Commentary: Inter-ethnic studies of breast cancer risk

Mona Okasha

In this issue of the International Journal of Epidemiology, Lagiou and colleagues present data comparing maternal anthropometric determinants of birthweight in USA and China.1 They performed two parallel cohort studies of pregnant women, and described the determinants of the offspring’s birthweight within each population. They then looked for determinants of the difference between the birthweights, in an inter-population comparison.

Higher birthweight has been repeatedly shown to be associated with a higher breast cancer risk in data from case-control studies2,3 and cohort studies.4,5 Although not all studies have replicated this finding,6,7 the weight of evidence suggests that there is a modest, positive association between birthweight and breast cancer. The strength of the relationship varies between studies, but is in the range of 50% to 100% increased risk when comparing the top to the bottom quartile of the birthweight distribution. It is of interest to note that most of the above

References

10 Lipworth L, Hsieh CC, Wide L et al. Maternal pregnancy hormone levels in an area with a high incidence (Boston, USA) and in an area with a low incidence (Shanghai, China) of breast cancer. Br J Cancer 1999;79:7–12.
studies were performed in Caucasian populations, and the only study carried out in a low-risk population (Shanghai) did not find any evidence of an association between birthweight and breast cancer.  

Lagiou's study found a number of interesting associations in the crude intra-population comparisons. These included higher birthweight among the offspring of women who were taller, heavier, and gained weight during pregnancy. What the authors do not comment on is the differences in magnitude of the associations found between US and Chinese women. For example, the birthweight increase associated with each 2 kg/m² higher pre-pregnancy body mass index (BMI) was 15 g (SE: 18 g) in the US and 129 g (SE: 28 g) in China. In the intra-population comparisons, the authors found that the difference in mean birthweight between American and Chinese infants (105 g) was entirely explained when adjusted for maternal anthropometric factors (height, pre-pregnancy BMI, and weight gain in pregnancy).  

Chinese women experience a considerably lower risk of breast cancer than Caucasian American women. Lagiou and colleagues speculate that their observations could allow an explanation of the pattern of higher breast cancer incidence among Chinese Americans over successive generations due to changes in maternal anthropometry. However, the epidemiological evidence regarding the change in disease rates in Chinese migrants remains equivocal. A review of Chinese migrants to North America found standardized mortality ratios (SMR) of 0.5 to 0.8 among first-generation migrants. Breast cancer mortality was similar in second compared with first generation immigrants. However, other studies have shown increases in breast cancer rates over generations, and these eventually approach the rates experienced by Caucasian Americans. A clearer understanding of determinants of inter-ethnic differences in breast cancer is required before accepting the suggestion that maternal anthropometry may be the key to understanding these differences.  

The authors acknowledge that the magnitude of the association between birthweight and breast cancer is too small for this to be the only explanation of the difference in the incidence of breast cancer between the US and China. They postulate that birthweight may be magnified by features of childhood growth to affect breast cancer risk through mammary gland mass.  

It has been suggested that birth size is related to breast cancer, since larger breasts may contain more cells susceptible to malignant change. Breasts are composed not only of glandular tissue, in which cancers arise, but also of fibrous and fatty tissue. Given the differences in levels of obesity between America and China, observed differences in breast size between the countries may be due to fat deposits rather than differences in the amount of glandular tissue in the breasts of women. This is supported by the observation that the difference in mammographically dense breast area between Caucasian and Chinese women in Hawaii is substantially attenuated having adjusted for BMI and other factors. New techniques in the manipulation of digital images can determine the relative volumes of glandular and fatty tissue in the breast. This will allow a better understanding in the future of the importance of breast components in relation to cancer risk.  

The authors suggest that small differences in birthweight and pre-adolescent growth may interact to produce large differences in mammary gland mass, leading to an increased risk of breast cancer. This suggestion is consistent with observed modification of the association between birthweight and breast cancer by childhood growth which has been demonstrated by De Stavola and colleagues. Using data from the 1946 UK birth cohort, they described fourfold risks of breast cancer among women who were born heavy (>3.5 kg) and grew to a taller height in childhood (>1.22 m at age 7), compared with those born light (<3.5 kg). Whether this observation could be related to the development of larger breasts among girls who grow taller in childhood is not suggested by De Stavola and colleagues. They do postulate that higher levels of insulin-like growth factors (IGF) may underlie observed associations between growth and cancer risk. Associations between height and cancers of the colorectum and prostate may also be explained by the actions of IGF.  

In conclusion, the results presented in Lagiou's paper are of relevance to breast cancer aetiology. They provide further evidence of an association between perinatal events and breast cancer in two populations that experience different risks of disease. To investigate the authors' hypothesis further, an ideal study would involve considerations of inter-generational effects of maternal and offspring anthropometric measures at birth and in childhood, as well as breast size and cancer incidence data among Chinese, Asian American, and Caucasian American women. In the absence of ideal research, we must continue to make inferences regarding breast cancer aetiology from studies such as Lagiou's.