The Effect of Mammographic Screening and Hormone Replacement Therapy Use on Breast Cancer Incidence in England and Wales

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Abstract

Design: An extended age-period-cohort model was used to estimate the effect of mammographic screening and hormone replacement therapy on breast cancer incidence in England and Wales between 1971 and 2001.

Results: Incidence of breast cancer increased noticeably in women attending screening for the first time compared with nonattenders [rate ratio (RR), 1.73; 95% confidence interval (95% CI), 1.67-1.80]. Incidence was also 18% to 35% higher in attenders relative to nonattenders in subsequent screening rounds. In the first 3 years after women left the screening program, rates of breast cancer were reduced (RR, 0.88; 95% CI, 0.86-0.90), but by 7 to 9 years after screening, the rates had returned to the expected level (RR, 0.97; 95% CI, 0.94-1.00). The estimated RR of hormone replacement therapy on breast cancer incidence was 1.55 (95% CI, 1.37-1.75). Screening is estimated to increase a woman’s lifetime risk of being diagnosed with breast cancer from 7.8% to 8.6%.

Conclusions: It is estimated that in the absence of screening, rates of breast cancer incidence would have continued to increase. A study at the individual subject level would be beneficial to assess the level of overdiagnosis associated with breast cancer screening. (Cancer Epidemiol Biomarkers Prev 2007;16(11):2257–61)

Introduction

The NHS Breast Screening Programme (NHSBSP) began inviting women for screening in 1988, and national coverage was achieved by the mid-1990s (1). The program was set up to invite women ages 50 to 64 years at 3-year intervals and has since been extended to invite women up to age 70 years.

Some younger women were also invited to screening between 1990 and 2005 as part of the Age Trial (2). The Age Trial was designed to study the effect on mortality from breast cancer of invitation for annual mammography from the age of 40 to 41 years; 54,073 women were randomized to the intervention arm of this study.

The introduction of population based mammographic screening has a considerable effect on observed age-specific incidence rates of breast cancer. An increase in incidence rates associated with screening in England and Wales was first noted in 1995 (3) and has also been observed in other countries with population screening (4, 5). The first screening round will bring about an increase in rates in the screened age groups; these should subsequently decrease although, due to lead time and possibly overdiagnosis, may not reach underlying or background levels (6). As screened women move into the age groups no longer invited to screening, incidence rates in those groups should decrease to a lower level than in corresponding, never-screened women.

Whereas randomized controlled trials have provided evidence of the beneficial effect of mammographic screening on mortality from breast cancer, it remains important to estimate the effect of population screening on both mortality and incidence rates (7).

The estimation of the underlying rates of breast cancer in the absence of screening is necessary to determine expected values for program outcome measures such as cancer detection rates and interval cancer rates (8). The NHSBSP largely relies on such measures to monitor performance, both of the program as a whole and of individual screening units (9).

Trends in incidence rates will also be affected by other factors besides screening. The age-standardized incidence of breast cancer has been increasing gradually in recent decades and in successive generations of women in industrialized countries (4, 10). The reasons for these increases are not entirely clear, but secular and generational changes in known risk factors such as early menarche, high age at first birth, low parity, late menopause, body height, and obesity could have a substantial effect on breast cancer rates (4, 11).

Recent research has shown that current use of hormone replacement therapy (HRT) is associated with an increased risk of breast cancer (12, 13), and an increasing use of HRT over recent years is likely to have had an important effect on incidence rates.
This study estimates the magnitude of the effects of both mammographic screening and HRT use on current rates of breast cancer and the underlying rates as they would have been in the absence of screening and HRT use.

Materials and Methods

Breast Cancer Incidence Data. Data on breast cancer incidence and associated population data in England and Wales by single year of age for the years 1971 to 2001 were obtained from Office of National Statistics.

