression of DNA is modified without a change in the DNA code itself. Such modifications are critical to early developmental cellular differentiation pathways and, for example, explain why, with the same DNA, epidermal cells are so different from neurons. Epigenetic modulation of DNA expression occurs through DNA methylation, histone acetylation, and micro-RNAs. A physical or chemical exposure can interact with an organism leading to a series of signaling events culminating in an epigenetic change.[7] This change in DNA expression may occur soon after

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the exposure, or persist until the particular gene is transcribed when the anomaly in DNA expression is expressed.

As these articles demonstrate, to date we have too few answers for how to prevent childhood cancers from arising in the first place; in other words, to do primary prevention. We propose a framework that would consider that in addition to genetic susceptibilities, inherited or acquired, interactions with physical, chemical, microbial, hormonal, and/or nutritional agents are involved in signal cascades that in turn are involved with epigenetic changes contributing to childhood carcinogenesis. Primary prevention would involve understanding the biochemical changes required for the initiation of carcinogenesis so that they can be prevented, blocked, or undone, so that no carcinogenesis would take place. Avoidance of substances that are known to cause mutations is an obvious step that has been taken in many contexts, but we now additionally need to focus on risk factors that cause harmful epigenetic changes. Additionally, several nutrients are being investigated for their ability to reverse or modify epigenetic changes. Finally, as the case of DES suggests, inappropriate hormonal stimulation may be a factor. We know very little about stress (maternal during pregnancy, familial, or in children) and how consequent changes in hormonal expression impact cancer. However, we do know that excessive caloric intake is associated with increased cancer among adults in one study accounting for 14% of all cancer deaths in men and 20% in women.[8] This is most certainly mediated via metabolic, and epigenetic, change. This is relevant for prevention during early life, as epigenetic changes are more prominent during fetal and postnatal development.

Another current topic in medicine that could play a role here is personalized medicine. Personalized medicine refers to a medical model that proposes the customization of health care, with medical decisions, practices, and/or products being tailored to the individual patient.[9] For example, DES exposure in utero to female fetuses results in an elevated risk of clear-cell adenocarcinoma of the vagina (CCAV); however, it is estimated that only 1 of 1000 women who were exposed in utero developed CCAV.[5] DES, like estrogen, passes through the plasma and nuclear membranes to bind to various sites on DNA and modify gene expression. The risk factors for developing CCAV are unknown, with the possibility of earlier exposure to DES in utero, or a second exposure to another hormone either through oral contraceptives or pregnancy being one.[6] The actual difference in susceptibility may be due to a genetic polymorphism that limits changes in the DES-modulated DNA expression or other unrelated factors like exposures to viruses. Further understanding of why one exposed person develops CCAV and another does not, would help in interpreting what exposure of a hormone to an individual means, which individuals should avoid exposure, and the discovery of cancer promoters that might be important for other cancers in addition to CCAV.

Another emerging issue is global climate change and the possibility that cancer may increase as a result. There are many ways that global climate change could cause increases in childhood cancer rates. Heavy rainfalls will increase, and these result in increased toxic runoff into water, including drinking water supplies. Bottle-fed newborn infants are among the heaviest consumers of water, and they may be disproportionately affected. A warmer planet will experience increased air pollution via volatilization of certain environmental chemicals. Because infants and children breathe more air per kilogram than adults, a higher exposure will occur. Other global processes are continuing to deplete the planetary stratospheric ozone layer, the so-called "good" ozone that shields the planet from UV radiation. Sunscreen is typically not recommended for infants younger than 6 months and is not readily available to many children around the world. With the increasing temperature, children are at higher risk of sun exposure and sun burns; such exposures before the age of 20 years are known to increase the risk of melanoma and other skin cancers.

This series of articles suggests that several policy changes would substantially reduce the risk of cancer from prenatal and early-life exposures. For prenatal exposures, increased testing of environmentally used chemicals in reproductive toxicity or hormonal activity (including estrogenicity) is warranted. Also, many carcinogens are part of the workplace, such as solvents and heavy metals. There are increased risks not only to the exposed workers, but also to their unborn children. Alcohol, a solvent and known teratogen, causes cancer in adults, and is suspected to lead to cancer in children with fetal alcohol syndrome.[10] We do not have evidence about cancer risks for children at lower doses, but we should, given that ethanol is widely used as a fuel and a fuel additive and in that way causes exposures generally. Maternal exposure to industrial solvents is also linked to development of acute lymphoblastic leukemia in their offspring.[11] These results strongly suggest that occupational exposure limits by the Occupational Safety and Health Administration be set to protect the fetuses of pregnant women.

