

High Birthweight and Cancer: Evidence and Implications

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Several studies have shown a positive association between high birthweight (defined as >4,000 g, or ~8.8 lbs) and increased risk of both childhood and adult malignancies, even after consideration of gestational diabetes. In a recent metaanalysis of 18 studies of childhood leukemia, Hjalgrim et al. (1) concluded that, for each 1 kg increase in birthweight, the risk of childhood acute lymphoblastic leukemia increases by about 14% (95% confidence interval, 1.08-1.20), and the risk of acute myeloid leukemia increases by about 29% (95% confidence interval, 0.73-2.20). Furthermore, there is evidence that, for children diagnosed under 2 years of age, weighing >4,000 g at birth increases leukemia risk by as much as 100% (2, 3). High birthweight is also associated with an increased risk of astrocytomas, but not with other types of childhood brain tumors (4-7). For adult malignancies, several studies have shown positive associations between high birthweight and breast, prostate, endometrial, and colon cancer, although the data are less consistent than for childhood cancers (8-12). Studying these relationships in adults is more difficult because of the long interval between birth and cancer onset. The positive associations with high birthweight may be related to other intervening, and biologically more relevant factors, e.g., childhood and adult obesity (13), breast density (14), and adult height (15). Nevertheless, the growing evidence linking high birthweight to increased risk of certain malignancies raises several questions.

What are the predictors of high birthweight, and what are the recent trends? Gestational diabetes is clearly associated with high birthweight. Positive associations have also been found for multiparity, a previous macrosomic infant, male fetus, maternal and paternal birthweight, ethnicity, gestational hypertension, preeclampsia, and increased interpregnancy interval (16). However, recent studies suggest that high prepregnancy body mass index, along with maternal weight gain during pregnancy, are the most important predictors of having a high-birthweight infant (17-19). With adult overweight and obesity increasing substantially over the last few decades in many developed countries (prevalence now approaching 66% in the U.S.), an increase in the prevalence of high-birthweight infants would be no surprise. In a recent analysis of U.S. and Canadian data, Ananth and Wen (20) showed that term large-for-gestational-age births (birthweight >90 percentile) increased in the U.S. (5% among Whites and 9% among Blacks) and Canada (24%) during the period 1985 to 1998. In Sweden (21) and Germany (22), the prevalence of infants who weighed >4,000 g at birth also increased significantly, from 16.7% to 20.0% and 9.1% to 10.1%, respectively, during the 1990s.

If high birthweight is a risk factor for malignancy, and the prevalence of high birthweight has been increasing over time,

are associated cancer incidence rates, perhaps first reflected in children, increasing? In the most recent analysis of the Surveillance, Epidemiology, and End Results Program data, during the period 1975 to 2002, the incidence of both childhood acute lymphoblastic leukemia and brain tumors increased by 64.8% and 60.6%, respectively; incidence rates were also notably higher when comparing the period 1989 to 2002 and the period 1975 to 1988 (23). Although several factors may account for these increases, including improvements in diagnostic imaging for brain tumors (24), increasing birthweight might be a contributing factor.

What are the potential mechanisms involved and how can they be studied? As noted above, the answer is probably complex and difficult to disentangle, particularly for adult malignancies, making studies of childhood cancer more likely to yield interesting results. We have speculated that relevant growth factor pathways (2) may be important to consider in childhood leukemia. In particular, levels of insulin-like growth factor-I are positively correlated with birthweight (25). With many childhood leukemias known to be initiated *in utero* (26), it would seem logical that high circulating levels of insulin-like growth factor-I may offer a proliferative advantage to already damaged cells. Other areas for investigation include disruption of genomic imprinting associated with overgrowth syndromes such as Beckwith-Wiedemann and Prader-Willi (27); and genetic susceptibility genes associated with birthweight including human leukocyte antigen-G (28), phosphoglucomutase locus 1 (29), and peroxisome proliferator-activated receptor γ 2 (30). In addition to the above growth-related genes, several other factors related to birthweight may be important to explore and to determine whether associations have changed over time (31, 32), i.e., leptin, adiponectin, and sex steroid hormones. The National Children's Health Study may be ideal for collecting pertinent survey and biological information, prospectively, to understand the influences and biological correlates of high birthweight on health in childhood and adulthood.

Much research has been conducted on understanding predictors and biological mechanisms for low birthweight and its prevention. Little attention has been paid to high birthweight. The growing evidence linking high birthweight with cancer makes investigating the mechanisms involved in high birthweight and preventing macrosomia in infants an important research area as well.

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