Screening Coverage. The number of women aged ≥50 years screened in each year in England and Wales was obtained from screening units for 1989 and from standard screening office returns for 1990 onward, by 5-year age groups, separately for initial and subsequent screens. For the initial years, 1987 and 1988, the number of women screened was calculated from coverage data, the level of uptake, and the population in a given age group. Between 1987 and 1991, all screens were assumed to be initial screens. Between 1991 and 1994, it was assumed that the proportion of initial screens was the ratio of the coverage 3 years previously to that in the current year, the remainder being subsequent screens. Data for women aged below 50 years of age were available from the Age Trial database for 1991-1993 (2). From 1994 onward, these women were included in the standard returns.

A series of indicator variables was assigned to the person-years for age groups and calendar years corresponding to the first, second, third, and fourth rounds of screening. These terms assumed that women aged 50 to 64 years were screened from 1990 and subsequently rescreened at 3-year intervals. Population data by single year and age were then used to apportion the estimated number of subsequent screens to one of the screening indicators.

Similar estimates were made for 3-year age groups ≥65 years from 1992 onward of the number of women outside the screening age range who had been screened previously.

The effect of screening has been aggregated over a 3-year period by multiplying the number of women screened in a calendar year by 3 when computing the screening rates to allow for the 3-year screening interval.

HRT use. Estimates of the prevalence of HRT use from 1990 for ages 40 to 89 years were obtained from the General Practice Research Database. In the absence of information for women aged <40 years, the prevalence of HRT use at ages 35 to 39 years was assumed to be four times lower than at ages 40 to 44 years. To account for the fact that some women prescribed HRT may not actually have used it, those who only had one HRT prescription were not included in the HRT prevalence rates.

The prevalence of HRT use among current users was extrapolated back to 1971 using expressions of the following form:

\[ \text{Rate} = A \times (\text{year} - 1970)^B \]

where A and B were estimated using ordinary linear regression.

Model. A Poisson age-period-cohort (APC) regression model was used (14, 15) and the proportions of women using HRT and attending each screen were then built into the model.

All analyses were done on the basis of 1-year groups of age and period. We included age groups from 20 to 89 years and calendar years from 1971 to 2001.

The model yielded parameter estimates of the effects of different screens and HRT use on the incidence rate of breast cancer. Parameter estimates are presented as incidence rate ratios. All screening and HRT parameters presented are adjusted for age, period and cohort effects.

Underlying estimates of breast cancer incidence in the absence of HRT and screening were calculated by multiplying the HRT and screening variables by their corresponding coefficients, and then subtracting from the fitted values from the full model.

Results

Figure 1 shows the observed breast cancer incidence rates for the period 1971-2001 in 5-year age groups. The incidence rate for ages 50 to 54 years increased sharply between 1989 and 1992 and remained high, consistent with women in this age category having a prevalent screen. From 1993 to 2001, the incidence rate for ages 50 to 54 years was above the rate in those ages 65 to 69 years.

In the age groups 55 to 59 and 60 to 64 years, sharp increases occurred from the late 1980s to a peak in 1991 to 1992, resulting in rates in these age groups surpassing the incidence in older women not invited for screening. After the initial screening round, incidence rates in these age groups decreased to a low in 1996 just above the pre-1990 level. After 1996, a second increase in incidence across all age groups invited for screening occurred until the rates stabilized around year 2000.

Table 1 gives the estimated rate ratios from the APC model for breast cancer incidence for the initial screen and subsequent screens, with adjustment for HRT use. The relative rate associated with the prevalence of HRT was 1.55 and the relative rate for the initial screen was 1.73. The rate ratios corresponding to the second, third, and fourth screens were 1.18, 1.25, and 1.35, respectively.

After age 64 years, when women were no longer routinely invited, the breast cancer incidence decreased to a lower than expected level. The estimated reduction was 12% in the first 3 years, 8% in the next 3-year period, and between 7 and 9 years the incidence rate reduction was 3%.

Figure 2A to D summarizes the observed rates (which are identical in all four figures) and the estimated rates based on model predictions. With both screening and HRT use accounted for, the model gave an excellent fit to the data (Fig. 2A).

