

Commentary

Breast cancer and childhood anthropometry: emerging hypotheses?

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Published: 11 March 2005

This article is online at <http://breast-cancer-research.com/content/7/3/83>

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Breast Cancer Research 2005, **7**:83-85 (DOI 10.1186/bcr1014)

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Abstract

In this issue of *Breast Cancer Research*, Baer and colleagues report a strong protective effect of childhood and adolescent body fatness on premenopausal breast cancer risk based on a large prospective study. Methodological issues are discussed, as are tentative biological interpretations regarding the findings.

In this issue of *Breast Cancer Research*, Baer and colleagues [1] report a strong protective effect of childhood and adolescent body fatness on premenopausal breast cancer risk. The report is based on the Nurses' Health Study II, a prospective cohort study including 116,671 US female nurses, aged 25–42 years at recruitment in 1989, in which 1318 breast cancer cases occurred during 12 years of follow up. There were slightly stronger associations between average childhood and adolescent body fatness and incidence of premenopausal breast cancer, with relative risks of 0.48 (95% confidence interval 0.35–0.65) and 0.57 (95% confidence interval 0.39–0.83) in women who were plump compared with those who were thin at ages 5–10 and 10–20 years, respectively. However, with two such highly correlated measures, it is difficult to assess whether body fatness at any one period is of importance, or whether they simply reflect the effects of one another. We are also presented with risk estimates claimed to support a protective role of increasing body fatness between the various young ages but, with only two measures presented (starting body shape and ending body shape), disentangling the effects of starting shape and ending shape from the impact of the actual change *per se* is problematic. This conundrum is often referred to as the 'horse-racing effect' (i.e. those who run faster always win the race), and those whose shape increases the most will always be in the highest ending categories [2]. A more notable observation in these findings

is that the often reported inverse association between adult body mass index (BMI) and risk is attenuated, and no longer statistically significant, after adjustment for childhood fatness.

As for causal mechanisms underlying the findings, we are left with few clues. The investigators found little evidence of any possible confounding or intermediate causal factors such as birth weight, adult body fatness, age at menarche and other menstrual characteristics associated with anovulation and hence reduced levels of ovarian steroids. The further adjustment of analyses for height, physical activity and diet had little impact on the estimated relative risks, strengthening the validity of the reported association between early life body fatness and breast cancer.

The investigators collected self-reported data on body fatness at ages 5, 10 and 20 years, using a nine-level somatogram, before breast cancer diagnoses. Thus, although misclassification may be present, it will be nondifferential with regard to case-control status. Any such misclassification will result in a dilution of the estimated associations, which renders the substantial protective influence of pre-adult body fatness in this study even more thought provoking. Ahlgren and colleagues [3] recently reported a weaker association with BMI at age 14 years, based on a large Danish study with more accurate measures of early life anthropometry retrieved from school records. Indeed, although the worldwide evidence supports a protective role of childhood and adolescent body fatness on breast cancer risk, the decrease in risk does not appear to match the findings of Baer and coworkers in magnitude [3–8]. Furthermore, it is notable that, in a validation study comparing measured height and weight at age 15 years with recalled childhood body shape assessed by somatogram 50 years later, those girls in the highest somatogram categories only had a BMI of

approximately 25 kg/m² [9]. Furthermore, the validity of the pictograms to discriminate between extreme levels of childhood obesity remains an open question, because the drawings corresponding to the highest scores have a range of adult features.

The influence of endogenous exposures in childhood and adolescence on breast cancer risk is a rather novel research theme that, while offering little prospect of identifying preventive strategies, promises new leads in breast cancer aetiology. Interest in this area was initiated by the recent recognition that early life exposures may be pertinent in aetiological research [10]. A few specific observations have led investigators to focus on adolescence as a particularly relevant exposure window with regard to breast carcinogenesis; studies of atomic bomb survivors have shown that the carcinogenic effect of ionizing radiation decreases with age of exposure, with the greatest increases in risk among women younger than 20 years at the time of the bombings [11]. This may tentatively be explained by findings from animal studies, which showed that the mammary epithelium is undifferentiated and highly proliferative – and thus particularly susceptible to carcinogens – from puberty to termination of the first pregnancy, when a momentous differentiation occurs [12].

Anthropometric measures appear to be fundamentally linked to breast carcinogenesis. Postmenopausal breast cancer risk increases with BMI, largely as a result of the related increase in endogenous oestrogen levels [13]. In contrast, obesity appears to protect against premenopausal breast cancer, a relationship that is often hypothesized – but still not proven – to be mediated by anovulatory menstrual cycles [14]. The biological interpretation of the relationship between childhood body fatness and breast carcinogenesis is even more intriguing. Because plump girls have on average an earlier menarche (a factor known to increase breast cancer risk) as compared with their thin peers, childhood body fatness could be assumed to increase breast cancer risk [15]. The current findings further fail to support a substantial role for progesterone-deficient menstrual cycles in the causal pathway between early life body size and breast cancer development. Childhood body fatness is inversely associated with adolescent peak height velocity, a factor that was recently demonstrated to be positively related to breast cancer risk [3,7,8]. However, results from the Danish study imply that BMI at age 14 years confers an influence on risk over and above that of stature at ages 8 and 14 years (as well as of high birth weight but interestingly not of age at menarche) [3].

Finally, increased levels of bioavailable oestradiol, which may result from increased production of oestrogen by aromatase in adipose tissue and lowered sex hormone-binding globulin concentrations, has also been suggested to be the causal link between early life obesity and breast carcinogenesis [8].

Although the aetiology of breast cancer is closely linked to oestrogen [16], it has been hypothesized to have a dual impact on breast cancer risk, depending on the timing of exposure [17]. Recent animal studies suggest that prepubertal oestrogen exposure may induce differentiation and thus eliminate targets for malignant transformation [17]. Oestrogenicity may also upregulate *BRCA1*, a tumour suppressor gene [17], and thereby maintain genomic integrity and DNA repair. As a corollary, prepubertal exposure to 17 β -oestradiol was shown to reduce later risk for chemically induced mammary tumours in rats [17]. However, the literature does not provide firm evidence that childhood body fatness is clearly associated with oestrogen levels [18]. Furthermore, the reduced risk for breast cancer is noted both with body fatness before menarche and in adolescence, although these effects are not easily separated. The association between adolescent obesity and breast carcinogenesis could not be accounted for by oestrogenicity if ovarian steroid production rather than adipose tissue is assumed to constitute the major source of oestrogen levels after menarche.

In conclusion, recent findings from the Nurses' Health Study II provide further support for a protective effect of childhood and adolescent obesity on breast cancer development, but the biological explanation for this association remains unclear. Epidemiologic studies are unlikely to unravel in great detail how adiposity at various early ages influences breast cancer risk, because such measures are highly correlated and may be subjected to non-differential as well as differential measurement errors. Instead, further knowledge about the physiological correlates of obesity and their effects on the prepubertal and adolescent mammary gland could provide important keys to our understanding of breast cancer aetiology.

Competing interests

The author(s) declare that they have no competing interests.

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