

## EDITORIAL

# Recent declines in breast cancer incidence: mounting evidence that reduced use of menopausal hormones is largely responsible

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See related research article by Marshall *et al.*, <http://breast-cancer-research.com/content/12/1/R4>

### Abstract

Substantial reductions in breast cancer incidence in women 50 years old or older have been observed recently in many developed countries, and falling use of menopausal hormone therapy (HT) remains the most plausible explanation. In keeping with recent observations from the Women's Health Initiative, a report from the California Teachers Study cohort in this issue of *Breast Cancer Research* adds to this growing evidence. The investigators found a 26% reduction in invasive breast cancer in the cohort from 2000-2002 to 2003-2005, which accompanied an estimated 64% drop in HT use between 2000-2001 and 2005-2006. By collating individual data on the use of HT and breast cancer incidence, they also demonstrated that the decline in incidence was concentrated in women who had ceased HT use. The decline reflected a decrease predominantly in oestrogen receptor-positive tumours in the context of stable screening patterns over the study period. Millions of women continue to use HT, and these findings support carefully targeted short-duration use as an important ongoing strategy to minimise breast cancer risk.

### The findings of the California Teachers Study

The report from the California Teachers Study cohort [1] in this issue of *Breast Cancer Research* adds to the mounting evidence that reductions in the use of menopausal hormone therapy (HT) are largely responsible for the recent declines in breast cancer that have been

observed in many countries in women 50 years old or older [2-4]. The study followed 74,647 female teachers and administrators from public schools; the women included in this analysis were 50 years old or older and were recruited to the study in 1995-1996 [1]. A total of 2,668 incident invasive and 565 *in situ* breast cancers were diagnosed in the cohort [1]. The prevalence of HT use at baseline was extremely high, with around 60% of women reporting current use. HT use was updated in 2000-2001, with illustrative data in 2005-2006 available for a subset of the cohort.

The investigators found a 26% reduction in invasive breast cancer in the cohort from 2000-2002 to 2003-2005 [1]. This accompanied an estimated 64% drop in HT use between 2000-2001 (58% current HT use) and 2005-2006 (21% current HT use) following publication of the main results of the Women's Health Initiative (WHI) trial [1,5]. By collating individual data on the use of HT and breast cancer incidence, they demonstrated that the decline in incidence was concentrated in women who had ceased HT use. The decline was greater in prior users of oestrogen-progestagen HT (47% decline;  $P < 0.001$ ) than in oestrogen-only HT (26% decline;  $P = 0.01$ ) but was substantial and significant in both groups and reflected a decrease predominantly in oestrogen receptor-positive tumours [1]. Almost 97% of the cohort reported mammographic screening according to recommended guidelines, and rates of *in situ* cancers remained stable, indicating consistent screening patterns over the period [1].

### The plausibility of a rapid drop in breast cancer incidence following cessation of use of menopausal hormone therapy

It is now clear that breast cancer risk is elevated in women using HT [6]; ecological [2,3] and observational [7,8] studies show that this elevated risk declines rapidly following cessation of use. The follow-up data from the California Teachers Study cohort build on the recently published analyses of the WHI trial and its associated

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observational cohort study [9]. These analyses demonstrated rapid reductions in breast cancer incidence following cessation of combined HT; in the WHI observational cohort, breast cancer incidence declined by 43% from 2002 to 2003 in women who had ceased use of HRT [9]. Because these cohort studies were large enough to identify statistically significant falls in breast cancer incidence from 2002 onwards, they confirm the ecological studies' findings [1,9]; and because both studies collated individual-level information on HT use, they have additionally confirmed that the declines in breast cancer occurred in women who had ceased HT [1,9].

The greater breast cancer decline in former users of oestrogen-progestagen versus oestrogen-only HT observed in the California Teachers Study is consistent with prior data on the magnitude of the risks associated with each [6,8]; and the fact that the decline was observed predominantly in oestrogen receptor-positive tumours is consistent with the emerging evidence that HT particularly increases the risk of oestrogen receptor-positive breast cancer [10,11]. Furthermore, the rapidity of the decline in breast cancer with HT cessation is in keeping with the historical precedents of declining endometrial cancer following reductions in oestrogen-only HT in the 1970s [12] and rapid reductions in lung cancer risk following smoking cessation [13].

### Current drug regulations and patterns of use

There is broad consensus in the guidance issued by drug regulatory authorities in the UK, US, Europe and Australia in recommending that HT be used only for treatment of moderate to severe menopausal symptoms, for as short a time as possible, and not generally for the first-line prevention of osteoporosis or other chronic disease [14].

The risks of use of HT, particularly prolonged use, are not trivial. The most recent independent quantitative review of the evidence finds that 5 years of use of combined HT among women in their fifties leads to the development of an excess potentially life-threatening condition attributable to HT among 1.4% of users; that is, net excess cases of breast cancer, stroke, ovarian cancer, endometrial cancer or venous thromboembolism that are not offset by reduced hip fracture or colorectal cancer incidence (number needed to harm = 71) [6]. This rises to 4.0% (number needed to harm = 25) with 10 years of use. The corresponding figures for oestrogen-only HT use in women in their fifties without a uterus are 0.5% for 5 years of use and 1.2% for 10 years of use [6]. The overall absolute risks related to HT are dependent on whether an oestrogen-progestagen or oestrogen-only preparation is used, the duration of use, a woman's age and body mass index and her background risk of the relevant conditions. The most comprehensive analyses to date do not support

the 'timing hypothesis'; hence, the relative risks and benefits are not influenced significantly by the time between menopause and commencing use [15].

In keeping with other US findings [2], the reduction in HT use in the California Teachers Study cohort from 2002 onwards was dramatic. Population-wide reductions in breast cancer have been widely attributed to more cautious and targeted use of HT [4]. Yet 21% of the California Teachers Study cohort were current HT users in the 2005-2006 resurvey, highlighting the fact that large numbers of women continue to use HT. The optimal prevalence of HT is not known. However, use should predominantly be short-term and should reflect both the prevalence of moderate to severe menopausal symptoms and the proportion of well-informed women who choose to use HT as treatment for these symptoms after due consideration of its risks and benefits.

### Abbreviations

HT = hormone therapy; WHI = Women's Health Initiative.

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### Competing interests

The authors declare that they have no competing interests.

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