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Reduced risk of oestrogen receptor positive breast cancer among peri- and post-menopausal women in Scotland following a striking decrease in use of hormone replacement therapy

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ABSTRACT

Many countries report a decline in breast cancer incidence among peri- and post-menopausal women following a decline in HRT prescribing. To investigate recent Scottish incidence trends, European age-standardised incidence rates from 1997 to 2005 were stratified by method of first detection, ER status and age group. We developed change point models of the annual age-specific cases for the peri- and post-menopausal age groups and ER status using Poisson regression.

In Scotland all HRT categories together show a 32.4% increase in the number of items dispensed in 1993–2000 followed by a striking 61.8% decline by 2007.

The incidence rates of screen-detected tumours increased gradually in the 50–64 and 65–74 age groups. For the older age group this increase accelerated after 2003 corresponding to an extension of the age range of screening.

For ER positive tumours in the 50–64 age group, age-standardised rates increased 31.5% from 1997 to 2000, followed by a statistically significant decrease of 11.2% by 2005 (change in slope = −0.0943, $P < 0.0001$). We conclude that an overall incidence in the 50–64 age group declined since 2000 reflecting the sudden fall in HRT dispensed items and is largely accounted for by the decrease in ER positive tumour incidence. A longer term decline in ER negative tumours for this age group was pre-existing and is unaffected by the collapse in HRT prescribing.

1. Introduction

We previously reported that the incidence of breast cancer among 50–64-year-old women in Scotland decreased in association with a striking decline in the use of Hormone Replacement Therapy (HRT) (Fig. 1).[1] The aim of the present study is to investigate these recent trends in breast cancer incidence according to age, screen detection status and oestrogen receptor status.

2. Methods

Items dispensed and preparation details are based on the Prescribing Information System held by the Information Services

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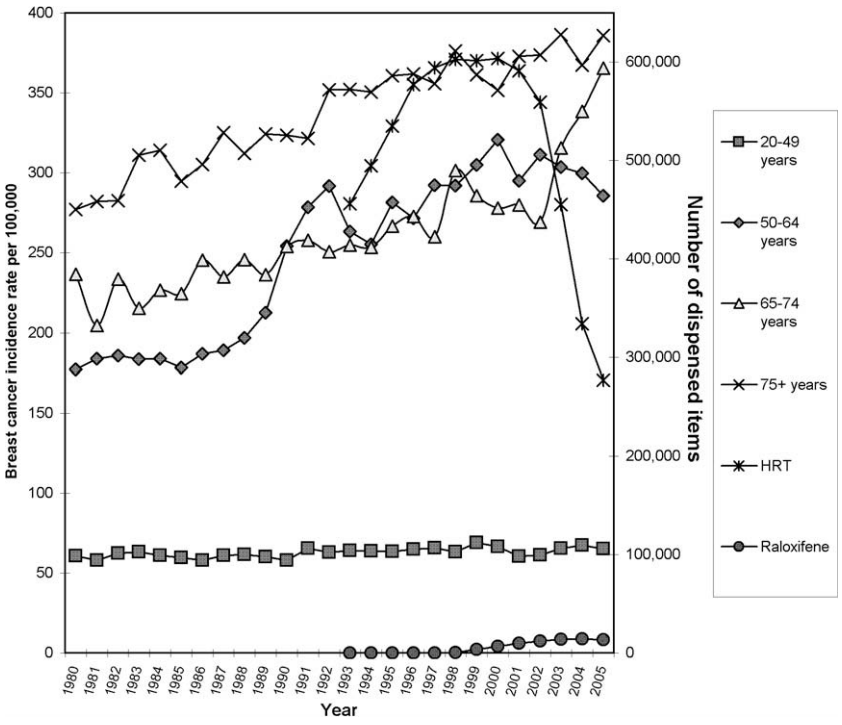

Fig. 1 – Age-standardised incidence of invasive breast cancer by age group in Scottish women (1980–2005), and numbers of dispensed items of HRT and raloxifene (1993–2005). (Reprinted from The Lancet, vol. 373, Brewster DH, Sharpe KH, Clark DI, Collin J. Declining breast cancer and decreased HRT use, p. 450, 2009, with permission from Elsevier.)

