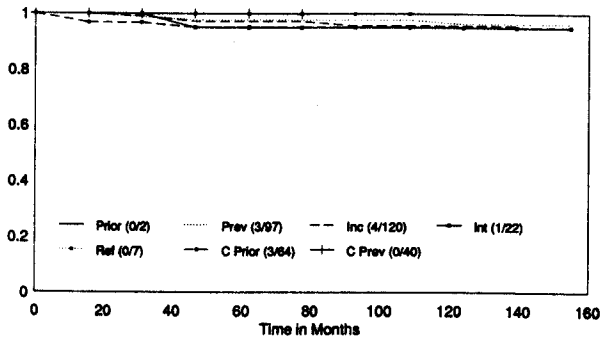
LETTERS to the EDITOR

Natural history of breast cancer

SIR,—Dr Schmidt (March 28, p 810) makes several points about our Feb 15 article. His major objections are: (1) that good survival of small tumours may be due to overdiagnosis by screening of non-aggressive tumours ("length bias" cases) or to observed survival being artificially prolonged by lead time; (2) that some small tumours may have a good prognosis despite being systemic; and (3) that tumours whose behaviour is restricted to local spread may be as life-threatening as those that metastasise to distant sites ("Why should breast cancer, acting as a systemic disease, necessarily have a poorer prognosis than disease that progresses locally?"). Our responses are:

(1) Our paper was primarily concerned with treatment of the sort of tumours now being diagnosed. It was not intended to be a justification of screening in terms of the results of the two-county trial. Such results have long been known and show a 30% reduction in breast cancer mortality in association with invitation to screening,[1] and these mortality findings are not subject to lead time or length bias. The 30% reduction is consistent with the HIP study,[2] has remained steady over time,[3] and is borne out by the more recent trial in Stockholm.[4] The benefit of a 30% reduction in breast cancer mortality is not questionable, contrary to Schmidt's assertion. To return to the subject of our paper, the treatment of breast cancer, the fact remains that in small tumours, local therapy was sufficient to achieve an excellent prognosis, both in screening detected and in clinically detected tumours. The fact that this result was not due to length bias was evident from the observation that it held good even for grade-3 tumours. It is further borne out by the accompanying figure showing survival by detection mode for tumours less than 10 mm in diameter. The screened and control survival profiles are similarly excellent. Exclusion of the prevalence screen tumours to eliminate most of the length bias[3] and subtraction of three or four years' lead time from the survival of screening detected tumours make no appreciable difference. The conclusion remains that systemic therapy has little or nothing to offer in such cases.

(2) Although theoretically these small tumours may have released malignant cells, our argument, backed up by the data, is that this does not justify systemic therapy.



Survival, for tumours <10 mm, by detection mode.

Tumours diagnosed between randomisation and start of screening (= Prior), at first (prevalence) screen (= Prev), at subsequent (incidence) screens (= Inc), in interval betweeen screens (= Int), in women refusing screening (= Ref), in unscreened control group (= C Prior), or in control group at first screen (at end of trial) (= C Prev).

(3) It is difficult to see the practical implication behind this point. It seems almost certainly incorrect: there is no evidence for a substantial subpopulation of breast tumours that threaten life but restrict themselves to local progression only. Further, all observations indicate that tumours with frank distant metastases have a considerably poorer prognosis than do those without.

We agree that the issue is not whether breast cancer is systemic but how best to treat tumours arising in the 1990s, which will tend to be smaller than those of the 1960s and 1970s. In his eagerness to discredit screening, Schmidt appears to have lost sight of this point.

Dr Alfonsi and Dr Cutrupi (March 28, p 810) seem to confuse invasion and metastasis. Almost 40% of invasive cancers diagnosed in the invitation to screening arm of the Swedish two-county trial were smaller than 15 mm and node negative. Most of these, we contend, were without viable metastases, as indicated by the excellent prognosis without systemic therapy. We see no contradiction here. If Alfonsi and Cutrupi were correct about cases in the control arm with distant metastases having all shown up before screening started in this group, what happened to those in the screened group? During the period of the study, the frequency of tumours with large diameter lymph node involvement and distant metastases was lower in the arm invited to screening. How could tumours with poorer prognosis anticipate the onset of screening? The good prognosis of tumours less than 10 mm in diameter, irrespective of grade or detection mode, shows that our survival results are not invalidated by length bias.

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Oestrogen and progesterone receptor dissociation and family history of breast cancer

SIR,—Several variants of the oestrogen (ER) and progesterone (PR) receptor have been identified[1,2] but for only a few of them is the functional significance known.[3] Futhermore, alterations in chromosome sequences in the regions of the ER and PR loci may have an important role in the development of breast cancer.[4] We report that the ER and PR dissociation constants (ERK_d and PRK_d) are significantly reduced in the breast cancers of women with a family history of the disease. This suggests that abnormalities within the receptors themselves are associated with the development of breast cancer.

