

Perspective

Birth Size and the Pathogenesis of Breast Cancer

Pagona Lagiou, Dimitrios Trichopoulos*

In a major undertaking reported in this issue of *PLoS Medicine*, a collaborative group co-ordinated by Isobel dos Santos Silva provide all but conclusive evidence that birth size is a predictor of breast cancer risk in adult life [1]. The researchers compiled and reanalysed individual participant data from 32 studies, comprising 22,058 cases of breast cancer. On the basis of reliable data retrieved from birth records, they found that an increase of birth weight by 500 grams was associated with a statistically significant 6% increase in breast cancer risk; whereas, controlling for birth weight, an increase of birth length by two centimetres was associated with a 9% increase in this risk. The relative size of the effects is small, but the individual studies driving the conclusion were of sound epidemiological design (cohort or nested case-control) and relied on objectively documented birth size parameters, allowing little room for selection or information bias. Now that the question of whether birth size is associated with breast cancer risk appears to be settled, a number of additional questions need to be addressed.

How Important Are These Findings in Biological and Practical Terms?

In practical terms, a 10% increase in breast cancer risk at the higher birth size category is certainly small, but not trivial for a common disease like breast cancer. Indeed, the gradient is in the same order of magnitude as that found for other common risk factors for breast cancer, such as age at menarche, age at menopause, or postmenopausal obesity [2]. And, from a biological point of view, it is certainly important to document a phenomenon that indicates the

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Linked Research Article

This Perspective discusses the following new study published in *PLoS Medicine*:

dos Santos Silva I, De Stavola B, McCormack V, Collaborative Group on Pre-Natal Risk Factors and Subsequent Risk of Breast Cancer (2008) Birth size and breast cancer risk: Re-analysis of individual participant data from 32 studies. *PLoS Med* 5(9): e193. doi:10.1371/journal.pmed.0050193

Isobel dos Santos Silva and Bianca De Stavola and colleagues reanalyzed individual participant data from 32 published and unpublished studies to obtain precise estimates of the association between birth size and breast cancer risk.

involvement of intrauterine processes in a major human cancer, as has already been done in animal models [3].

Can the Results Help To Explain Patterns in Breast Cancer Incidence Around the World?

The observation of sharp ecological contrasts in breast cancer incidence around the world is one of the most challenging features in the epidemiology of the disease, and every hypothesis on the aetiology of breast cancer should be able to accommodate these contrasts. Breast cancer incidence among women of European descent in the Western world is several times higher than that among Chinese or Japanese women in Asia. The gradual elimination of this difference over several generations among Asian migrants in Western countries implies that genetic factors are not responsible for the ecological contrasts [2].

In our view, the results of the new collaborative group study [1] are compatible with the ecological patterns of breast cancer incidence. Newborns

in China have lower birth weight than newborns of European descent in the United States, largely due to differences in maternal anthropometry that impose physical constraints on newborn size [4]. Migration from China to the US is associated with increased energy intake, leading to increased adult body size (including pelvic size), and consequently to the removal of constraints on birth weight. The cycle tends to repeat itself over consecutive generations of Asians migrating to the West and is associated with a gradual increase of breast cancer incidence in this population [4]. In the collaborative group study [1], controlling for adult height only slightly reduced the association of birth size with breast cancer risk, but, as the authors indicate, the adjustment was based on a small number of cases and misclassification may have hindered documentation of an important mediating role of adult height.

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Pagona Lagiou and Dimitrios Trichopoulos are in the Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts, United States of America. Pagona Lagiou is also in the Department of Hygiene, Epidemiology and Medical Statistics, School of Medicine, University of Athens, Athens, Greece.

* To whom correspondence should be addressed. E-mail: dtrichop@hsph.harvard.edu

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Can We Integrate the Study's Findings into Our Current Understanding of the Early Stages in the Natural History of Breast Cancer?

Our current understanding of the early stages in the natural history of breast cancer is limited. Hilakivi-Clarke and de Assis have suggested that epigenetic modifications associated with large birth size lead to modifications in mammary gland development and increased vulnerability of epithelial targets for malignant transformation [3]. It has also been postulated that higher birth size is associated with higher levels of pregnancy hormones, including estrogens and insulin-like growth factor 1, which favour the generation of a higher number of susceptible stem cells with compromised genomic stability [5]. In this context, mammary gland mass, an important determinant of breast cancer risk, could be viewed as an adult life correlate of the number of mammary cells susceptible to transformation [5,6]. The group led by Chung-Cheng Hsieh of the University of Massachusetts is doing important work in this field. This group has reported that high levels of insulin-like growth factor 1 and estradiol are associated with larger pools of stem cells in the cord blood [7], and that birth size is also associated with the stem cell pool [8].

Are There Implications for the Primary Prevention of Breast Cancer?

Documentation of a positive association of birth size, particularly birth length, with breast cancer risk in adult life may improve prediction of disease risk, but does not offer much opportunity

for prevention, particularly since birth size is inversely associated with cardiovascular risk [9]. The situation could change if other periods in early life, particularly postnatal life, were found to be related to adult life breast cancer risk. In any case, recognition of early life influences as critical in the aetiology of breast cancer helps to explain why several adult life primary prevention practices have been of limited effectiveness.

Are Perinatal Exposures Important for Breast Cancer Only, Or Could They Affect Risk of Other Cancers As Well?

The mammary gland seems to be the only organ that is not fully developed at birth [10], which implies that mammary tissue-specific stem cells may remain in a quiescent stage for longer periods than tissue-specific stem cells for other organs. This could provide an explanation for why intrauterine factors are more important for breast cancer than for other cancers. It is reasonable, however, to expect that intrauterine factors could affect the risk of other forms of cancer, albeit to a lesser extent. In fact, weak birth weight associations have been reported for other cancers, although the evidence is still limited [11].

The intrauterine life has been implicated in the aetiology of breast cancer on the basis of theoretical arguments and epidemiological considerations [12]. However, the documentation of its role in breast cancer risk has relied on studies linking birth size to this risk. The Collaborative Group on Pre-Natal Risk Factors and Subsequent Risk of Breast Cancer has elegantly and most efficiently

reanalysed these studies and, by pooling together data at the individual level, has provided the strongest evidence yet that birth size is a critical determinant of breast cancer risk in adult life. ■

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