With HRT omitted from the model, the difference between observed and fitted rates built up gradually in the age group 50 to 64 years from the mid-1980s, corresponding to the increase in the prevalence of HRT use over the same period (Fig. 2B).

Without consideration of screening, the observed and estimated rates diverged in the age group 50 to 64 years from around 1989 and remained divergent throughout the period to 2001 (Fig. 2C). This corresponded to a large
immediate effect and a sustained increase due to screening. With neither HRT nor screening accounted for, the discrepancy between observed and estimated rates was substantial (Fig. 2D).

The estimated difference in the rates of cancers due to screening by calendar year indicated that the effects of screening had reached a steady state by the mid-1990s. Table 2 focuses on these effects predicted by the model in the most recent year available (2001). The cumulative rate of breast cancer up to age 75 years in the absence of HRT and screening was 7.8%. The absolute increases to this figure due to HRT and screening were 0.7% and 0.9%, respectively.

Discussion

The analysis shows that both mammographic screening and HRT use need to be considered when attempting to explain the patterns in breast cancer incidence observed in England and Wales. Having estimated the increase in incidence due to screening and HRT, it has been possible to estimate the incidence as it would have been in the absence of these factors.

The long-term increase in the incidence of breast cancer is evident in data for England and Wales from the trends in Fig. 1 in young and middle-aged women up to the mid-1980s and in older women (65+ years) in the entire period up to 2001. The effect of mammographic screening and HRT use on breast cancer incidence must be assessed in this context of generally increasing rates.

The APC modeling approach attempts to take account of underlying variations between age groups, between calendar periods, and between generations. These differences can be estimated reliably from the data because only a small segment of the available person-years experience are influenced directly by the recent introductions of mammography and HRT in middle-aged women. However, it should be emphasized that the characterization and assessment of screening states and HRT use is indirect and at a group level. A study with individual information about screening histories, HRT use, and other breast cancer risk factors would be inherently more reliable. On the other hand, such a study would typically be based on a smaller sample of women, and it is a distinct advantage of our study that it is based on a large, national population.

Because mammographic screening actively seeks to identify preclinical breast cancers, a sharp increase in incidence after the initial screen is entirely expected. Screening can only serve its intended purpose of reducing breast cancer mortality if the time of diagnosis of cancer is effectively brought forward. A large proportion of the increase in incidence in the first round of screening is due to anticipated cases (i.e., breast cancers diagnosed by mammographic screening, which would have become clinically manifest at a later time if the women had not been screened). However, any application of a screening test entails a likelihood of diagnosing “excess cases” that would not otherwise have become clinically manifest in the lifetime of the woman. The great majority of these excess cancers will occur either as a result of early death from another cause or because of a very slow-growing cancer which would remain undiagnosed into very old age. It is possible to infer from the data the magnitude of all excess cases combined.

The sharp increase in breast cancer incidence associated with the initial screen is well documented in other studies (5, 6, 16). However, our results also show a sustained increase in incidence during the period of subsequent screens. Our analysis was set up on account of the fact that participation in the screening program has been <100% and that a small proportion of screens in

| Table 1. Relative rates of breast cancer incidence from the APC model |
|----------------|----------------|
| Effect          | Relative rate* (95% confidence interval) |
| Initial screen  | 1.73 (1.67-1.80) |
| 2nd screen      | 1.18 (1.14-1.23) |
| 3rd screen      | 1.25 (1.20-1.30) |
| 4th screen      | 1.35 (1.29-1.42) |
| 1st time period after screening | 0.88 (0.86-0.90) |
| 2nd time period after screening | 0.92 (0.90-0.94) |
| 3rd period after screening | 0.97 (0.94-1.00) |
| HRT prevalence  | 1.55 (1.37-1.75) |

*Adjusted for all other terms in the model.
slightly older women were in fact first screens. Our analysis, however, did not consider that the screening technology has gradually improved over the period and increases in sensitivity of the mammographic test would effectively have led to a prolongation of the “prevalence” phase of the program. This may, in part, explain the sustained increase in incidence.