Division (ISD) of NHS National Services Scotland.[2] The preparation groupings used by the Million Women Study were adopted and include: oestrogen only, oestrogen and progestogen and other (tibolene, progestogen only, androgens and vaginal preparations).[3]

Invasive female breast cancer incidence data (ICD-10 C50) including method of first detection and oestrogen receptor (ER) status were sourced from the Scottish Cancer Registry held by ISD.[4] Cancers were identified as 'screen detected' if the diagnosis occurred after a positive assessment by screening mammography regardless of route of screening (e.g. organised national programme or private). The ER status entered into the Scottish Cancer Registry reflects the test result interpretation recorded in the medical record regardless of the method or threshold employed. Our analysis covered the years 1997–2005 reflecting the availability on the Scottish Cancer Registry of ER status and method of first detection, the period of change in HRT use and breast cancer incidence reported world wide.[5–12]

Annual breast cancer incidence rates were age-standardised by direct standardisation using the European standard population[13] for each of the broad age groups. Rates were stratified by method of first detection (screening, other), ER status (positive, negative, not known) and age group (50–64 and 65–74) reflecting changes in breast screening invitation and focusing on those age groups most likely to be taking HRT. In Scotland, breast screening was introduced for women 50–64 years old in 1988. Between 2003 and 2005 the age of women invited was increased to include women 65–70 years old; prior to 2003 women aged 65–70 years and older could self-refer. Two-view mammography for subsequent (incident) screening rounds has only very recently been introduced in Scotland and would not be expected to have any detectable effect on breast cancer incidence until at least the incidence year 2008.

We developed change point models in STATA v.9 of the annual age-specific cases for two age groups and each ER tumour status separately using Poisson regression. The log of population size was used as an offset. To identify the best fit linear line for the two periods 1997–2000 and 2000–2005, we focused on identifying a change in the slope of invasive breast cancer incidence after 2000 representing the peak in HRT use. The change point Poisson regression model can be described as follows:

$$\log(\text{rate}) = \beta_0 + \beta_1(\text{year-2000}) + \beta_2(\text{year-2000})I(\text{year} \geqslant 2000)$$

where β_0 is the estimated log invasive breast cancer incidence rate in Scotland in 2000; β_1 the slope of the relationship between the log incidence rate in Scotland and time; β_2 the estimate of any change in slope for the two periods: 1997–2000 and 2000–2005; if no change occurred, the estimated value would be 0, if HRT dispensing drop resulted in reduced incidence, the value would be <0; I (year $\geqslant$ 2000) is an indicator that allows the slope to change.

3. Results

3.1. *Hormone replacement therapy prescribing*

All HRT categories together show a 32.4% increase in the number of items dispensed from 1993 to 2000 followed by a striking 61.8% decline in number of items dispensed by 2007

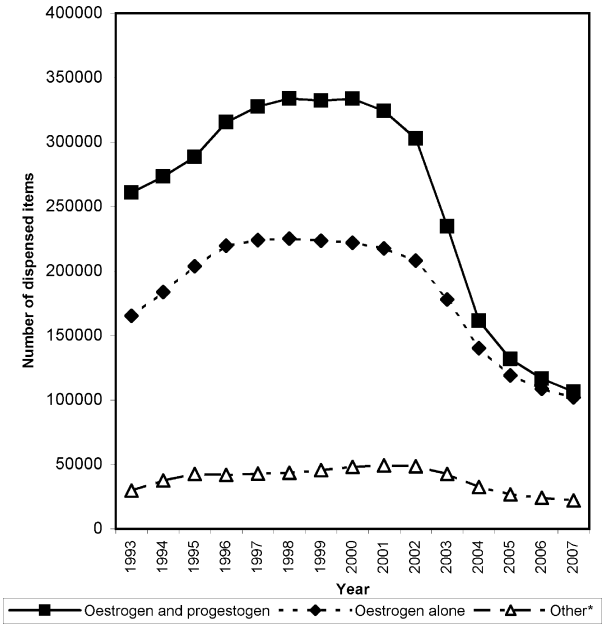

Fig. 2 – Numbers of dispensed items of HRT by type (1993–2005). (Other* include tibolene, progestogen only, androgens and vaginal preparations.)

