Impact of use of hormone replacement therapy on false positive recall in the NHS breast screening programme: results from the million women study

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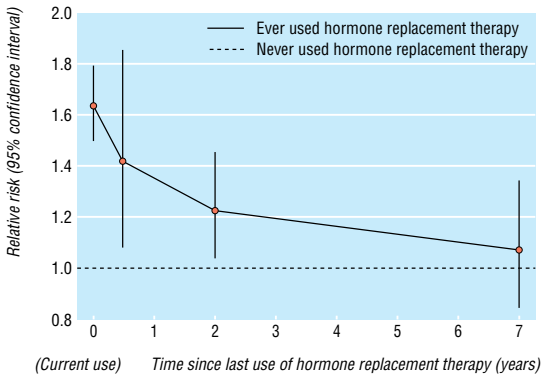
Introduction

About half of the women attending the NHS breast screening programme have used hormone replacement therapy.[1] Although previous studies have reported that use of hormone replacement therapy increases the risk of being recalled after mammography for further assessment, with no subsequent diagnosis of breast cancer ("false positive recall"), the effect of different patterns of use is unclear.[2]

Participants, methods, and results

From June 1996 to March 1998, 87 967 postmenopausal women aged 50-64 invited to routine breast cancer screening at 10 NHS breast screening programme centres joined the million women study,[3] by completing a self administered questionnaire before screening, and were followed up through records from screening centres for their screening outcome. Overall, a diagnosis of breast cancer was made in 399 (0.5%) and 2629 (3.0%) had false positive recall (recall to assessment with no diagnosis of breast cancer during that screening episode). Among women with false positive recall, 398 (15.1%) had a negative biopsy (fine needle aspiration cytology, wide bore needle biopsy, or open surgical biopsy, with no diagnosis of breast cancer). We used conditional logistic regression, stratified by the factors listed in the figure, to calculate the relative risk of false positive recall.

False positive recall was significantly increased in current users of hormone replacement therapy (relative risk 1.64, 95% confidence interval 1.50 to 1.80, $P<0.0001$) and past users (1.21, 1.06 to 1.38, $P=0.004$), compared with never users. The relative risk of false positive recall decreased significantly with increasing time since last use of hormone replacement therapy (χ^2 (df = 1) for trend = 14.0, $P<0.0001$), and was still significantly raised among women ceasing use within the past five years (figure). We found no significant variation in the relative risk of false positive recall between current users of oestrogen only (1.62, 1.43 to 1.83) and combined oestrogen and progestogen (1.80, 1.62 to 2.00) (χ^2 (df = 1) for heterogeneity = 2.3, $P=0.1$), nor were there significant differences in risk according to the dose or hormonal constituents of these types of hormone replacement therapy. Current, but not past, users of hormone replacement therapy had a significantly increased risk of having a negative biopsy compared with never users (relative risk 1.42, 1.14 to 1.78, and 0.94, 0.69 to 1.30, respectively (χ^2 (df = 1) for heterogeneity = 6.5, $P=0.01$)).



Relative risk of false positive recall in postmenopausal women in relation to time since last use of hormone replacement therapy. (Relative risk compared with never users (1057/44 427 recalled) stratified by screening centre, age, previous screening, body mass index, previous breast operation, and time since menopause in: current users of hormone replacement therapy (relative risk 1.64, 95% confidence interval 1.50 to 1.80; 1157/28 634 recalled); past users ceasing use <1 year ago (1.42, 1.08 to 1.86; 63/1758 recalled), 1-4 years ago (1.23, 1.04 to 1.46; 176/5910 recalled), and ≥ 5 years ago (1.07, 0.85 to 1.34; 92/3800 recalled)). Results are plotted according to the median number of years since last use of hormone replacement therapy in each of these categories

When these relative risks and the prevalences of use of hormone replacement therapy in the million women study[1] are applied to recall rates in the NHS breast screening programme,[4] use of hormone replacement therapy during the study period is estimated to have been responsible for around 20% of the cases of false positive recall in the NHS breast screening programme, amounting to an excess of 14 000 cases per year.

Comment

The risk of false positive recall is significantly and substantially increased in current and recent users of hormone replacement therapy; this effect persists for several years after use ceases and, in current users, is accompanied by an increased risk of having a biopsy performed.