The women had been referred for radiotherapy and most of them had early tumours. A nurse administered a questionnaire on family

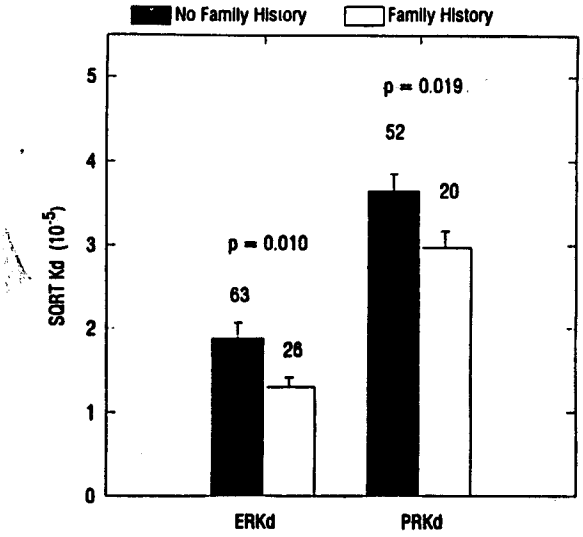

Fig 1—ERK_d and PRK_d (mean and SE) in breast tumours.

Numbers of cases indicated above SE bar. Values as square-roots of nanomolar K_d values.

history. Breast tumour ER, ERK_d, PR, and PRK_d concentrations were measured with a Rianen Assay Systems kit (DuPont).

There was a significant reduction in ERK_d and in PRK_d in the tumours of women with a family history of breast cancer. The results are expressed as the square-roots of nanomolar values, to normalise variances (fig 1). There was no significant association of ER or PR with family history (fig 2).

15 women had a first-degree family history of breast cancer in mother, daughter, or sister. The other women had affected aunts or cousins. There was no significant difference in the proportion of women with or without a family history who were premenopausal (23% and 19%, respectively).

Although K_d values are estimated in several laboratories, little has been published about their character or clinical usefulness.[5] In one study, postmenopausal patients with high K_d values tended to have shorter recurrence-free survival.[6]

Since K_d reflects binding affinity between receptor and ligand, the "true" K_d value should be identical within the same tissue in the same species. But the observed K_d depends on assay method[6] and receptor phosphorylation.[7] Menopausal status also affects K_d because of high endogenous oestrogen and progesterone levels in premenopausal women.[6] However, there was no significant difference in the proportion of women with or without a family history of breast cancer who were premenopausal, so menopausal status is not a confounding variable in our study.

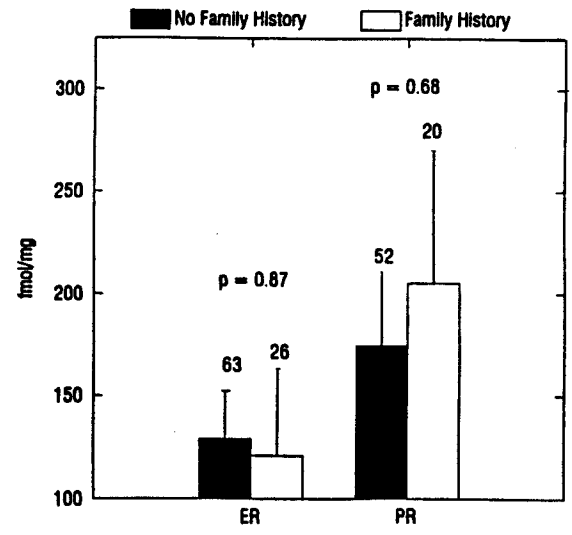

Fig 2—ER and PR.

An additional factor affecting K_d could be receptor protein structure. Multiple polymorphisms of ER and PR have been identified, and the results presented here suggest that some women with a family history of breast cancer might inherit a variant receptor gene with an altered K_d. The same inherited structural abnormality might also induce familial breast cancer susceptibility.

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Gene therapy for cancer

SIR,—Dr Gutierrez and colleagues' review (March 21, p 715) was a useful introduction to some of the gene therapy ideas circulating in cancer research. However, in the context of tumour-cell-targeted gene therapy, insufficient emphasis was given to the important point that the genes must either reach all the target cells or destroy indirectly those tumour cells they cannot reach. Tumour-suppressor genes, MHC genes, and the varicella-zoster virus thymidine kinase gene proposed for virus-directed enzyme prodrug therapy (VDEPT)[1] have no "bystander effect" and influence only the tumour cells to which they have been successfully delivered. To cure cancer these genes would have to be delivered to all the patient's cancer cells but the heterogeneity and inaccessibility of the target cells make this an elusive goal. 100% efficient delivery is not required for genes encoding secreted proteins that can (directly or indirectly) mediate the destruction of surrounding tumour cells. Bystander effects, apparently mediated through paracrine stimulation of host antitumour effector cells, have been demonstrated after expression of interleukin-2 and interleukin-4 genes in rodent tumour models.[2-4] Many other gene products may be capable of stimulating local antitumour immunity or generating locally cytotoxic "crossfire". Examples include other immunostimulatory cytokines, chemotactic peptides, antibodies, and toxins. Also, it may be possible to modify the VDEPT approach by engineering the genes to encode the drug-activating enzyme in a cell surface-associated or secreted form. Extracellular activation of the prodrug by enzyme derived from a small number of gene-transduced tumour cells might then lead to wholesale tumour destruction.

The major obstacle to tumour-targeted gene therapy is inability to deliver genes efficiently to tumour deposits in vivo.[5] Until gene transfer technology is up to this task the potential of this form of gene therapy cannot be tested, even in animal models. Virus vectors, the most promising vehicles for in-vivo gene delivery, are too large to cross the vascular endothelial lining of tumour blood vessels in numbers large enough to reach more than a small fraction of target cells. Vectors capable of replicating and spreading through a tumour may provide part of the answer to this problem but there are serious concerns about safety. Even on the most optimistic view, it is