(Figs. 1 and 2). This pattern of increase during the nineties followed by a sharp fall beginning in 2000 was mirrored in all three categories of HRT (Fig. 2). However, the decrease was most pronounced for the oestrogen and progestogen combined category which declined by 68.1% by 2007 (Fig. 2).

3.2. *Screen-detected cancer*

Over the period 1997–2005, the age-standardised rates of screen detected tumours have increased gradually in the 50–64 and 65–74 age groups. In both groups, the age-standardised rates for tumours detected by other means declined slightly. For the older age group this increase in screen detected tumours accelerated after 2003, reflecting the screening age extension while in the 50–64 age group the rate reached a high in 2000, the midpoint of the HRT peak (Fig. 3a and b). This group is most likely to be prescribed HRT[14] and HRT users are more likely to attend screening.[15]

3.3. *Oestrogen receptor status of tumour*

Among women aged 50–64 years with ER positive breast cancer, age-standardised rates increased 31.5% from 1997 to 2000, followed by a statistically significant overall decrease of 11.2% by 2005 (change in slope of −0.0943, $P < 0.0001$). ER negative breast cancer rates fell by 44.3% from 1997 to 2005. Incidence rate for tumours of unknown ER status declined 35.7% over the period (Fig. 4a).

Age-standardised ER positive tumour incidence rates for women 65–74 years old increased 30.4% from 1997 to 2000, followed by a short slight decrease of 4.1% from 2000 to 2002 which was reversed in 2003 with a sharp increase in incidence rate of 41.3% from 2002 to 2005. Age-standardised ER negative tumour incidence rates remained relatively stable and tumours of unknown ER status declined 45.8% from 1997 to 2005 (Fig. 4b).

4. Discussion

We previously reported that the incidence of breast cancer among 50–64-year-old women in Scotland decreased in association with a striking decline in the use of HRT following a peak during the period 1998–2001.[1] In this analysis we demonstrate the fall in overall incidence primarily reflects a significant decrease in ER positive tumours. In the 50–64 age group, ER positive tumours are the most common.[16]

