With few exceptions, most studies have shown an increased risk of premenopausal breast cancer in women who weighed >4,000 g at birth. Postmenopausal breast cancer has also been associated with higher birth weight, although the data are less consistent. Paradoxically, higher body mass index in young adulthood is associated with a decreased risk of breast cancer prior to menopause, although, as might be expected, higher body mass index beyond menopause is associated with an increased risk. Three recent studies have explored some of these associations in more detail.

Ahlgren et al. (1) evaluated growth during childhood and the risk of breast cancer in Danish women. During the period 1930 to 1975, girls in the municipality of Copenhagen had undergone regular school health examinations that included annual measurements of weight and height. Birth weight was recorded as reported by parents. Complete information on weight and height at the ages of 8, 10, 12, and 14 years, as well as age at peak growth, was available for over 117,000 girls. In addition, information on age at menarche was retrieved for a subset of women. Using linkage with the Danish Cancer Registry, 3,340 cases of breast cancer were observed through 2001 over 3,333,359 person-years of follow-up. The investigators found that age at menarche, estimated age at peak growth, and body mass index at age 14 years were all inversely associated with risk of breast cancer. In contrast, birth weight and height at age 14 years were positively associated with breast cancer. Moreover, height at age 8 years, and height increase between the ages of 8 and 14 years were associated with a significantly higher risk. These relationships were unaffected by adjustment for parity, age at first childbirth, or age at menarche. The authors conclude that factors affecting fetal, childhood, and adolescent growth may be important independent risk factors for breast cancer. Michell and Willett (2), in a companion editorial, eloquently remarked: “Currently available data paint a complex picture of the lifetime body build associated with the lowest risk of breast cancer: one would want to be born light, to grow slowly but steadily into a chubby, short child, and to maintain one’s fat mass until one reached menopause, at which point, one would want to shed the excess pounds immediately in order to keep the risk of breast cancer low”. As they later note, however, this outlined life course may not be conducive in avoiding other diseases.

Lahmann et al. (3) explored the association between birth weight and risk of postmenopausal breast cancer in a nested case-control study within the Malmö Diet and Cancer cohort study, which is one of the sites participating in the European Prospective Investigation into Cancer and Nutrition. Breast cancer incidence was assessed during the period 1991 to 2001 among 5,313 women born in Malmö, Sweden between 1924 and 1950. Analyses included 89 female cases ages 55 years and older at breast cancer diagnosis and age-matched controls without a history of breast cancer. Birth characteristics as well as maternal information was available from birth records. Overall, breast cancer cases weighed 93.5 g more than controls, and there were fewer cases with birth weights under 3,000 g compared with controls. Women who weighed >4,000 g at birth had an excess risk of postmenopausal breast cancer (odds ratio, 2.59; 95% confidence interval, 0.95-7.15) compared with controls who weighed <3,000 g. Multivariate adjustment for other breast cancer risk factors including body mass index, age at menarche, parity, age at first birth, use of hormone replacement, or alcohol consumption did not substantially attenuate this risk estimate.

Vatten et al. (4) investigated birth length, birth weight, and head circumference in relation to subsequent breast cancer risk in a cohort of over 16,000 women in Norway born between 1920 and 1958. Using linkage with the Norwegian Cancer Registry, a total of 312 women were diagnosed with breast cancer during the period 1961 to 2001. These included 167 women diagnosed before the age of 50 years and 145 diagnosed at 50 years of age and higher. The median age at diagnosis was 49.1 years. Overall, there was a modest positive association with increasing birth weight (P trend = 0.14), with risk higher among women whose birth weight was ≥3,840 g (relative risk, 1.5; 95% confidence interval, 1.0-2.2) compared with women with birth weight <3,040 g. Adjustment for birth length, however, attenuated this risk. Importantly, the investigators found a statistically significant positive trend across the five categories of birth length. Women in the highest quintile of birth length (≥53 cm) were 80% more likely to develop breast cancer (relative risk, 1.8; 95% confidence interval, 1.2-2.6) compared with women in the lowest (<50 cm) category. This relationship was unaffected by additional adjustment for birth weight. Head circumference at birth was also independently associated with breast cancer risk; women in the highest quintile (≥37 cm) had a relative risk = 1.5 (95% confidence interval, 1.0-2.2) compared with the lowest quintile (<34 cm). Finally, women in the combined highest category for birth weight and length were twice as likely to develop breast cancer (relative risk, 2.1; 95% confidence interval, 1.2-3.6) compared with the smallest group. None of these relationships varied according to whether breast cancer was diagnosed before or after the age of 50 years.

COMMENT: At any given stage in human development, the hormonal environment is complex, so it is difficult to speculate on mechanisms. High birth weight is associated with higher circulating levels of certain growth factors (e.g., insulin-like growth factor-1), which may provide a proliferative advantage to damaged cells. The difficulty with making the link to breast cancer is the long latency period accompanied by several intervening factors (such as age at menarche, growth during puberty, etc.) that may also play a role. Intriguingly, high birth weight has also been associated with an increased risk of childhood malignancies, including acute lymphoblastic leukemia and neuroblastoma (5-7). Because the latency period is much shorter for children, our understanding of how high birth weight increases cancer risk might be more readily answered in a younger population. With the exception of gestational diabetes, we also know very little about the causes of high birth weight, and studies in this area may be of interest. Finally, we need to design studies that bring us closer to understanding why increased body mass index in adulthood is a risk factor for many malignancies. While it can be speculated that the
obesity-cancer link involves “hormones” or “immune dysregulation”, clinical and animal studies are needed to answer key questions. For example, prospective cohort studies with stored sera could illuminate the biological mechanism(s) underlying the apparently paradoxical, negative association of increased body mass index with premenopausal breast cancer and its positive association with postmenopausal breast cancer. —Julie A. Ross (University of Minnesota, Minneapolis).

References

Breast Cancer and Body Mass: When is it OK to be Too Little, Too Big, or Just Right?

Julie A. Ross


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