European Journal of Cancer Vol. 32A, No. 11, pp. 2029–2030, 1996

Printed in Great Britain
0959-8049/96 $15.00 + 0.00

Letters

PII: S0959-8049(96)00215-8

Letters to the Editor: Comments on *Does Age at Last Birth Affect Breast Cancer Risk?*, Hsieh *et al.*, *European Journal of Cancer*, 32A, No. 1, pp. 118–121, 1996

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WE ARE glad that at last the effects of age at last full-term pregnancy (FTP) on breast cancer risk have been seriously examined [1] in the light of our article [2] in which we suggested that age at last FTP could have an independent effect on breast cancer risk and that this may be more important than age at first FTP. In the interim, we have had the opportunity of expressing our ideas on this topic [3, 4] which is indeed a very complicated area of biostatistical research due to the inherent confounding between the various variables. Thus, for the sake of brevity, we shall make only some specific comments on the paper by Hsieh and colleagues [1].

It was found by Hsieh and colleagues [1] that first FTP was a stronger risk factor for breast cancer than last FTP. This is not surprising as their report used the same data on which the age at first FTP hypothesis was originally founded. Indeed, it was in reference to MacMahon's original paper [5] that we previously [3] commented that the first FTP hypothesis may not be so "simple and plausible" [1] as it may at first seem. If one examines the graph [5] presented in the original paper by MacMahon and colleagues, of how breast cancer risk increases with age at first pregnancy, one observes that the risk exceeds that of nulliparous women at around 33 years of age. This observation challenges the hypothesis in that the first pregnancy "induces irreversible changes" [5] in the breast which provide subsequent protection; length of exposure is surely greatest among nulliparous women. The most probable explanation is that pregnancy also incurs a certain degree of risk that is related to age; the older the woman, the greater the detrimental effect could be. In this case, the most relevant pregnancy would be the last.

With regards to the comment by Hsieh and associates that "misleading results may be obtained when parity is only adjusted in broad categories . . ." [1], practically identical results to our "grouped parity" results were found when parity was adjusted as a factor with a separate level for each different parity. The use of the larger groups was statistically more efficient.

The use of age at all pregnancies [1] by Hsieh and colleagues in the more refined model probably confuses somewhat the relationships. Firstly, the colinearity between the age variables could produce rather erratic results. Secondly, it is not clear how these variables were handled; for instance, age at the fifth pregnancy must have had a great deal of missing values (especially as conditional logistic regression was used) if some value was not given to this variable, as few women will have had five pregnancies. For these reasons, the final results are a little hard to interpret. As was carried out, it is of interest to restrict the analyses by removing uniparous women, although these results had been adjusted by age at all births.

Their study size permitted reducing analyses to only those women with two pregnancies. In this case, all the problems of confounding by parity are removed and the results are relatively clean. Consistent with all their results [1], this subanalysis produced an increased risk of 12% for first FTP and 8% for last FTP, but neither were statistically significant. The relative magnitudes of the effects of first FTP and last FTP, as suggested from our Brazilian case–control study [2] and by Kvåle and Heuch in their Norwegian cohort study [6], do differ from the study by Hsieh and colleagues [1]. This could be a chance fluctuation, as our study was relatively small in comparison with the sample used by Hsieh and colleagues [1], although the Norwegian cohort was certainly not small (63,090 women followed up for 20 years). More recently, a further Norwegian study [7], this time a cohort of 1 million women, was indicative of an independent effect of last FTP; this study should have been cited. In correspondence concerning this Norwegian study, it was commented that it is difficult for epidemiological data to decipher whether the underlying mechanism can be viewed as "decreased risk associated with low age or as increased risk associated high age" [8]; the former would favour the hypothesis of age at first FTP, the latter favouring last FTP. It is probably more prudent, at present, to consider that pregnancies exert a dual effect (risk and protection) that is determined by age at the pregnancy.

We are happy that Hsieh and colleagues undertook this study as the original MacMahon hypothesis [55] of age at first FTP deserves to be challenged due to the complexity of the interrelationships involved. However, the evidence presented does not refute the suggestion of an independent effect of age at last FTP, indeed, some evidence has been presented that indicates that last FTP is related to breast

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cancer risk. Further work along the lines proposed by Hsieh and colleagues [1] should be undertaken.

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European Journal of Cancer Vol. 32A, No. 11, p. 2030, 1996

Printed in Great Britain
0959-8049/96 $15.00 + 0.00

PII: S0959-8049(96)00216-X

Response from C.-C. Hsieh,[1] M. Lambe,[2] A. Ekbom,[2] H.-O. Adami,[2] H.-W. Chan,[3] and D. Trichopoulos[3]

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WE AGREE with Maguire and Kalache that age at any pregnancy including the first and the last should be carefully studied because nature may be hiding an important clue about the origin of breast cancer in the complex way that successive pregnancies affect human physiology. At this stage, given a recent large population-based study from Sweden that has reported almost exact findings as ours [1], it cannot be conclusively stated whether the data of Kalache and colleagues [2] or our data are out of line. However, cessation of protection against breast cancer by a pregnancy that occurs after a certain age (perhaps around 35 years) has been given an adequate explanation even in the earlier paper by MacMahon and associates [3]. Experimental evidence has also shown that the mammary gland is particularly vulnerable to carcinogenic stimuli between puberty and the first pregnancy [4]. Thus, in comparison to subsequent pregnancies, the first birth in a multiparous woman represents a more significant biological event as it determines the duration of this period of increased susceptibility.

Many of the issues raised by Maguire and Kalache have been addressed in a recent paper of ours [5], and we cannot but agree with them that there are complex statistical issues and biological considerations that defy simple answers. A conceptual concern that we have with the notion that the last pregnancy has an overwhelming effect is that, contrary to first pregnancy which would always be the first, every pregnancy is the last until a new one occurs. In other words, no single pregnancy can be identified as the last in a fertile woman until much later. Hence, while unique biological effects on the breast are likely to occur during a first pregnancy, they are unikely to occur during a last pregnancy. This duality requires that the effect of every pregnancy with respect to breast cancer risk should interact with time since that pregnancy, an issue that has only recently received attention [5–7].

Correspondence to C.-C. Hsieh.

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