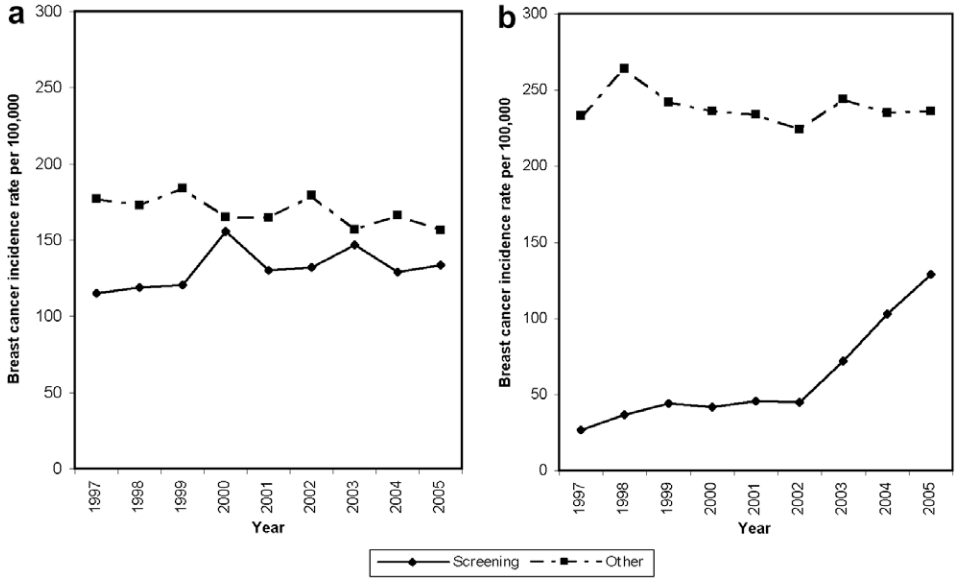

Fig. 3 – (a) Age-standardised incidence rates of invasive breast cancer by detection method in Scottish women aged 50–64 years (1997–2005). (b) Age-standardised incidence rates of invasive breast cancer by detection method in Scottish women aged 65–74 years (1997–2005).

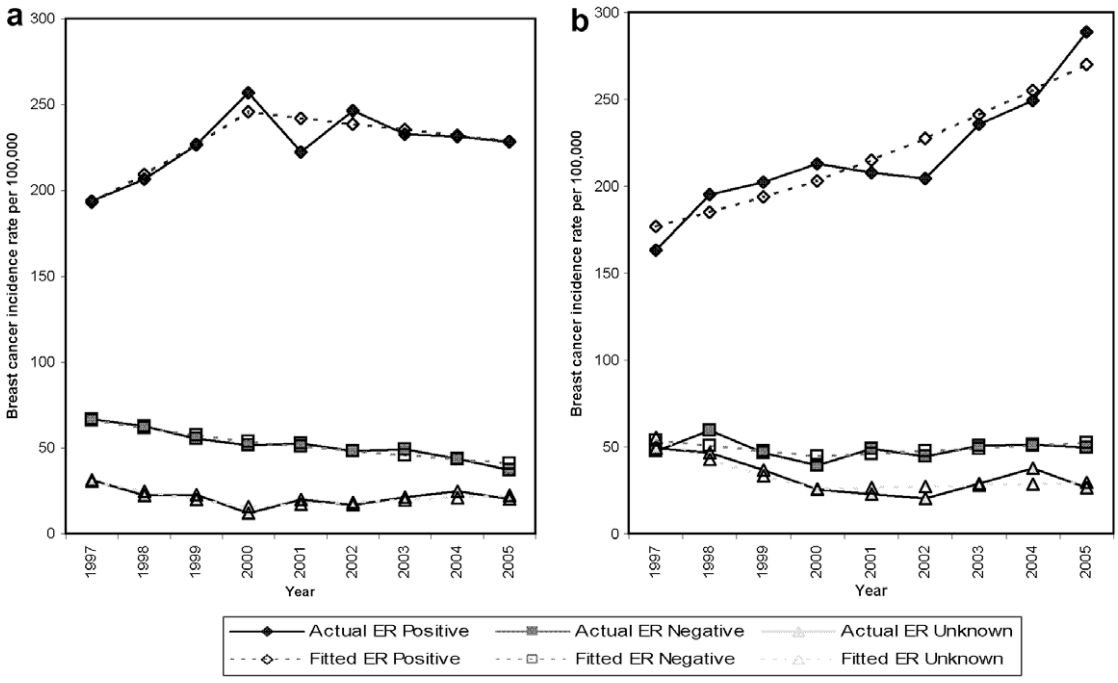

Fig. 4 – (a) Fitted and actual age-standardised incidence rates of invasive breast cancer by oestrogen receptor status in Scottish women aged 50–64 years (1997–2005). (b) Fitted and actual age-standardised incidence rates of invasive breast cancer by oestrogen receptor status in Scottish women aged 65–74 years (1997–2005).

