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Is the recent fall in incidence of post-menopausal breast cancer in UK related to changes in use of hormone replacement therapy?

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ABSTRACT

There has been a substantial decline in the use of female sex hormone replacement therapy (HRT) in the United Kingdom, particularly by post-menopausal women, since around 2000–2001. Given what is known of the risk of breast cancer in women receiving HRT, the decline in use should have resulted in a decrease in risk, and incidence rates about 14% lower than expected were predicted for the age group 50–59 in 2005.

There has been a recent slowing and reversal of the increasing trends in incidence of breast cancer in the age group 45–64. This is most marked at ages 50–59, where rates since 1999 have been decreasing at 0.8% a year, following a long period of sustained increase.

It seems probable that these two events are causally related.

1. Introduction

The use of hormonal preparations in UK has declined dramatically in the recent years: after increasing throughout the early 1990s, prescription of hormone replacement therapy (HRT) for women aged 40 and over fell by about 50% between 2001 and 2005.[1]

HRT is known to increase the risk of developing cancer of the breast[2]; the magnitude of the risk has been quantified based on studies conducted in the United States of America and the UK.[3] Recent data obtained from the United States report a decline in the incidence of breast cancer in post-menopausal women since around 2003,[4–6] coinciding with a decline in dispensing and use of hormone therapy, following publication of the findings of Women's Health Initiative trial in 2002, demonstrating an increased risk of breast cancer in women taking combined oestrogen/progestin.[7]

In this paper, trends in usage of female sex hormones in UK between 1992 and 2006 are presented, by age group and type of preparation, along with the recent trends (1975–2005) in the incidence of breast cancer. The possible influence of the reduced use of hormonal preparations on the risk of breast cancer in post-menopausal women is estimated as a potential explanation for the observed changes in incidence.

2. Materials and methods\

Incidence rates (per 100,000) for breast cancer in Great Britain (England, Wales and Scotland) were provided by the Statistical Information Service of Cancer Research UK, and were based on cancer registrations for the years 1975–2005.

Data on prescription of sex hormones in women aged 15–85 and over were obtained for each year from 1992 to 2006 from the General Practice Research Database (GPRD).[8] This

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Table 1 – Excess relative risks of breast cancer in current users and ex-users of hormonal preparations.[9]

	Excess RR in current users	Excess RR in past (<1 year) users
Oestrogen only	0.3	0.06
Oestrogen + progestagen combinations	1.0	0.21
Progestagens	1.02	0.22
Tibolone	0.45	0.10
All	0.66	0.14

collects information on over 3.4 million active patients from around 450 primary care practices throughout the UK. Prevalence of use in a given year is taken to be the number of patients with a prescription per 1000 patients registered at calendar year mid-point, stratified by calendar year, 5-year age group and agent (according to BNF code).

The prevalence of use of sex hormones in women aged 45 and over is used to calculate excess risk in current users, by age, given the excess relative risk (ERR)[a] associated with their current use, from the Million Women Study (MWS), as shown in Table 1.[9] To estimate the prevalence of ex-users, a simplified assumption is made that users do not stop and restart the same preparation. Thus, the prevalence of ex-users of <1 year (Pex(1)) is given by

$$\mathrm{Pex}(1)_{i,a} = [\mathrm{Pcurrent}_{i-1,a-1}] - [\mathrm{Pcurrent}_{i,a}]$$

where i is the year and a is the age.

Excess relative risk by year and age group is obtained by summation of risks in current users and ex-users. It was assumed that prescription of progesterone only preparations in post-menopausal women was accompanied by oestrogens (with each hormone dispensed separately, rather than as a combined preparation), so that prevalence of use of unopposed oestrogens (P(oes)) is given by the difference (P(oes)–P(prog)).

3. Results

Prevalence of use of female sex hormones is greatest in the age group 20–24, when about 60% of women were receiving a prescription for contraceptive agents, during the period 1992–2006. Use of hormonal (non-contraceptive) agents exceeds the use of contraceptive agents by ages 45–49, and increases to reach a maximum prevalence in the age group 50–54.

Use of hormonal preparations in the older age groups has shown a marked change over time. In women aged 45–69 (Fig. 1), use of hormonal preparations increased for several years from 1992 to reach a maximum of about 25% around 2000–2001, then declined to half this level by 2006. Fig. 2 compares prevalence of use of different types of hormonal preparations, by age group, in the years 2000 and 2006. The maximum decline in use in this period was in the age groups 50–54 (–51%) and 55–59 (–59%), and concerned combined oestrogen–progesterone preparations (–64%) and oestrogen only (–49%) prescriptions.

