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Hormone replacement therapy and tumour grade in breast cancer: prospective study in screening unit

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Several studies report an increased incidence of breast cancer in women taking hormone replacement therapy (apparently a duration dependent phenomenon)¹⁻³; however, a decreased mortality from breast cancer has been reported in women using the treatment.¹ We assessed the prognostic factors for breast cancers detected by screening at one unit to determine if cancers developing in women who used hormone replacement therapy have a better prognosis.

Patients, methods, and results

All postmenopausal women (>12 months since last menstrual period or women over 50 who had had a hysterectomy) with invasive breast cancer detected at our screening unit between 1989 and 1994 were identified. Prognostic factors and history of use of hormone replacement therapy were recorded. Women taking hormone replacement therapy for more than three months within the year before their breast cancer diagnosis were considered "users." After definitive surgery, pathological tumour size, grade, axillary node metastases, and steroid receptor status were compared between users of hormone replacement therapy and non-users.

Of the 433 postmenopausal women with screen detected cancer, fewer women diagnosed in the prevalence round than in the incident (second) screen were using hormone replacement therapy (74/325 (23%) v 34/108 (32%); $\chi^2 = 3.3$; $P > 0.05$). Median duration of use was 24 (range 3-264) months.

Well differentiated grade I cancers occurred more often in users of hormone replacement therapy than non-users (45% v 20%; $P < 0.001$; table 1); 15% (16) of users compared with 45% (146) of non-users had grade

Table 1—Tumour grade of breast cancers in users and non-users of hormone replacement therapy

Hormone replacement therapy	Grade I tumour	Grade II tumour	Grade III tumour
Users (n=108)	49 (45)	48 (44)	11 (10)
Non-users (n=325)	65 (20)	208 (64)	52 (16)

I, well differentiated tumours ($P < 0.001$). The likelihood of cancers detected in the users being well differentiated increased from the prevalence screen (relative risk 2.19; 95% confidence interval 1.54 to 3.12) to the incident screen (2.49; 1.38 to 4.49). Tumour size and steroid receptor status (analysed by immunocytochemical assay) were similar in the groups. The excess of grade I tumours was seen equally in the 72 women using oestrogen only and the 36 using a combined preparation.

In women undergoing axillary surgery, node positivity occurred in 23 (26%) of users and 68 (28%) of non-users (difference -2.6%; -14% to 8.5%). In the total group, positivity was 21% in users and non-users (69/325 v 23/108).

A total of 28 women developed recurrent cancer after a median follow up of 45 (range 12-96) months. Recurrence was similar in users and non-users (8 (7%) v 20 (6%); $P = 0.99$, log rank test).

Comment

Although an increased breast cancer risk (up to two-fold) has been linked with long term use of hormone replacement therapy, a large British cohort study has

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shown that mortality from breast cancer in hormone replacement therapy users is almost halved,¹ a finding supported by a subsequent American case-control study.² The American study included both screen detected and symptomatic cancers, with significantly more screen detected cancers included among cases than controls, which would account for the differences in node positivity and mortality between the two groups. By studying only screen detected cancers we eliminated such surveillance or ascertainment bias.

Tumour grade is important for predicting survival from breast cancer, and prognostic indices usually include grade.⁴ Among screen detected cancers, hormone replacement therapy users had better differentiated tumours than non-users, which may explain their reduced mortality.^{1,5} In both screening rounds, women who used hormone replacement therapy had better grade tumours. As users and non-users were screened equally in the screening rounds, this effect is not due to ascertainment bias. Combined hormone replacement therapy (containing progestogens) has recently been claimed to increase the risk of breast cancer,³ but we found that better grade tumours developed with both types of treatment. Although our follow up remains short, no difference in recurrence has been seen between the two groups.

Prescribing hormone replacement therapy after breast cancer treatment remains controversial, but its

use at the time of breast cancer diagnosis is unlikely to effect mortality adversely. Therefore hormone replacement therapy after breast cancer treatment should not be denied to patients if warranted by symptoms and if alternatives for the control of severe menopausal symptoms have failed.

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Correction

Cost effectiveness of screening for and eradication of *Helicobacter pylori* in management of dyspeptic patients under 45 years of age

Owing to an editorial error the authors' corrections were not incorporated in table 3 of this paper by A H Briggs and colleagues (25 May, pp 1321-5). The correct table is published below, giving the correct alignment of data in the last two columns.

Table 3—Results of sensitivity analysis

Parameter	Base case value	Range of values*	Payback period (years)†
Prevalence of <i>Helicobacter pylori</i>	40%	20% - 60%	12 - 7
Proportion of patients with <i>H pylori</i> and peptic ulcer	25%	20% - 50%	10 - 5
Proportion of patients without <i>H pylori</i> but with peptic ulcer	3%	0% - 10%	8 - 8
Cost of serology test	£12.77	£6 - £24	7 - 9
Sensitivity of serology test	77%	60% - 100%	7 - 9
Specificity of serology test	89%	70% - 100%	9 - 7
Cost of formulation of eradication treatment	£38.49	£20 - £60	8 - 8
Effectiveness of eradication treatment (after two attempts)	94%	70% - 100%	10 - 7
Cost of endoscopy	£76.38	£50 - £100	7 - 9
Sensitivity of endoscopy	100%	80%	8
Specificity of endoscopy	100%	80%	9
Cost of breath test	£30.80	£20 - £40	}‡ 8 - 8
Cost of outpatient attendance	£38.66	£30 - £50	
Cost of antisecretory healing dose	£21.00	£10 - £35	}‡\$ 5 - 18
Cost of antisecretory maintenance dose	£10.00	£5 - £20	
Four week healing rate on cimetidine	80%	60% - 90%	7 - 8
Rate of recurrence of ulcer (with maintenance cimetidine treatment)	2.49%	1% - 4%	}‡ 9 - 7
Ulcer recurrence rate (without treatment)	5.72%	4% - 8%	

*In the absence of good quality data on likely variation in each parameter, ranges of values have been chosen arbitrarily by us to show likely importance of variation in each parameter for results of analysis.

†Payback period has been rounded to nearest whole year.

‡Parameters varied simultaneously in sensitivity analysis.

\$Upper estimates refer to 20 mg healing dose/10 mg maintenance dose of proton pump inhibitor daily for four weeks; lower estimates refer to same dose of generic rather than proprietary cimetidine.