Maturitas 64 (2009) 80–85

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Review

The incidence of breast cancer and changes in the use of hormone replacement therapy: A review of the evidence

Helena M. Verkooijen[a,b,d,*], Christine Bouchardy[d], Vincent Vinh-Hung[e], Elisabetta Rapiti[d], Mikael Hartman[a,b,c,f]

[a] Department of Epidemiology and Public Health, National University Health System, Singapore
[b] Center for Molecular Epidemiology, National University Health System, