How Much of a Contribution Do Exposures Experienced between Conception and Adolescence Make to the Burden of Cancer in Adults?

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There is now reliable evidence that the in utero environment influences developmental plasticity, with health consequences later in life (1). Infancy and childhood represent critical windows during which there is a particular pattern of exposures and potential heightened sensitivity to those exposures (2, 3). Adolescence is an additional developmental stage associated with physiologic changes that may be formative in terms of future cancer development. For some carcinogens, risk can increase as a power of exposure period, meaning that beginning exposure slightly earlier could translate to a substantial variation in subsequent risk (4).

These principles are consistent with reports of early life exposure and cancer in adulthood. For example, in utero and childhood exposure to arsenic was associated with a higher mortality rate from lung and kidney cancer in adults (5, 6); severe energy restriction during childhood and adolescence was linked to a reduced risk of colorectal cancer (7); and interesting evidence points to an association between soy intake in childhood and adolescence with a decreased breast cancer risk later in life (8).

In addition to these observational studies, plausible underlying mechanisms are being described. For example, pregnant women’s exposure to traffic-related air pollution has been correlated with DNA damage in maternal and placental cord blood (9). In relation to arsenic and severe energy restriction, intriguing epigenetic data show that arsenic exposure in pregnant women results in altered gene expression in cord blood (10), whereas gene promoter methylation was decreased in colorectal tumors from individuals who experienced severe famine early in life compared with those who did not (11). Results from both studies are consistent with suggestions that early life exposures can result in epigenetic changes relevant to subsequent cancer development (12). The issue of transgenerational effects of exposure on cancer risk further enhances the arguments (13, 14).

Understanding the importance of early life exposure therefore represents an important challenge for cancer research. Yet, paradoxically, much of the current orientation in cancer epidemiology is toward exposure and risk over a narrower age range, typically middle age onwards. This age range is investigated in case–control studies or in prospective cohorts designed to yield enough cases for analyses within a decade or two. Although some studies of this kind include estimates of past exposure, the methodologies to do this are imperfect. Emphasis on adult exposure and adult cancer risk is therefore driven partly by study design and partly by methodologic limitations. In trying to address cancer control through prevention, does this matter?

It might matter a lot. The above evidence implies that consideration of the first decade and a half of life would provide substantial improvements in cancer risk assessment. However, the major challenge remains of reconstructing past exposure histories either by questionnaires.
or biomarkers, the latter being generally limited by their inherent biological instability. So is there anywhere to turn to better address the questions of early life exposure and cancer risk?

One opportunity rests with birth cohorts, which have been established in a number of countries. These cohorts range from a few thousand subjects to several hundred thousand (15, 16). Some have progressed to such an extent that their participants are young adults, but a relative paucity of adolescent cohorts remains. Many comprise not only detailed questionnaire and clinical data but also valuable banks of biological specimens. Encouragingly, international consortia of birth cohorts such as the I4C (15) or NewGeneris (16) have been formed and promise much in terms of pooled analyses. However, while these cohorts permit opportunities for associations between early life exposures and such childhood conditions as asthma or behavioral problems, what of cancer? Childhood cancers are mercifully rare and thus pose problems in terms of statistical power. For cancer in adults the answers would be many decades away even if the follow-up for these extended periods could be ensured.

Nevertheless, much can be achieved with these resources. Notably, biomarkers of exposure and early biological effects can be applied to the stored biospecimens. The rapid advances in epigenetics (12) and the new technologies offered through "omics" research (17) permit precise questions to be asked about the effect of early exposures on biological pathways implicated in carcinogenesis. This methodology allows comparison of early exposure-driven genetic and epigenetic events with those found in precancerous and cancerous lesions in adults. This is not to trivialize or ignore the many remaining questions to be answered concerning the predictive value of such early effects and the related biomarkers. Nevertheless, through the use of these new tools and a refined understanding of mechanisms one may begin to bridge the gap between early life exposure, early biological effects, and susceptibility to cancer later in life.

There is a problem though. Many birth cohorts are under-resourced, lacking sustainable funding. Cohorts of some age ranges, notably adolescence, are underrepresented. The cancer community and its funders therefore need to recognize the rich resources of data and biospecimens in existing birth cohorts and gaps in coverage by cohorts of other critical periods of life. The opportunities are significant. However, a strategic decision is needed now to provide support, preferably within international consortia, for the kinds of study mentioned above. This effort should specifically include cohorts from low- and middle-income countries. Without such a commitment the risk is that a key component of cancer prevention, namely public health guidance for those in the most vulnerable period of life, will remain without the requisite evidence base for a generation to come.

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**References**


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