

Review

The rise and fall in menopausal hormone therapy and breast cancer incidence

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ABSTRACT

Studies conducted in different areas of North America and Europe showed a 5–10% decline in the incidence of breast cancer following reductions up to 70% in menopause hormone therapy (HT) use after 2002. The observation that the decline was larger in (or limited to) women aged ≥ 50 years weighs in favour of an effect of reduced HT use on breast cancer incidence. However, changes in screening are also likely to play a role in the decreasing incidence of breast cancer observed in several countries. In particular, the technical improvements and the increased effectiveness of breast cancer screening and detection during the 1990s led to a decreased number of pre-clinical cases found by screening in subsequent years. Further, disentangling the effects of HT use and screening is difficult, as women who stop using HT may also undergo mammography screening less frequently. Thus, the reasons of the falls in incidence remain open to discussion.

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The evidence derived from observational epidemiological studies and from randomized trials indicated that the risk of breast cancer is elevated among women using menopause (combined) hormonal therapy (HT).^{1,2} The risk of breast cancer depends on duration of HT use and is reduced after cessation of use, levelling off after 5 years since quitting HT.³

In July 2002, the U.S. National Institute of Health issued a press release stating that, in the Women's Health Initiative (WHI) randomized controlled primary prevention trial, combined HT use posed more risks than benefits.⁴ This was based on increased risks not only of breast cancer, but also of cardiovascular disease, stroke and blood clots. A combined analysis of four randomized trials confirmed significant excesses of breast cancer, stroke and pulmonary embolus in women randomized to HT compared with placebo.⁵ The release and publicizing of the WHI results was associated with a rapid, substantial decline in use of HT not only in the USA,^{6–8} but also in Canada,⁹ Australia,¹⁰ the UK,^{11,12} Nordic¹³ and western European countries.^{14–18}

Several recent papers reported a downturn in breast cancer incidence rates since 2002, i.e. the year after the publication of the WHI results.⁴ In most countries, the decline in rates was larger in women ≥ 50 years. These falls were attributed to the drop in HT use, but also to changes or saturation in mammography use.^{8–18}

We review here recent evidence on trends in HT use and breast cancer incidence, and add previously unpublished data from the Swiss Canton of Vaud.

Materials and methods

Data were abstracted over the period 1986–2006 from the Vaud Cancer Registry files, which include incident cases of malignant neoplasms in the canton,¹⁹ whose population according to the 2000 Census was about 616,000 inhabitants. We computed age-standardized rates (on the European standard population) for subsequent age groups (20–39, 40–49, 50–69 and ≥ 70).

With reference to the review of the literature, we included investigations on HT use and trends in breast cancer incidence published between January 2006 and February 2009, identified through Medline and by searching papers quoted as references in these studies.

Results

Breast cancer incidence in Vaud

Fig. 1 shows trends in age-standardized incidence rates of breast cancer in Vaud between 1986 and 2006 in subsequent age groups. With reference to women aged 50–69 years, rates increased from the late 1980s to the early 2000s, and decreased thereafter, though the trends were inconsistent. At age 70 and over there was a rise up

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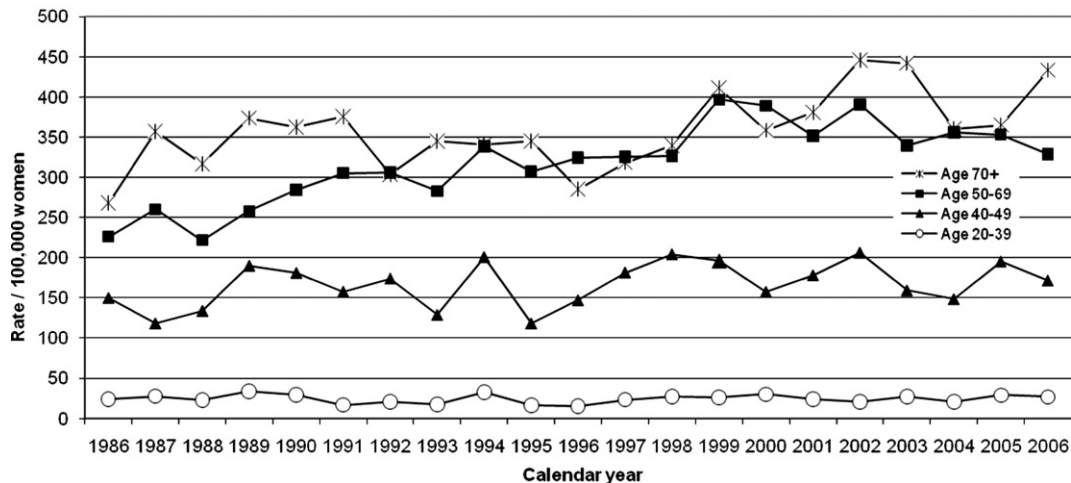