Increased cessation of combined HRT is expected to produce effects on breast cancer incidence because breast cancer risk is higher in current users and declines quickly after cessation; the ex-users' risk reduces to the level of non users in 2–5 years.[16–18]

4.1. *Hormone Replacement Therapy prescribing trends*

The timing and extent of change in incidence trend may reflect the preparation, formulation and prevalence of HRT use in Scotland. Studies have shown that breast cancer incidence is significantly increased for current users of preparations containing oestrogen only, combined preparations and tibolene; but the magnitude of the associated risk is substantially greater for combined therapy than for other types of HRT.[3]

Raloxifene is prescribed to prevent osteoporosis and has been shown to have preventative breast cancer effects specific to ER positive tumours in post-menopausal women.[19] Increase in raloxifene dispensed items could result in reduced breast cancers among post-menopausal women; however, because the volume of dispensed items is very low in comparison with the volume of HRT preparations dispensed (Fig. 1), the favourable effect of raloxifene is likely to have limited impact.

When compared to Scottish trends, the more dramatic falls in breast cancer incidence reported by others[5–9,11] and in particular the United States (US)[12] may reflect the differences in the number of post-menopausal women who have had a hysterectomy and the resulting mix of HRT use. Due to the increased risk of endometrial cancer with unopposed oestrogen use, oestrogen only HRT preparations are generally prescribed for women who have had a hysterectomy.[12] The US mix of HRT preparation is approximately 70% oestrogen only preparations[20,21] compared to 44% in Scotland with combined preparations representing 46%.[4]

This may suggest that Scottish breast cancer incidence should reflect a more pronounced trend given that the Scottish preparation mix is weighted to the higher risk combined therapy; however, the overall prevalence of HRT use is very different. Assuming the peak of HRT use amongst Scottish women is similar to the United Kingdom (UK)[22]; at approximately 25%, Scottish use is less than US use for approximately the same time period (42%).[20]

4.2. *Screen-detected cancer*

Mammography trends affect the breast cancer incidence trends identified. Breast cancer incidence increases as women undergoing routine screening mammography have 2–3-fold higher breast cancer detection rate.[9] In Scotland, women are invited to attend screening once every 3 years. Based on 3-year rolling attendance figures, uptake is increasing slowly from 71.0% in 1994 to 76.5% in 2007.[23] This slow, steady increase in screening participation may slightly increase the breast cancer incidence trend in the 50–64 year age group. However in the present study, the major impact of mammography on breast cancer incidence rate is the increase in mammography-detected cancer amongst the 65–74 age group reflecting the phased extension of the age range for routine invitation from 50–64 to 50–70 years in 2003–2005. In the 65–74 age group, breast cancer incidence appears to fall from 1998 to 2002 followed by the sharp increase reflecting extension of mammography screening invitations to include women 65–70 years old (Fig. 1). The lower HRT use amongst

women 65–74[14] years old makes the possible effect of HRT cessation on breast cancer incidence in this age group more difficult to evaluate. This possible HRT effect also appears to be masked by the increased incidence due to the extended mammography screening.

HRT may result in decreased breast cancer detection by mammography due to increased breast density when taking combined HRT, which decreases the sensitivity and specificity of the mammogram and is most evident with continuous combined HRT.[24] Breast density may lead to the delayed detection of 20% of breast cancers[25] by increasing the minimal screen detectable tumour size.[9] Cessation of HRT might be expected to result in a more immediate temporary increase in breast cancer incidence as breast density is reduced and tumours are more easily detected[9] obscuring the longer term trend of reduced breast cancer incidence following a fall in combined HRT. However HRT reduces sensitivity of mammography in a fairly modest proportion of users.[24]

Others have suggested that the detection of ductal carcinoma in situ (DCIS) through screening activities 15–18 years ago followed by surgical removal of pre-invasive DCIS may explain the reduction in invasive breast cancers occurring around 2000.[26] The Scottish invasive breast cancer rates for the 50–54 and 60–64 age groups beginning 1988, the year that screening started, to 2005 shortly after the approximate time of reported incidence rate change do not support this suggestion.[27] Despite having higher cumulative exposure to screening, the downward trend in invasive breast cancer incidence was less marked in 60–64-year-old women than in 50–54-year-old women. This suggests that changes in HRT use which are likely to have occurred more commonly among younger peri- and post-menopausal women, is a more feasible explanation of recent breast cancer incidence trends among 50–64-year-old women than an effect of screening.