A reduction in incidence after cessation of screening at age 65 years is in line with expectations. It is of interest to note that the reduction in screening cessation is transient.

Figure 2. A, observed rates of breast cancer incidence and corresponding rates predicted from the APC model. B, observed rates of breast cancer incidence and corresponding rates predicted from the APC model without the HRT effect. C, observed rates of breast cancer incidence and corresponding rates predicted from the APC model without the screening effect. D, observed rates of breast cancer incidence and corresponding rates predicted from the APC model without the screening and HRT effects.

Table 2. Effects of HRT and screening predicted by the APC model in 2001

<table>
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<tr>
<th>Age (y)</th>
<th>Rate (/100) in absence of HRT and screening</th>
<th>Cumulative rate in absence of screening and HRT (5 × rate/100)</th>
<th>Difference due to HRT (age-specific rate/100)</th>
<th>Cumulative difference due to HRT (5 × rate/100)</th>
<th>Difference due to screening (age-specific rate/100)</th>
<th>Cumulative difference due to screening (5 × rate/100)</th>
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<td>0</td>
<td>0.76</td>
<td>0</td>
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and that the rates return to the level expected in the absence of screening after ~10 years. In England and Wales, the breast screening program is currently being extended to include women ages 65 to 70 years in the routine invitation system. This should eventually lead to a shift of the observed reduction in incidence to the age group 70 to 74 years.

Research has also shown duration of HRT use to be an important risk factor associated with breast cancer incidence (12). An exploratory analysis included in the model estimates of the duration of HRT use in current users. Models including length of HRT use indicated a larger combined effect of HRT and reduced relative rates of breast cancer associated with the subsequent screens. This modeling used data on length of HRT use for ages 50 to 64 years for the years 1996 to 2001 from the Million Women Study (12). However, this analysis required a number of assumptions about the length of HRT use in ages above 65 and in the years before 1996. A study of individual level information about screening and duration of HRT use would therefore be beneficial to accurately quantify the effect of mammography and HRT on breast cancer incidence.

Approximately 20% of the breast cancers detected in the NHSBSP are in situ cancers (9). Detection of in situ disease should result in a decrease in the incidence of invasive disease; however, this effect is likely to be small and difficult to observe in population trends (17). This analysis does not include in situ cancers in the breast cancer incidence rates modeled. Screening approximately doubles the rate of ductal carcinoma in situ. Therefore, if ductal carcinoma in situ cancers were included in our analysis, the predicted excess of breast neoplasms would be higher in all screening rounds.

In this analysis at the population level, we were unable to assess any affect that hormone therapy has on the sensitivity and specificity of mammographic screening (18). Our estimates suggest that underlying rates in women in the age group 50 to 64 (including the effect of HRT use) are ~11% higher than the estimated rates used to set targets for the NHSBSP in 1998 (8). This may, in part, explain the high standardized detection ratios currently being observed. We estimate that the overall standardized detection ratio of 1.32 in 2002/2003 would be reduced to 1.19 on this basis.

General Practice Research Database data indicate that use of HRT has decreased markedly in recent years, and this is likely to be a direct consequence of publication of results from the estrogen plus progesterin arm of the Women’s Health Initiative postmenopausal hormone therapy trial in July 2002 (19, 20). It is possible that further changes in the prevalence of hormone therapy use will affect incidence of breast cancer in the future.

Acknowledgments
S. Moss and H. Møller had the original research idea, which was developed in collaboration with a subcommittee of the Department of Health Advisory Committee on Breast Cancer Screening for their 2006 publication (1) chaired by Professor Valerie Beral. M. Waller carried out the statistical analysis. J. Watson supplied information on HRT use both from the General Practice Research Database and the Million Women Study. All authors contributed to the writing of the paper and approved the final version of the manuscript. All the authors are guarantors for the study.

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