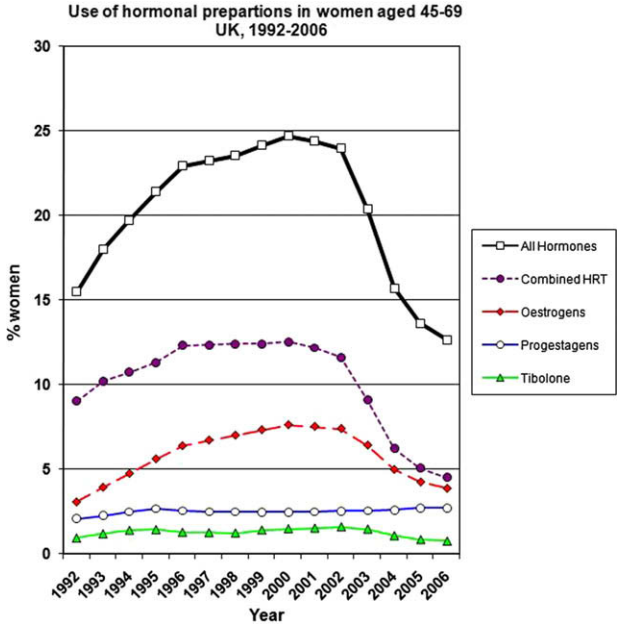

Fig. 1 – Prevalence of use (%) of hormonal preparations in women aged 45–69, by year.

Fig. 3 shows trends in the age-specific incidence rates of breast cancer in Great Britain for 5-year age groups between ages 40 and 79. The sharp increase in incidence in the age group 50–64 around 1990 was the result of the introduction of the national screening programme for women in this age range in 1988–1990. In the 50–54 age group where screening tests are 'incident' tests – i.e. first time examinations – incidence rates remain elevated. In the older age groups (55–64), the great majority of tests after the first few years of the programme are 'prevalent' tests (in women previously screened), so that the initial high rates are somewhat reduced. In 2002, screening was extended to women aged 65–70, and a corresponding brisk rise in incidence can be seen in this age group. There has been a recent decline in incidence rates in age group 50–54, and a flattening at ages 55–59; overall, in women aged 50–59, incidence of breast cancer has decreased by 0.8% per year since 1999. However, the incidence in age group 60–64 continued to increase until 2003, since when there has been a small decline, and there is a continuing brisk rise at ages 65–69, so that incidence in the age range 60–69 has been increasing at the rate of 4.1% a year since 1999. These effects are summarised in Fig. 4, showing rates in 10-year age groups. The increasing incidence rates of breast cancer in women

[a] Excess relative risk (ERR) = Relative risk–1.

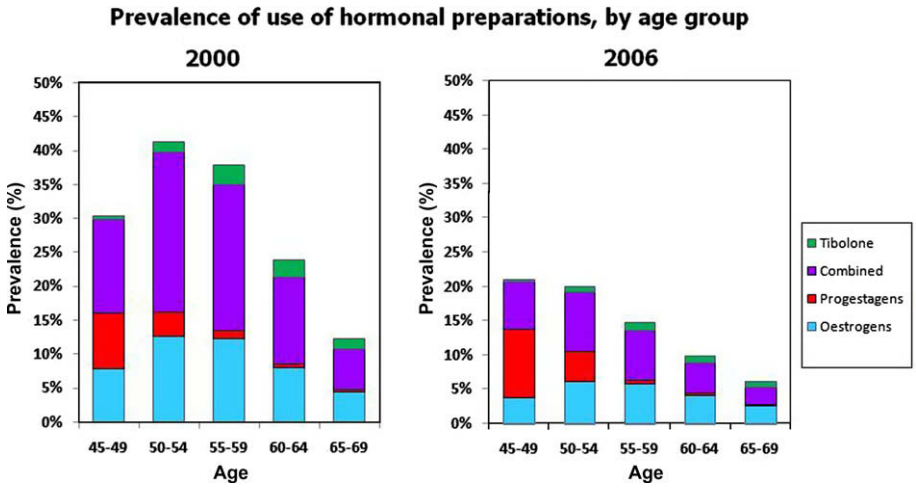

Fig. 2 – Prevalence of use (%) of hormonal preparations, by type of hormone and age group. (a) 2000 (b) 2006.