Supporting our argument, a recent Swedish cohort study estimates the standardised incidence ratio for women with DCIS aged 60 years or older and established that the observed to expected incidence ratio of invasive breast cancer is 4.2 (95% CI = 3.2, 5.5) indicating that individuals who were previously diagnosed with and treated for DCIS are 4.2 times more likely to be diagnosed with invasive breast cancer in the future.[28] Therefore, any reduction in invasive breast cancer incidence seems unlikely to be due to increased DCIS detection and treatment.

4.3. *Oestrogen receptor status of tumour*

The fall in ER negative tumours was not entirely expected as HRT is generally associated with ER positive tumours[15,29]; ER positive tumours exhibit incidence rates that rise continuously with ageing rather than slowing after menopause,[30] ER positive tumours are the most common type of breast cancer in post-menopausal women[16] and finally, combined HRT, the most prevalent post-menopausal therapy in Scotland, has been associated with a stronger risk for ER positive breast cancer than ER negative breast cancer.[29] However, others have also reported decreases in ER negative tumours with a fall in HRT.[12,15,16]

To understand the longer term fall in ER negative tumour incidence, we considered the possible role of exogenous hormones generally in tumour development. Some evidence suggests that oral contraceptives are more consistently associated with ER negative tumours, most strongly related to recent use and with increased risk for women younger than 35 years. However the association between oral contraceptive use and ER negative tumours may reflect confounding related to age at diagnosis.[30] Others have proposed that ER expression is a dynamic phenotype of breast cancer given that ER expression can be induced with drug therapy and propose that the effect of HRT appears to be on ER expression generally,[31] affecting the incidence trend for ER negative tumours as well as the trend for ER positive tumours. However, the role of exogenous hormones in differentially increasing risk of hormone sensitive tumours continues to be debated.

Alternatively, it has been suggested that the more long-standing decline in ER negative tumours reflects a post-screening 'compensatory drop' in incidence among older previously screened women, largely unaffected by the rise and fall in HRT prescribing.[32] Unfortunately we do not hold data on ER status extending back far enough in time to assess this hypothesis. Our results are partially consistent with this interpretation: the decline is evident for a longer period compared to the ER positive tumour incidence and appears unaffected by the change in HRT dispensed items. However, as we have already observed, screening seems less likely to explain recent breast cancer incidence trends among 50–64-year-old women than changes in HRT use.

A more likely explanation for the fall in ER negative tumours in the 50–64 age group is anecdotal evidence suggesting that in Scotland the threshold for ER positive tumours has reduced over time reflecting that tumours with lower levels of positive ER status may respond favourably to treatment. Over time, this would increase the proportion of tumours classified as ER positive and reduce the proportion classified as ER negative (Fig. 4a).

In the 65–74 age group, one might expect the increase in incidence rate due to screening age extension to be present in both ER positive and ER negative tumours; however, this increase was only statistically significant for ER positive tumours. Incidence rates for ER negative tumours appear to increase slightly (Fig. 4b); however, the increase is not statistically significant. When compared to screen-detected cancers, previous studies have shown that interval cancers consist of a higher proportion of fast-growing tumours, a higher proportion of ER negative tumours, and are less likely to occur in women over 50 years old.[33,34] Given the screening age extension in the 65–74 age group, our findings of a pronounced increase in ER positive tumour incidence and relatively stable incidence rates for ER negative tumours are consistent with these established characteristics of interval and screen-detected cancers.

Strengths of our study include a high breast cancer case ascertainment rate estimated to exceed 98% in one study[35] and high reliability of cancer registration data in Scotland for method of first detection and tumour ER status with percentage of discrepancies at 3.4% and 4.8%, respectively.[36]

As a population-level study examining aggregate data our study does not explore other risk factors not measured or

known that could explain the incidence trends described. The change point Poisson regression models adopted assumed a single change point at 2000, the midpoint of the HRT dispensed items peak. It is possible that the change occurred at some other point in time. Furthermore and as demonstrated for the 65–74 age group, a single defined change point may not best describe the underlying data. The limited availability of ER status information (since 1997) reduces the years of data available to consider alternative modelling approaches with no defined and multiple change points.

