

development in offspring as well as in mothers.² Besides breast cancer, cancers in mothers included large bowel, endometrium, and melanoma. The risk of tumour development was higher in mothers in whom cancer was diagnosed after age 50 years.²

Large-baby birth is related in later life in mothers not only with diabetes mellitus and cancer development, but also with polycystic ovarian disease, psoriasis,³ and some other pathological states. By contrast, the higher risk of death from ischaemic heart disease in adulthood is related not to large but to low birthweight.⁴ The cause of such a difference deserves further consideration. Intrauterine effects of large-baby birth on risk of cancer development can (as Michels and colleagues also state) be mediated not only by hyperproduction of oestrogens during pregnancy but also by other factors. As a highly plausible additional explanation we mention the role of hyperinsulinaemia² and increase in IGF secretion, whose combined effect may lead to both cellular hyperproliferation and cellular hypertrophy in fetal and maternal tissues.⁵

We believe that large-baby birth should be viewed not only as a marker and predictor of increased risk for cancer development in offspring and mothers^{1,2} but also should be the focus of preventive efforts in oncology and as an indirect criterion of their effectiveness;² this is especially important because the secular trend for birthweight to increase has not yet stopped.

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SIR—Michels and colleagues¹ and Vatten² in his accompanying commentary speculate on possible working mechanisms for the prenatal origin of breast cancer. I would add the following points. In 1979 we published the first article on the long-term consequences of an abnormal intrauterine environment.³ After a few years of scepticism our finding was confirmed by several research groups.

In our experimental work in the rat we have further shown that fetal macrosomia, associated with hyperinsulinism, is related to reduced insulin secretion in later life, and that fetal growth retardation, associated with hypoinsulinism, is related to insulin resistance in later life.⁴ Moreover in the man we have shown that fetal growth retardation predisposes to later pre-eclampsia.⁵ Vatten thinks that fetal growth per se could contribute to the pathogenesis of breast cancer. Fetal overgrowth is mainly associated with increased insulin and IGF activity. Both are the most important growth factors during fetal life. More pronounced insulin and IGF activity might result in increased mitosis in the fetal mammary gland, which in turn could be responsible for later development of breast cancer.

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- 1 Michels KB, Trichopoulos D, Robins JM, et al. Birthweight as a risk factor for breast cancer. *Lancet* 1996; **348**: 1542-46.
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Authors' reply

SIR—The sole purpose of the standard 95% CI, displayed in Peto's and our tables, is to provide valid pairwise comparisons between the first (4 kg or more) birthweight category and another category. The standard intervals are just right for this purpose, neither too narrow nor too wide. The floated intervals are not confidence intervals for odds ratios and should not be confused with them. For example, the interval around the odds ratio in the first category can have no such meaning since the odds ratio of 1.0 has no sampling variability. We agree with Peto that it would in general be useful to provide additional information that would allow an approximate statistical comparison of any two odds ratios but only in addition to, not in place of, the standard intervals. The best way of doing so might be to report the floated variance of the log odds in each group, which in decreasing order of birthweight, would be 0.0254, 0.0109, 0.0070, 0.0137, and 0.0459. Since we

reported trend tests and provided explicit comparisons of those categories we found most scientifically relevant to compare, the analyses we published were sufficient for proper assessment.

Van Assche, Stoll, and Berstein for possible mechanisms for the association between birthweight and future breast cancer risk. Birthweight is likely to be only a proxy for a mechanism yet to be unveiled. We agree that levels of IGF1 could well play a part. Pursuit of mechanisms that account for this relation is warranted as this may provide leads for preventing this disease.

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Escherichia coli O157: outbreak in central Scotland

SIR—The recent extensive community outbreak of *Escherichia coli* O157:H7 (phage type 2, VT2+) in central Scotland has once again focused attention on this troublesome bacterium. The epicentre of the Lanarkshire cases (185 to date confirmed by culture) was within the area served by this hospital, with most primary isolations being made by our laboratory.

Although *E coli* O157:H7 has previously created havoc in Lanarkshire,¹ the incidence from 1984 to 1994 was reported to be below the Scottish average.² In this laboratory, selective screening by clinical criteria began in 1987.³ By 1994, all outpatients in addition, were being screened, and in January, 1996, following publication of the report on verotoxin-producing *E coli*,⁴ the decision was taken to screen all faeces, without qualification. 27 isolations were made during the 10-year period, arising from 17 incidents. 14 incidents involved apparently unlinked single patients. Isolations post-1990 declined up to 1996, despite the extension of screening. The bacterium was absent in 2 of the past 4 years.

Low prevalence is no excuse for overlooking this destructive micro-organism. I am aware of at least one laboratory in the UK that still does not include screening for *E coli* O157 in its repertoire, even when a relevant clinical history is noted, its perceived rarity locally being the governing factor. The recent exhortation to "remember to test diarrhoeal stools for *Escherichia coli* O157"⁵ should be religiously followed. This is a devastating pathogen which