For children, the critical element of time is lacking from the 2020

model of Healthy People. Time is important in many senses of the word: time of exposure, time of biologic development/status, time in the sense of linear progression; what went before influences current health status such that an individual may be more susceptible or more resilient to the carcinogen at every stage of development. Simply put, we as pediatricians know that children are not little adults, but we also know that a fetus is not a little infant, an infant is not a little child, and a child is not a little adolescent. Thus, although we categorize children into stages of human development, it may be that every day is a critical window of susceptibility for yet another molecular event; and the influences on this ever-changing biological organism are complex.

Chemical exposures can appear to be straightforward (absorption, metabolism, interaction with target molecule, health outcome) biologically, but there are complex interactions with a number of other factors (stress, hormonal responses, epigenetically altered target molecules, and nutritional state) that add complexity. All of these determinants rely on unique attributes of the organism that occur only during a narrow window of time. If the parts of our DNA that are translated to encode proteins (the exome) are not complicated enough, we now know that we must be concerned about the nontranslated parts and the exponentially complex epigenome. Even with major breakthroughs in mathematics or informatics, we may never be able to precisely understand the factors that contribute to any 1 case of cancer. What we can learn is which factors are increasing risks of cancer. The more relevant model to consider when thinking of cancer prevention during early life may be that of the kaleidoscope presented in the National Academies Press publication, *Children's Health, the Nation's Wealth*.[12] Such complexity suggests that a simplified overarching approach to cancer-prevention policies may be to consider the health of fetuses and children as well as the preconception of health of parents in all policy decisions.

ABBREVIATIONS

CCAV: clear cell adenocarcinoma of the vagina
DES: diethylstilbesterol

REFERENCES

1. Guy GP Jr, Berkowitz Z, Ekwueme DU, Rim SH, Yabroff KR. Annual economic burden of productivity losses among adult survivors of childhood cancers. *Pediatrics*. 2016;138(suppl 1): e20154268D
2. US Department of Health and Human Services. Healthy People 2020. Determinants of Health. Available at: www.healthypeople.gov/2020/about/foundation-health-measures/Determinants-of-Health. Accessed November 16, 2015
3. Terry MB, Forman MR. Empowering pediatricians to prevent chronic disease across generations. *Pediatrics*. 2016;138(supp 1):e20154268K
4. Massetti GM, Thomas CC, Ragan KR. Disparities in the context of opportunities for cancer prevention in early life. *Pediatrics*. 2016; 138(supp 1):e20154268J
5. Melnick S, Cole P, Anderson D, Herbst A. Rates and risks of diethylstilbestrol-related clear-cell adenocarcinoma of the vagina and cervix. An update. *N Engl J Med*. 1987;316(9):514–516
6. Palmer JR, Anderson D, Helmrich SP, Herbst AL. Risk factors for diethylstilbestrol-associated clear cell adenocarcinoma. *Obstet Gynecol*. 2000;95(6 pt 1):814–820
7. Guerrero-Preston R, Herbstman J, Goldman LR. Epigenomic biomonitors: global DNA hypomethylation as a biodosimeter of life-long environmental exposures. *Epigenomics*. 2011;3(1):1–5
8. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med*. 2003;348(17):1625–1638
9. Wikipedia. Personalized medicine. Available at: https://en.wikipedia.org/wiki/Personalized_medicine. Accessed November 16, 2015
10. Burd L, Peterson L, Kobrinsky N. Fetal alcohol spectrum disorders and childhood cancer: a concise review of case reports and future research considerations. *Pediatr Blood Cancer*. 2014;61(5):768–770
11. Abadi-Korek I, Stark B, Zaizov R, Shaham J. Parental occupational exposure and the risk of acute lymphoblastic leukemia in offspring in Israel. *J Occup Environ Med*. 2006;48(2):165–174
12. Committee on Evaluation of Children's Health; Board on Children, Youth and Families. Division of Behavioral and Social Sciences and Education; National Research Council; Institute of Medicine. *Children's Health, the Nation's Wealth: Assessing and Improving Child Health*. Washington, DC: The National Academies Press; 2004. Available at: www.nap.edu/catalog/10886/childrens-health-the-nations-wealth-assessing-and-improving-child-health. Accessed November 16, 2015

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