Other limitations include the possibility that ER status cut off points may vary with laboratory practice and lead to misclassification of tumours. The HRT dispensed items information are not patient specific data, therefore it has not been possible to present trends in patient age distribution with respect to HRT dispensing over the period studied, however our study has the benefit of being population-based. UK studies providing HRT prescribed information by patient age generally use samples sourced from general practitioner databases and therefore only cover a sub-set of patients. In addition, the information provided is dispensed as opposed to prescribed items. Nevertheless dispensed items are a reasonable approximation of clinician prescribing behaviour and patients' actual use not withstanding differences introduced by, as an example, patient compliance with the prescription.

In conclusion our data indicate that overall incidence of invasive breast cancer in the 50–64 age group declined between 2000 and 2005 reflecting the sudden fall in HRT dispensed items. This is largely accounted for by the decrease in ER positive tumour incidence. The longer term decline in ER negative tumours for this age group was pre-existing and is unaffected by the collapse in HRT prescribing.

Ethics committee approval

Research Ethics Committee approval was not sought because the study was carried out using anonymised and aggregated data.

Conflict of interest statement

None declared.

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REFERENCES

1. Brewster DH, Sharpe KH, Clark DI, Collins J. Declining breast cancer incidence and decreased HRT use. *Lancet* 2009;**373**:459–60.
2. Information Services Division Scotland. Prescribing information system, dispensed items (extracted 27 August 2008).
3. Anon, Million Women SC. Breast cancer and hormone-replacement therapy in the million women study. *Lancet* 2003;**362**:419–27.
4. Information Services Division Scotland. Scottish Cancer Registry [extracted August 2008].
5. Allemand H, Seradour B, Weill A, Ricordeau P. Decline in breast cancer incidence in 2005 and 2006 in France. A paradoxical trend. *Bull Cancer* 2008;**95**:11–5.
6. Bakken K, Lund E, Eggen AE. The impact of hormone replacement therapy on the incidence of breast cancer in Norway. *J Clin Oncol* 2005;**23**:3636–7.
7. Canfell K, Banks E, Moa AM, Beral V. Decrease in breast cancer incidence following a rapid fall in use of hormone replacement therapy in Australia. *Med J Aust* 2008;**188**:641–4.
8. Katalinic A, Rawal R. Decline in breast cancer incidence after decrease in utilisation of hormone replacement therapy. *Breast Cancer Res Treat* 2008;**107**:427–30.
9. Kerlikowske K, Miglioretti DL, Buist DSM, Walker R, Carney PA. Declines in invasive breast cancer and use of postmenopausal hormone therapy in a screening mammography population. *J Natl Cancer Inst* 2007;**99**:1335–9 [2007; 99:1335].
10. Kliewer EV, Demers AA, Nugent ZJ. A decline in breast-cancer incidence. *N Engl J Med* 2007;**357**:509–10.
11. Kumle M. Declining breast cancer incidence and decreased HRT use. *Lancet* 2008;**372**:608–10.
12. Ravdin PM, Cronin KA, Howlader N, et al. The decrease in breast-cancer incidence in 2003 in the United States. *N Engl J Med* 2007;**356**:1670–4.
13. Anon, Office of National Statistics. Distribution of the European standard population; 1998; Available from: <http://www.statistics.gov.uk/StatBase/xsdataset.asp?vlnk=1260&More=Y>.
14. Scottish Executive Health Department. Scottish Health Survey 1998, vol. 1; 2000. p. 400.
15. Chen WY, Hankinson SE, Schnitt SJ, et al. Association of hormone replacement therapy to estrogen and progesterone receptor status in invasive breast carcinoma. *Cancer* 2004;**101**:1490–500.
16. Glass AG, Lacey JV, Carreon JD, Hoover RN. Re: breast cancer incidence, 1980–2006: combined roles of menopausal hormone therapy, screening mammography, and estrogen receptor status – response. *J Natl Cancer Inst* 2007;**99**:1152–61.
17. Anon, Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 2003;**362**:419–27.
18. Anon, Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. *Lancet* 1997;**350**:1484 [1997; 350:1047].
19. Olevsky OM, Martino S. Randomized clinical trials of raloxifene: reducing the risk of osteoporosis and breast cancer in postmenopausal women. *Menopause* 2008;**15**:790–6.
20. Hersh AL, Stefanick ML, Stafford RS. National use of postmenopausal hormone therapy – annual trends and response to recent evidence. *JAMA* 2004;**291**:47–53.
21. Merrill RM. Hysterectomy Surveillance in the United States 1997 through 2005. *Med Sci Monit* 2008;**14**:CR24–CR31.
22. Parkin DM. Is the recent fall in incidence of post-menopausal breast cancer in UK related to changes in use of hormone replacement therapy? *Eur J Cancer* 2009;**45**:1649–53.
23. Information Services Division Scotland. Breast screening. <http://www.isdscotland.org/isd/servlet/FileBuffer?namedFile = Uptake.xls&pContentDispositionType=inline> [accessed 8 June 2009].
24. Khan HN, Bendall S, Bates T. Is hormone replacement therapy-related breast cancer more favorable? A case–control study. *Breast J* 2007;**13**:496–500.

