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

Emily Banks, Gillian Reeves, Valerie Beral, Diana Bull, Barbara Crossley, Moya Simmonds, Elizabeth Hilton, Stephen Bailey, Nigel Barrett, Peter Briers, Ruth English, Alan Jackson, Elizabeth Kutt, Janet Lavelle, Linda Rockall, Matthew G Wallis, Mary Wilson, Julietta Patnick

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, $P = 0.01$)).
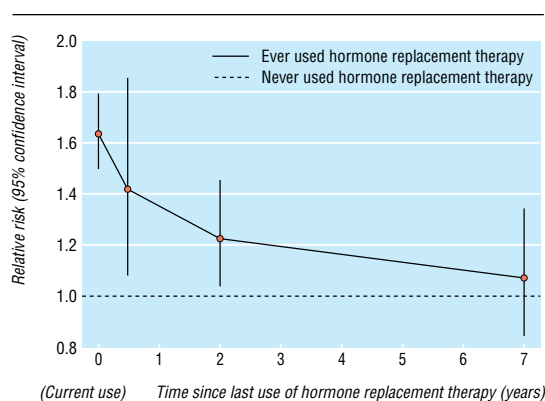
Relative risk of false positive recall in postmenopausal women in relation to time since last use of hormone replacement therapy. (Relative risk compared with never users (1057/44 427 recalled) stratified by screening centre, age, previous screening, body mass index, previous breast operation, and time 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

Cancer Research UK Epidemiology Unit, Gibson Building, Radcliffe Infirmary, Oxford OX2 6HE
Emily Banks
deputy director
Gillian Reeves
statistical epidemiologist
Valerie Beral
director
Diana Bull
senior statistician
Barbara Crossley
chief data manager
Moya Simmonds
clinical co-ordinator
Elizabeth Hilton
clinical co-ordinator

Breast Screening Service, Princess of Wales Community Hospital, Bromsgrove B61 0BB
Stephen Bailey
clinical director

West of London Breast Screening Service, Charing Cross Hospital, London W6 8RF
Nigel Barrett
clinical director

Gloucestershire Breast Screening Service, Cheltenham GL53 7AS
Peter Briers
clinical director

Breast Care Unit, Oxford Radcliffe Hospital NHS Trust, Churchill Hospital, Oxford OX3 7JH
Ruth English
clinical director

Patricia Massey Breast Screening Unit, Queen Alexandra Hospital, Portsmouth PO6 3LY
Alan Jackson
consultant radiologist

Avon Breast Screening, Central Health Clinic, Bristol BS2 0JD
Elizabeth Kutt
clinical director

North Lancashire Breast Screening Service, Royal Lancaster Infirmary, Lancaster LA1 4GG
Janet Lavelle
clinical director

West Sussex Breast Screening Service, Worthing Hospital, Worthing BN11 2DH
Linda Rockall
clinical director

Breast Screening Unit, Coventry and Warwick Hospital, Coventry CV1 4FH
Matthew G Wallis
clinical director

Greater Manchester Breast Screening Service, Nightingale Centre, Withington Hospital, Manchester M20 0PT
Mary Wilson
clinical director

NHS Breast Screening Programme, Sheffield S11 9PS
Julietta Patnick
national coordinator

Correspondence to:
E Banks
mailto:emily.banks@anu.edu.au

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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DRUG POINTS

Teicoplanin induced drug hypersensitivity syndrome

C M Perrett, S R McBride

Department of Dermatology, Royal Free Hospital, London NW3 2QG
C M Perrett
clinical fellow
S R McBride
consultant

Correspondence to:
sandy.mcbride@rfh.nthames.nhs.uk

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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 28×10^9/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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