Fig. 1. Trends in age-standardized (European population) incidence rates of breast cancer in various age groups. Vaud, Switzerland, 1986–2006.

to the early 2000s, but trends were not consistent. Some of the yearly changes (e.g., about 20% rise between 1998 and 1999 and between 2005 and 2006) also indicate the major role of variations in mammography – as well as of the play of chance – on breast cancer incidence.

There are no data on the prevalence of HT use in Vaud. In the neighbour Canton of Geneva, HT use increased from 29% of women aged 35–74 in 1994 to 46% in 2002, and then decreased to 31% in 2003.¹⁸

HT use and breast cancer incidence: a review of the evidence

Several data on trends in HT use and incidence of breast cancer in the USA have been published.^{8,20–25} Prescriptions for the two most common forms of HT in the USA fell from 61 million in 2001 to 20.21 million in 2004.²² Using information from the SEER Program, covering about 9% of the US population, Ravdin et al.²² reported an over 11% decrease in breast cancer incidence between 2001 and 2004 for women ≥ 50 years old, whereas no significant change occurred in those < 50 years. The reduction in incidence was restricted to estrogen receptor-positive tumours, thus supporting a role of hormone-related factors. These findings were confirmed by a joinpoint analysis of data from the 9 oldest SEER cancer registries.²³ The main finding was a 9.1% incidence decrease between 2002 and 2003 for estrogen receptor-positive breast cancer. Estrogen receptor-negative tumours decreased by 1.1% per year between 1990 and 2003, and by 4.8% between 2002 and 2003. That study also suggested a second pattern of decrease in rates between 1999 and 2003 for women ≥ 45 years, that was attributed to saturation in screening mammography. However, the decrease in the incidence of breast cancer was not observed in Black women, despite a substantial fall in HT use after 2002 in black women, too.²⁶

Kerlikowske et al.²⁴ investigated the issue using prospective data from 4 screening mammography registries that collected data from 1997 to 2003 on women aged 50–69 years, and confirmed a significant decrease in estrogen receptor-positive breast cancer rates between 2001 and 2003 (–13%), suggesting that screening alone is unlikely to explain the downward trends. Estrogen receptor-negative tumours were stable from 2000 to 2003.

With reference to regional US data, in the Kaiser Permanente Northern California database,²⁰ the use of combined estrogen–progestin and estrogen-only HT decreased by 68% and 36%, respectively, between 2001 and 2003. During the same period, breast cancer incidence rates decreased by 10% in study members and 11% in the state. Consistently with SEER findings,²² the rates

started to decline since 1999, but more substantial reductions were observed during 2003. A subsequent investigation on the same data²⁵ found that the downward trends in incidence observed in Northern California after the publication of the WHI results were in part due to a drop in screening mammography in women who had stopped using HT after 2002.

Another study from California examined the correlation between regional changes in HT use and breast cancer incidence in 58 Californian counties. During 2001–2003, the change in HT use in Californian counties was correlated with change in incidence between 2001 and 2004 (of –8%, –14% and –23% in the counties, with, respectively, the lowest, intermediate and the largest estrogen–progestin HT reductions). It was estimated that each 1% decrease in the prevalence of HT was associated with an incidence decrease of 3.1 cases per 100,000 women.²¹

In the Kaiser Permanente Northwest plan,⁸ including 7386 invasive breast cancer cases, incidence rates of estrogen receptor-positive breast cancers tended to increase up to 2001 and declined thereafter (on average, –2.7% per year). Trends in estrogen receptor-negative tumours showed a slight decrease until 1999, and a steeper decline thereafter (–9.8% per year). The incidence of estrogen receptor-positive breast cancer followed patterns in both screening mammography and HT use.