25. Soerjomataram I, Coebergh JWW, Louwman WJ. Does the decrease in hormone replacement therapy also affect breast cancer risk in the Netherlands? *J Clin Oncol* 2007:5038–9.
26. Cady B, Chung MA, Michaelson JS. A decline in breast-cancer incidence. *N Engl J Med* 2007;**357**:511.
27. Information Services Division Scotland. Trends in incidence. <http://www.isdscotland.org/isd/servlet/FileBuffer?named-File=i_cancer_breast.xls&pContentDispositionType=inline>.
28. Warnberg F, Yuen J, Holmberg L. Risk of subsequent invasive breast cancer after breast carcinoma in situ. *Lancet* 2000;**355**:724–5.
29. Colditz GA, Rosner BA, Chen WY, Holmes MD, Hankinson SE. Risk factors for breast cancer according to estrogen and progesterone receptor status. *J Natl Cancer Inst* 2004;**96**: 218–28.
30. Althuis MD, Fergenbaum JH, Garcia-Closas M, et al. Etiology of hormone receptor-defined breast cancer: a systematic review of' the literature. *Cancer Epidemiol Biomarkers Prev* 2004;**13**:1558–68.
31. Byers T, Trujillo S, Hines L. Re: Breast cancer incidence, 1980–2006: combined roles of menopausal hormone therapy, screening mammography, and estrogen receptor status. *J Natl Cancer Inst* 2008;**100**:596.
32. Boyages, J. Organised mammography screening programmes: a positive perspective. *Brit Med J Rapid Response* 2009. Available from: http://www.bmj.com/cgi/eletters/339/jul09_1/b2587#216948.
33. Vitak B, Stal O, Manson JC, et al. Interval cancers and cancers in non-attenders in the Ostergotland mammographic screening programme. Duration between screening and diagnosis, S-phase fraction and distant recurrence. *Eur J Cancer* 1997;**33**:1453–60.
34. Porter PL, El Bastawissi AY, Mandelson MT, et al. Breast tumor characteristics as predictors of mammographic detection: comparison of interval- and screen-detected cancers. *J Natl Cancer Inst* 1999;**91**:2020–8.
35. Brewster DH, Stockton DL. Ascertainment of breast cancer by the Scottish Cancer Registry: an assessment based on comparison with five independent breast cancer trials databases. *Breast* 2008;**17**:104–6.
36. Brewster DH, Stockton D, Harvey J, Mackay M. Reliability of cancer registration data in Scotland, 1997. *Eur J Cancer* 2002;**38**:414–7.