—In reply

Our two main conclusions[1] have been supported by subsequent evidence. The first was that many, and perhaps most, breast cancers arise in a susceptible minority of women. A recent segregation analysis[2] suggests that half of all breast cancers arise in the most susceptible 12% of the population. Our second conclusion concerned the incidence rate in relatives at ages older than the index patient's age at diagnosis. The recent overview[3] confirms our observation that this eventual rate in her relatives is independent of the index patient's age at diagnosis. In the data we analyzed, the rate in breast cancer patients' relatives at ages older than the index patient's age at diagnosis showed no trend with age up to age 70. We observed an increase above age 70, however, and stated that incidence rates in first-degree relatives would be expected to increase slightly with age under the 'constant risk' model that we proposed, in which the rate in patients' contralateral breasts (and in their monozygotic twins) is roughly constant at all ages. This increase must be weaker than in the general population, as the relative risk in patients' relatives declines as they get older[3]. The only data presented by Hemminki at ages older than the mother's age at diagnosis are for ages 40–54 in daughters whose mothers were diagnosed at 30–39 and for ages 50–66 in daughters of women diagnosed at 40–49. Confidence intervals are not shown, but these rates are probably consistent with a weak increase with age of this sort. Breast cancer rates have, however, been distorted by recent age-related changes in diagnosis and treatment. In Britain, for example, the recorded breast cancer rate at ages 50–64 rose by almost 60% while mortality fell by 30% after routine mammography and modern chemotherapy were widely adopted in the late 1980s, and the contralateral rate is substantially reduced by prolonged treatment with tamoxifen. The incidence patterns that we observed may therefore be altered, perhaps substantially, in more recent series such as Hemminki's.

Julian Peto

Section of Epidemiology, Insitute of Cancer Research, Sutton, Surrey, UK and London School of Hygiene and Tropical Medicine, London, UK. e-mail: j.peto@icr.ac.uk

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