Several investigations considered data from other industrialized countries. In Canada,⁹ where HT prescription rates fell by 27% between 2002 and 2003, breast cancer rates started to decrease since 2000 (about –1.5% yearly) in all age groups (i.e., 20–49, 50–74 and ≥ 75 years), and a steeper decline was evident in 2003 (–5.6%) particularly for 50–74 years old women. In Australia, HT use dropped by 40% between 2001 and 2003.²⁷ During the same period, breast cancer incidence rates fell by 6.7% in women ≥ 50 years old, while no significant change occurred in women aged < 50 years.

In Europe, UK data are difficult to interpret because of substantial changes in screening practices introduced in 2002.²⁸ However, there are indications of a decline in rates since 1999 in women aged 50–64 in Scotland,¹² as well as in the whole UK.¹¹

Three papers reported on Norwegian trends, and their results were somewhat inconsistent. A first report from 4 counties (covering about 40% of the Norwegian population) found no appreciable decline in breast cancer incidence among women aged 50–69 years, in spite of a more than halved number of women receiving HT when comparing 2005 to 1999.²⁹ However, a subsequent investigation based on national statistics showed a decrease in rates since 2003 in women of the same age group.²⁸ This was explained through differences in the prevalence of screening

mammography among the population of the 4 counties and the rest of Norway.³⁰ In another analysis of Norwegian data, Hemminki et al.¹³ considered women aged 50–64, and found little change in breast cancer incidence between 2000 (i.e., 1-year after the peak in HT use) and 2005. The latter paper also presented data for other Nordic countries, including Sweden, Finland and Iceland. Sweden showed appreciable decreases (about –10%) in incidence in women aged 50–59 between 1999 and 2005, and an increase in 60–64 years old women (+12.7%). Iceland trends showed an abrupt fall after 1999, but the annual incidence fluctuated largely because of its small population. In Finland, there was a later and smaller reduction in use of HT than in other Nordic countries (i.e., –25% between 2002 and 2005; Sweden: –61% between 1999 and 2005; Norway: –51% between 2000 and 2005; Iceland: –43% between 2000 and 2004), while rates of breast cancer continued to increase slightly, except for women aged 60–64 (–3.7%).

In the Netherlands,¹⁷ until 2005, there was no evidence of decline in breast cancer rates. The proportion of HT users was, however, low (i.e., in the 1990s, about 13% of 49–70 years old women used HT). On the other hand, HT was used by more than 25% of postmenopausal women in Belgium and France in the 1990s,^{14,16} and its use dropped by 41% in Belgium and 62% in France during the early 2000s. A report from the Limburg Cancer Registry, Belgium,¹⁶ showed a strong decrease in breast cancer incidence in 50–69 years old women during 2003 and 2004 (–9.5% per year), that was however followed by an increase during 2005 (+15%). In France, the decline in incidence in women above age 50 was –6% between 2004 and 2005 and –5.3% between 2005 and 2006, notwithstanding an increase in mammography screening during the same period.

In a cohort of over 100,000 women enrolled in a quality assurance project of breast cancer diagnosis in Schleswig-Holstein,¹⁵ Germany, HT was used by 46.3% of women in 2001 and by 30% in 2005. Breast cancer incidence, from the Schleswig-Holstein Cancer Registry, decreased by over 8% in ≥ 50 years old women during 2002–2005. Breast cancer incidence started to decline about two years after the fall in HT use.

Discussion

Two important issues emerged from various studies analyzed, which raise some doubts on the actual contribution of HT use in the rapid decline in breast cancer incidence. First, there was some heterogeneity in findings from different regions, as European studies showed inconsistent results and generally smaller declines than in the USA. The impact of HT use on the incidence of breast cancer in different countries depends, however, on their pattern of use, with particular reference to prevalence, duration and type of preparation used. HT was used less frequently and generally for shorter duration in several regions of Europe as compared to the USA, even before the publication of the WHI results, thus the impact was expected to be smaller in Europe.^{17,31} On the other hand, in European populations where use of HT was common, such as France, Germany or Belgium,^{14–16,32} the impact of cessation of use on breast cancer trends was consistent with US data. Thus, in Europe as in North America, registry-based studies conducted in areas with high prevalence of hormone use consistently indicated a decline in breast cancer incidence following the reduction in HT use.^{15,16,23,33}

