Letters to the Editor

Risk Factors for Breast Cancer in Brazil

From ANDREW MAGUIRE AND ALEX KALACHE

Sir—In a recent article by Gomes et al.\(^1\) they report the findings of a case-control study of risk factors for breast cancer in Brazil. They conclude that potential risk factors behave in the same way as demonstrated in the rest of the world and that the study provides clear documentation of 'breast cancer epidemiology' (p. 292)\(^1\) in Brazil. We would like to highlight some apparent oversights by the authors and to draw attention to the analytical complexities of breast cancer research especially when reproductive risk factors are being evaluated.

They mention that Brazil shows an apparent contrast in that the breast cancer rates are relatively high in comparison with their Latin American neighbours. Previous research on breast cancer had already indicated the importance of conducting studies in Brazil because of such contrasts,\(^2\) which, if classified, could lead to a better understanding of breast cancer. However, they erroneously state that the study 'represents the first large hospital-based, case control study of risk factors for breast cancer conducted in Brazil' (p. 294).\(^1\) Two other studies on breast cancer in Brazil have been published,\(^3,4\) the first in the early 1970s.\(^3\) The second relates to a case-control study on risk factors for breast cancer, and was undertaken in the early 1980s\(^5\) in Recife and Fortaleza, two large cities of Northeast Brazil. The cases were breast cancer patients admitted to any of the several hospitals which deal with breast cancer in these two cities, to whom hospital and community matched controls were assigned. This study was larger than that of Gomes et al.\(^1\) and used interview based questionnaires instead of medical records. Results have subsequently been published.\(^4\) These results, presented by Kalache et al.\(^4\) suggested that age at last Full-Term Pregnancy (FTP) was an independent risk factor for breast cancer. This challenged the view that age at first FTP was the principal reproductive risk factor for breast cancer. The close similarity to the findings of a very different study, namely that of a large cohort of Norwegian women,\(^5\) gave plausibility to the results of the previous Brazilian study.\(^4\)

Determination of risk factors for breast cancer is complex due to the inherent interrelationships between the potential risk factors. This has recently been discussed elsewhere.\(^6,7\) However, once again we feel it appropriate to remark on these complexities and to warn against systematic modelling without considering such interrelationships. Gomes et al.\(^1\) included in their final multivariate model only those variables that had been shown to be univariately significant. However, a variable may have its true effects suppressed if other correlated variables are not taken into account. This can be denominated as 'negative confounding'. In the case of the effect of age at last FTP such a situation arises due to its positive correlation with parity (protector). Thus univariately, the effect of age at last FTP would be reduced or even non-significant if not adjusted by parity. The existence and direction of interrelationships should be considered so that appropriate models are constructed and changes in risk factor coefficients are viewed in light of their expected changes.

The 'Oestrogen Window' hypothesis\(^8\) on which the supposed causal relationship of the age at first FTP is based, is questionable. This has been discussed elsewhere.\(^6\) This together with the growing evidence that pregnancies other than the first exert independent effects on breast cancer risk\(^9\) suggest that research on reproductive risk factors for this cancer should be widened to include events occurring later on in the woman's reproductive history. This is not to say that age at first FTP should be overruled.

In the light of the findings of the previous Brazilian study\(^4\) and the Norwegian study\(^5\) as well as the possible lack of coherence\(^6\) of the 'Oestrogen Window' hypothesis, it would have been desirable if age at last FTP could have been considered by Gomes et al.\(^1\) Indeed, the Brazilian population offers a special opportunity to study these potential risk factors due to the wide range of parity.\(^10\) Naturally, there are other considerations such as the possible effect modification of risk factors by menopausal status that should be analysed. Also data

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quality was not evaluated. It would be of interest to know if there were systematic differences in age or other covariables between women with more complete medical records than those for whom information such as age at first FTP was lacking. Indeed, age at first delivery was available for only 49% of the cases; however for the controls this figure was reduced even further: 25.5%.

Lastly, it is unlikely that a single case-control study based in one single hospital in a large city, relying on information recorded in medical notes over a ten-year period, could provide ‘clear documentation of breast cancer epidemiology in Brazil’ (p. 292).\(^1\) no rates or population denominators are given, and the larger and more systematic previous studies\(^3,4\) on this disease in Brazil are not cited.

We agree with their final comment\(^1\) that further large studies are needed. Naturally, these should be well designed and have data of sound quality. We also hope that future investigations will take a broader look at reproductive variables and their role in breast cancer aetiology. Indeed, those carried out in areas where parity may be highly variable, such as Gomes et al.,\(^1\) can provide especially appropriate study bases. In such circumstances it is easier to disentangle the interrelated effects of the reproductive variables.

**Authors’ Response**

From ANA L R R GOMES, M D C GUIMARAES, C C GOMES AND A F CAMARGOS

Sir—Firstly, we would like to thank Kalache and Maguire for their comments regarding our recent paper on risk factors for breast cancer.\(^1\)

The aim of our study\(^1\) was to evaluate selected socio-economic, demographic and reproductive risk factors for breast cancer in an urban area, Belo Horizonte, as clearly stated in the paper. We never intended to extrapolate our findings as the letter from Kalache and Maguire seems to imply. The study site, the Mastology Clinic at the Federal University of Minas Gerais was the major centre for breast cancer treatment in the city during the study period, 1978–1987.

At the time of our literature search (December 1991), we believed that our study was the largest hospital-based case-control study published using data from Brazil. The study by Recife and Fortaleza,\(^2\) although carried out in the early 1980s, was only published in 1993. Unfortunately, we could not include that reference in our paper. On the other hand, we did reference the multicentre study which included Sao Paulo as one of the centres and was cited in the Macmahon reference.\(^3\) This reference and the analysis of reproductive factors in our paper may, indeed, have had limitations in modelling of the variables. This point is clearly stated in the paper and it was our final recommendation that other studies be conducted in order to ascertain better the relationship between breast cancer and reproductive factors. We do not think, however, that this would substantially change our main conclusions. According to Kelsey,\(^4\) the various reproductive variables are highly correlated with each other and since the effect of any one of them on breast cancer risk appears to be modest, chance or slight methodological variations may cause different studies to find one or other of these reproductive variables to be more ‘important’.

In the absence of known biological mechanisms of pathogenesis, studies conducted to sort out the effects...