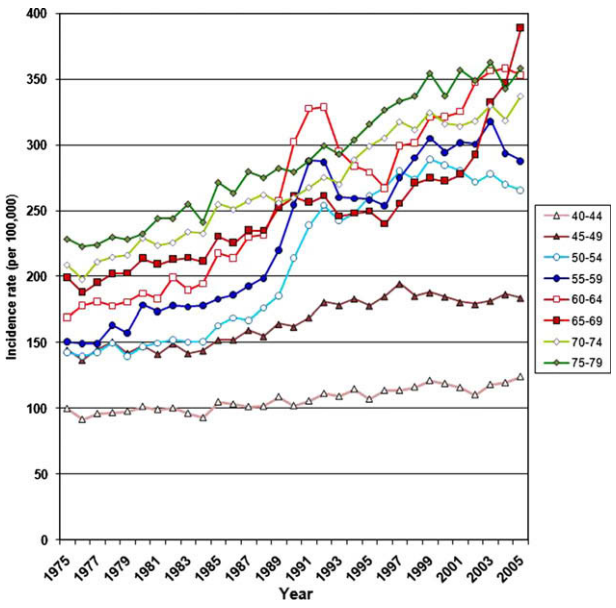

Fig. 3 – Age-specific incidence rates (per 100,000) of breast cancer in Great Britain, by 5-year age group, 1975–2005.

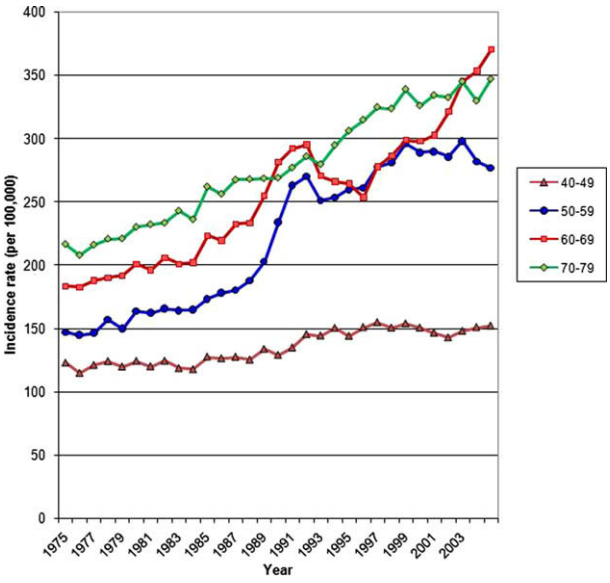

Fig. 4 – Age-specific incidence rates (per 100,000) of breast cancer in Great Britain, by 10-year age group, 1975–2005.

aged 40–49, 50–59, and 70–79 observed in the last quarter of last century have ceased, and there has been almost no change in the incidence rates in the last 5–6 years.

In the year 2000, the estimated excess risk of breast cancer due to HRT was 30.9% at ages 50–54 and 27.6% at ages 55–59, and was rather lower in the next decade of life (17.1% at 60–64 and 8.9% at 65–69). Fig. 5 shows the risk of post-menopausal breast cancer, by age group, relative to that in the year 2000, estimated to result from changes in use of HRT. Between 2000 and 2005, risk in women in their 50s was estimated to decline by some 12–13%. For women in their 60s, however, there was little predicted change until after 2002, after which there were smaller declines of 9% (at 60–64) and 4.6% (at 65–69) by 2005.

4. Discussion

Incidence rates of breast cancer have in general been increasing in Europe over the last decade,[10] so that the recent decline in incidence in post-menopausal women in UK is of particular interest. It seems reasonable to suppose that the dramatic decline in use of hormonal preparations in post-menopausal women in UK would be reflected by a decrease in the incidence of breast cancer, or at least, by an attenuation of the increasing trends observed over the last quarter of the 20th century. The magnitude of the change has been estimated using the relative risks of breast cancer observed in the Million Women Study (MWS).[9] MWS recorded the use of HRT in women aged 50–64 at the time of enrolment, and followed them for an average of 2.6 years (for cancer incidence). The risk among women who were current users of HRT was 1.66

