CORRESPONDENCE

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Management of early-onset breast cancer and *BRCA1* or *BRCA2* status

Sir—From the work of Bruce Haffty and colleagues (April 27, p 1471)[1] women younger than 42 years seem to have a 26% risk of ipsilateral relapse and a 15% risk of contralateral relapse at 12 years' follow-up. The risk is higher among women with *BRCA1* or *BRCA2* mutations—49% and 42%, respectively. The histology and location data show that most relapses, among those with harmful mutations, were new primaries.

If we believe that these data are representative of breast cancers in women younger than 42 years, clinicians would need to counsel young women diagnosed with breast cancer that over the next 12 years they have a 20% risk of carrying a high-risk mutation in the *BRCA1* or *BRCA2* gene; even if they do not harbour a deleterious mutation, their risk of relapse is 21% for ipsilateral breast and 9% for contralateral breast, rising to 49% and 42%, respectively, if they harbour the gene mutation.

The obvious step for such women might be to ask for genetic testing and choose bilateral mastectomy, especially if a high-risk gene mutation is present. However, other things need to be taken into account before jumping to this conclusion.

The overall risk of local recurrence (26%) in Haffty and colleagues' study is unacceptably high. In the overview's data,[2] the risk of local relapse in women younger than 50 years is 23% (790 of 3366) for those who did not receive radiotherapy compared with 8% (272 of 3382) for those who did receive radiotherapy. Did their patients receive adequate surgery and radiotherapy? If they did, what is the explanation for the high local recurrence? Are these patients being followed up particularly exhaustively and subclinical dormant tumours being detected that may not have surfaced otherwise?[3] Could radiotherapy have induced cancers in these young women?

If the risk of recurrence is indeed so high a repeat randomised trial comparing unilateral or bilateral mastectomy with conservative breast surgery plus radiotherapy in such women is the next step forward. For detection of a difference in recurrence between 26% and 8%, a sample size of 100 young patients is needed in each group, with 90% power and 95% CI. The Early Breast Cancer Trialists' Collaborative group have shown that an 18% reduction in local relapse would be expected to have a 3–4% improvement in survival.[2] This question might even be answerable through reanalysis of previous trials, because although no trial was large enough to include enough young patients, a meta-analysis of raw data by The Early Breast Cancer Trialists' Collaborative group may already hold the answer.

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1 Haffty BG, Harrold E, Khan AJ, et al. Outcome of conservatively managed early-onset breast cancer by *BRCA1/2* status. *Lancet* 2002; **359:** 1471–77.

2 Early Breast Cancer Trialists' Collaborative Group. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. *Lancet* 2000; **355:** 1757–70.

3 Vaidya JS, Vyas JJ, Chinoy RF, Merchant N, Sharma OP, Mittra I. Multicentricity of breast cancer: whole-organ analysis and clinical implications. *Br J Cancer* 1996; **74:** 820–24.

Author's reply

Sir—The local relapse rates in the overview's young age-group was driven primarily by most patients being aged 40–50 years, whereas the mean age of our cohort was 37, and all were younger than 42 years. Since younger age substantially alters local relapse rates, higher rates of local relapse in our study are expected. Furthermore, given the multiple sources of data from the overview, local relapse rates are more likely to be underestimated.

It is more valid to compare our data with those of conservatively managed patients from other large institutional series in similar age-groups and with similar follow-up duration;[1,2] in many newer and older studies the findings are comparable (table). Changes in surgical-pathological technique, and the routine use of adjuvant systemic chemotherapy and hormonal therapy, will probably, however, lower rates of local relapse.

I do not believe that the suggested repeat randomised trial is necessary, since local relapse rates in younger patients treated currently are likely to be lower than the historical rates. Although a meta-analysis of available trial data of younger patients would be interesting, I suspect any difference in survival between mastectomy and conservative surgery among younger women will be small and non-significant.

As we pointed out in our discussion, the local relapses, particularly in our genetic cohort, were generally detected at an early stage and effectively salvaged with mastectomy. It is difficult to envision the feasibility of a doing a trial in which newly diagnosed breast-cancer patients with germline mutations are randomly assigned to breast conservation compared with bilateral mastectomy, with or without prophylactic oophorectomy.

Appropriate local-regional management of young women with breast cancer, with or without a genetic predisposition, continues to be a challenging issue. For me, conservative surgery, with attention to microscopic margin status, followed by radiation therapy to the whole breast, with a boost to the tumour bed,[3] and appropriate systemic therapy remains a viable option for most women with early-stage breast cancer, irrespective of age or genetic predisposition.

Our data suggest that young women with a germline mutation face the added risk of ovarian carcinoma and late secondary events in the ipsilateral and contralateral breast, which should be considered in disease management. Although bilateral mastectomy would keep to a minimum the risk of secondary events in both breasts, breast conservation with other prophylactic interventions remains an option.

The patients in our series with germline mutations had no prophylactic oophorectomy or oestrogen-receptor

	Number of patients in young age-group	Age cut off (years)	Local relapse
Study			
Taboul	39	40	35% at 10 years
Recht	47	35	26% at 5 years
Fowble	64	35	24% at 8 years
Kurtz	62	40	21% crude rate
Leborgne	83	40	36% at 10 years
Haffty	127	42	26% at 12 years

Local relapse rates in conservatively treated women younger than 42 years

modulators, although these treatments do lower the risk of developing breast cancers in germline mutation carriers.[4,5] Given available data, for women with germline mutations who choose breast-conserving surgery with radiation over mastectomy, I would counsel them about the risks of second malignant diseases in the breasts and ovaries, and strongly recommend these prophylactic measures. Bilateral mastectomy is also a viable option that would keep to a minimum the risk of secondary events. Additional data on whether specific mutations carry greater or lesser risks, and whether other clinical, pathological, molecular, or environmental factors modify these risks, is eagerly awaited.