Second, in various countries a decrease in incidence rates was observed before 2003. This point is more difficult to address. A stabilization or even a small decrease in HT use occurred in various countries since the end of the 1990s, too. Other possible explanations for the earlier decrease in incidence are a saturation effect (i.e., when the penetrance of a screening test reaches a plateau, generating a decrease in incidence rates due to a reduced pool of

prevalent cases) of mammography screening in selected countries,^{23,34} or the existence of other yet unidentified factors protecting women born after 1945.^{35,36} Still, in most populations where a downward trend in incidence was seen before the drop in HT use in 2002, the decrease in incidence was modest during 1999–2001 and steeper in 2003–2004.

HT is a promoting agent in breast cancer and the risk of breast cancer decreases in a relatively short time after stopping HT use.^{3,37,38} Withdrawal of HT could slow tumour growth and decrease the incidence and/or the detection of breast cancer in the short term.²³ In some populations, a substantial decline in rates was already observed during the second half of 2002. If the drop in the 50–69 age group in the United States in 2003 was caused by cessation of HT treatment, then the impact would have been almost immediate.²²

Consistently with these findings, the WHI trial on combined HT use³⁷ reported that the risk of breast cancer started to decrease soon after the end of the intervention. The hazard ratio of HT as compared to the placebo group was 1.48 during the last year of intervention, and declined to 1.20 during the first year after the intervention, 1.43 during the second year, and 1.19 after 2 or more years after the intervention ended. This was independent of mammography screening, as the frequency of mammography both before and after stopping trial was similar in the intervention and placebo groups.

On the other hand, the changes observed in some countries are not consistent with such a rapid effect of HT cessation. Most of the drop in HT use in France occurred between 2002 and 2004, but breast cancer rates increased until the middle of 2003, and then did not start decreasing until the early part of 2005.¹⁴ It is possible that a rather large increase in screening between 2002 and 2004 masked the impact of declining HRT use on breast cancer trends in France.

This shows the difficulty in trying to make the case for consistency of the international trend data in supporting an association between HT cessation after the WHI report and breast cancer risk. It is particularly difficult to disentangle the effect of mammography screening from that of HT use. In fact, women who stop using HT might also undergo mammography screening less frequently.²⁵ In any case, it is unlikely that gradual changes such as those occurring in screening could totally explain the large and sudden decreases in the incidence of breast cancer observed in several countries.³⁸

Though we have no data on the prevalence of HT use in Vaud, and thus we cannot draw any definite conclusion for this population, this line of reasoning applies to the Vaud database, too. The substantial rise in the 1990s in the 50–69 age group is partly or largely due to the progressive introduction of organized screening programs in that age group,³⁹ but this cannot largely explain the more recent trends in the same age group.

An additional finding that weighs in favour of HT in the declining incidence of breast cancer was that the decrease in US incidence rates that occurred between 1999 and 2004 was somewhat stronger (–4.6% per year) for invasive lobular cancers (i.e., the cancer subtype more strongly associated to HT use) than for invasive ductal cancers (–3.3% per year), and that the difference between subtypes emerged for – or was limited to – years 2003 (–8.5% for invasive lobular and –4.5% for invasive ductal cancer) and 2004 (–4.1% and 0%, respectively).⁴⁰

In conclusion, it is now established that breast cancer incidence has been declining since 2002 in most western countries, particularly in middle age women. The decline of estrogen only and combined estrogen–progestin HT use is probably the main factor that led to reduced incidence rates of estrogen receptor-positive breast cancer, which represents the majority of new cases, but

reasons for the falls are complex, and quantification of the role of various factors remains open to discussion.

Conflict of interest statement

The authors state that there are no conflict of interest.

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Authorship: CP performed literature search and review, and wrote the manuscript. FL abstracted and analyzed original data from the Vaud Cancer Registry, and contributed to writing the manuscript. CLV had the original idea for the study, and contributed to writing the manuscript. All authors revised and approved the final version of the manuscript.

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