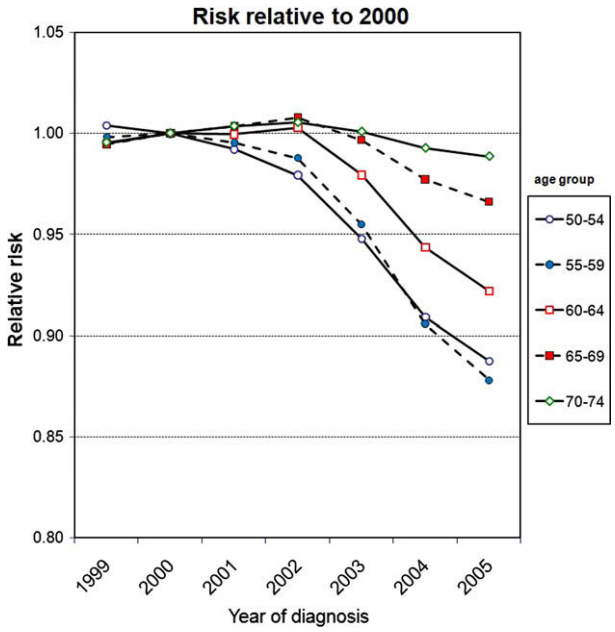

Fig. 5 – Risk of breast cancer, by age group, relative to 2000, estimated to result from change in use of HRT.

[95% CI 1.58–1.75], $p < 0.0001$), varying with the type of preparation used: oestrogen only (1.30), progestagen only (2.02), oestrogen–progestagen (2.00) and Tibolone (1.45). Results varied little between specific oestrogens and progestagens or their doses, or between continuous and sequential regimens. Past users of HRT were not at an increased risk of disease (1.01 [0.94–1.09]), although among women who ceased the use of HRT in the previous year, the relative risk of breast cancer was slightly increased (1.14 [1.01–1.28]).

In the earlier combined analysis of 51 studies (analysed as case-control studies),[11] relative risk in current users was 1.21 (1.35 in users for five years or more); risk was around 1.1 in those who were ex-users of 1–4 years, and was not raised in ex-users of five or more years. In Women's Health Initiative randomised trial,[12] on women aged 50–79, the risk of breast cancer in women taking oestrogen plus progesterone was 1.49 after an average 5.6 years of follow-up; the significantly increased risk, relative to the placebo group emerged after 3 years, and continued to widen until the maximum follow-up period of 7 years.

Risk of breast cancer among users of HRT increases with the duration of use.[9,11,12] Since data on the prevalence of HRT use were not available according to the duration of use, we assumed that the average relative risk for current users, as observed in the MWS, was applicable to women of all ages. It is possible that among younger women (50–54) average duration of use is less than that among older women (65–69, say), so that relative risks are overestimated in the former and underestimated in the latter, although in the MWS, risk of breast cancer in current users of HRT was unrelated to age.[9]

Recent data obtained from the United States report a decline in the incidence of breast cancer in post-menopausal women since around 2003.[4–6,13] This is generally ascribed to the decrease in the use of post-menopausal hormones, although there may be contributions from a decrease in screening intensity, or to a 'saturation' of the population by screening. Introduction of screening results in increases in incidence in the age groups concerned (due to detection of asymptomatic 'prevalent' disease), and incidence remains elevated as long as screening continues, largely due to advancing the time of diagnosis of incident cancers.[14,15] Incidence rates may decline below non-screening values some years after screening ceases. However, in the UK screening has been well established since the early 1990s, and the intensity of screening, as measured by the tests performed per 100 women at risk, and coverage (percentage of women with a test in the last three years) has been more or less constant in the age group 50–64 since then.[16] One would not therefore expect to observe any decline in incidence in these age groups; indeed, the gradual introduction of two-view mammography for incident screens (i.e. subsequent examinations) since 1999 might have been expected to rather increase the observed rates, in view of the improved detection rates.[17] It seems more plausible, therefore, to ascribe the decreasing incidence in age group 50–59 (and in other age groups unaffected by the recent change in screening policy) to decreased exposure to exogenous hormones.

A decline in the incidence of breast cancer since 2001 in women aged 50 and over has been noted in Australia, and linked to trends in prescription of HRT,[18] and an even more striking reduction has been reported from Schleswig–Holstein (Germany), where prevalence of HRT use was reported to be 61.7% in women aged 50–69 in 2001.[19] Conversely, in two regions of the Netherlands, where HRT use was much lower (13% of women aged 49–70 in 1993–1997), no decline in incidence was observed up to 2005.[20]

5. Conclusions

The results presented here suggest that the decline in incidence of breast cancer since 1999 at ages 50–59 and since 2003 at ages 60–64 is a consequence of the reduced use of HRT. The increasing incidence at ages 65–69 is clearly the result of the extension of screening to this age group (predominantly subsequent tests in women already screened). It will be important to monitor incidence rates over the next few years, as trends due to changes in hormone use should become more evident. The reduction in risk due to this cause at ages 50–59 can be estimated as 14% between 1999 and 2005; this implies that there were 1400 fewer cases in this age group in 2005 (and 3300 fewer over the period) than would have been observed if no fall in hormone use had taken place.

Conflict of interest statement

None declared.

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