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1 Leborgne F, Leborgne JH, Ortega B, Doldan R, Zubizarreta E. Breast conservation treatment of early stage breast cancer: patterns of failure. *Int J Radiat Oncol Biol Phys* 1995; **31:** 765–75.
2 Touboul E, Buffat L, Belkacemi Y, et al. Local recurrences and distant metastases after breast-conserving surgery and radiation therapy for early breast cancer. *Int J Radiat Oncol Biol Phys* 1999; **43:** 25–38.
3 Bartelink H, Horiot JC, Poortmans P, et al. Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. *N Engl J Med* 2001; **345:** 1378–87.
4 Rebbeck TR, Lynch HT, Neuhausen SL, et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. *N Engl J Med* 2002; **346:** 1616–22.
5 Kauff ND, Satagopan JM, Robson ME, et al. Risk-reducing salpingo-oophorectomy in women with a *BRCA1* or *BRCA2* mutation. *N Engl J Med* 2002; **346:** 1609–15.

Clinical relevance of the HERS trial

Sir—The publication of the HERS study by Hulley and colleagues[1] has changed the perspective on the cardioprotective role of hormone-replacement therapy (HRT) in postmenopausal women and has affected the clinical recommendations on the indications of such treatment.[2,3]

The HERS results have frequently been overemphasised and misinterpreted. Although the HERS study was done in women with established coronary disease, its results have been extrapolated as guidelines for use in healthy and younger postmenopausal women. Because of the misinterpretation of the HERS results, some women have had their HRT stopped.

In menopause clinics, women with characteristics similar to those of patients included in HERS are unlikely to be seen, and, therefore, it is important to assess to what extent HERS results are applicable to women more commonly considered for HRT. We compared characteristics of 1459 women attending our menopause clinic with those of patients in the HERS study.

The mean age of women attending our clinic was 53 years (SD 5), compared with 67 years (7) in HERS. More importantly 86% of our population was younger than 60 years. The mean body-mass index of our population was 24·5 kg/m^2 (<25·9 kg/m^2 in 64%, 26·0–30·0 kg/m^2 in 28%, and >30·0 kg/m^2 in only 7%). 57% of HERS patients had body-mass index of greater than 27 kg/m^2.

In our population, 4·2% had diabetes compared with 19% in HERS. The average total cholesterol was 5·8 mmol/L (0·32) (>7·7 in 6·5%, 6·7–7·7 in 22·7%, 5·6–6·6 in 36·9%, and <5·6 in 34%). Mean LDL cholesterol was 44 mmol/L (0·5), compared with 38·0 mmol/L (1·0) in HERS (>5·7 mmol/L in 2·4%, 5·0–5·7 mmol/L in 7·8%, 4·7–4·9 mmol/L in 5·8%, and <4·7 in 84%). Mean HDL-cholesterol was 1·45 mmol/L (0·3), compared with 1·25 mmol/L (0·1) in HERS; most of our patients had HDL cholesterol higher than 1·1 mmol/L.

Arterial hypertension was detected in 19% of our women but was adequately controlled pharmacologically in only 14%. Only three women had had a previous myocardial infarction, and 28 had documented cardiovascular disease. Unlike HERS patients, in our population, only 2·8% were taking lipid-lowering drugs and no patient was taking cardioactive drugs other than antihypertensive agents. 63% of women had an overall cardiovascular risk higher than 20% in 10 years. Only 0·4% of women attending our clinic matched the HERS entry criteria.

Postmenopausal women with clinical characteristics similar to those of patients included in the HERS study are rarely seen in our high-volume menopause clinic. The HERS results might, therefore, be relevant only in a limited number of postmenopausal women considered for HRT. This should be taken into account when considering HRT to avoid denying women the beneficial effects of this treatment.

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1 Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA* 1998; **280:** 605–13.
2 Genazzani AR, Gambacciani M. Controversial issues in climacteric medicine. I. Cardiovascular disease and hormone replacement therapy, International Menopause Society Expert Workshop, position paper. *Climacteric* 2000; **3:** 233–40.
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Nocturnal enuresis in patients with nephrogenic diabetes insipidus

Sir—Dominik Müller and colleagues (Feb 9, p 495)[1] report two unrelated families with congenital nephrogenic diabetes insipidus. Two children had coexistent nephrogenic diabetes insipidus and primary nocturnal enuresis, and one child had primary nocturnal enuresis only.

This report supports this group's previous hypothesis that desmopressin is effective in patients with nocturnal enuresis because of a mechanism other than an effect on renal concentrating ability.[2]

Jonat and colleagues[2] reported a boy aged 8 years with coexistent primary nocturnal enuresis and nephrogenic diabetes insipidus. Treatment with hydrochlorothiazide and dietary measures reduced urine output to a third of the pretreatment volume, but nocturnal enuresis persisted. Daily intranasal desmopressin did not reduce the urine output further, but strikingly improved nocturnal enuresis.

In Müller and colleagues' study, nocturnal enuresis resolved on treatment with desmopressin in all three children with primary nocturnal enuresis. The children with primary nocturnal enuresis and nephrogenic diabetes insipidus woke and went to the toilet to void, and the child with primary nocturnal enuresis only slept through and was dry. They suggest that the therapeutic action of desmopressin might be consequent to a CNS effect.

We agree that the therapeutic action of desmopressin in the two children with nephrogenic diabetes insipidus was not due to an effect on renal concentrating ability. However, a therapeutic effect of desmopressin on renal concentrating ability is still possible in the child who had primary nocturnal enuresis only. Primary nocturnal enuresis is a genetically and