False positive mammography is important, because of the anxiety, extra investigations, and inconvenience recalled women experience and its resource implications.[2] Moreover, recalled women are less likely to accept subsequent invitations for screening, despite having a higher incidence of breast cancer than women who have not been recalled.[5] An increased risk of false positive recall can be justified if it improves cancer detection, but current use of hormone replacement therapy reduces the ability of mammographic

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screening to detect breast cancer,[2] such that the increase in false positive recall is not offset by improved cancer detection.

Our finding that the effect of hormone replacement therapy takes several years to wear off does not support suggestions that the high rates of false positive recall in current users could be largely reversed if women ceased use of hormones weeks or months before mammography.

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Contributors: Emily Banks, Gillian Reeves, Valerie Beral, and Julietta Patnick had the original idea for the study, with important input on practical aspects of study design from Barbara Crossley, Elizabeth Hilton, and Moya Simmonds. Diana Bull analysed the data; Emily Banks, Gillian Reeves, Valerie Beral, Julietta Patnick, and Matthew Wallis interpreted the data. Stephen Bailey, Nigel Barrett, Peter Briers, Ruth English, Alan Jackson, Elizabeth Kutt, Janet Lavelle, Linda Rockall, Matthew Wallis, and Mary Wilson contributed to local study design and conduct. All of the authors participated in drafting the paper and gave final approval of the version to be published. Emily Banks, Gillian Reeves, and Valerie Beral are guarantors.

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DRUG POINTS

Teicoplanin induced drug hypersensitivity syndrome

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Drug hypersensitivity syndrome (also known as drug rash with eosinophilia and systemic symptoms) is characterised by a generalised skin eruption, fever, lymphadenopathy, eosinophilia, and visceral involvement. Sulphonamides and anticonvulsants are most often implicated as causal agents.[1 2] Teicoplanin, a glycopeptide antibiotic used in the treatment of Gram positive infections, has not previously been associated with drug hypersensitivity syndrome.

A 47 year old man with previously stable psoriasis and taking acitretin was admitted with generalised pustular psoriasis, precipitated by cellulitis, which had been treated in the community with oral prednisolone and co-amoxiclav plus a potent topical steroid. On admission, he was erythrodermic with a fever of 38°C, a C reactive protein concentration of 400 mg/l, a neutrophil count of $28x10^9$/l, and hypoalbuminaemia. The cellulitis was treated with intravenous benzylpenicillin and flucloxacillin; the generalised pustular psoriasis required intramuscular methotrexate 5 mg followed by 7.5 mg five days later. Both conditions dramatically improved. Recovery was complicated by pneumonia, treated with intravenous ceftriaxone and oral clarithromycin (benzylpenicillin was discontinued). Methicillin resistant *Staphylococcus aureus* (MRSA) isolated from blood cultures prompted substitution of flucloxacillin with intravenous teicoplanin 400 mg daily. Four days after starting teicoplanin and six days after starting ceftriaxone and clarithromycin, he developed urticaria on both flanks and a peripheral eosinophilia, suggesting a drug reaction. Ceftriaxone and clarithromycin were stopped. Teicoplanin was discontinued after nine days' treatment.

Two hours after the final teicoplanin dose, the patient developed a fever of 38.5°C, generalised lymphadenopathy, and raised C reactive protein concentration and hepatic transaminases. His symptoms were attributed to persistent MRSA infection. Teicoplanin was restarted. Investigations for a focus of MRSA infection were negative. He remained pyrexial, his C reactive protein concentration and hepatic transaminases continued to rise, and he became increasingly unwell.

A diagnosis of drug hypersensitivity syndrome was considered and teicoplanin was discontinued. Within 24 hours his fever resolved. Over the following week his liver enzymes, C reactive protein concentration, and skin returned to normal.

The diagnosis of teicoplanin induced drug hypersensitivity syndrome was made on the basis of symptoms and signs of the syndrome that rapidly resolved when teicoplanin was withdrawn.

Drug hypersensitivity syndrome secondary to teicoplanin does not seem to have been reported previously. Toxicity and allergic reactions secondary to teicoplanin are uncommon.[3]

Several factors contributed to a delay in diagnosis. Precipitation of psoriasis within the rash (Koebner's phenomenon) masked the persistent drug eruption; drug hypersensitivity syndrome, generalised pustular psoriasis, pneumonia, and MRSA bacteraemia have common clinical features; and, importantly, teicoplanin was not a known culprit for the syndrome.

We suggest that teicoplanin be added to the list of drugs associated with this potentially life threatening reaction.

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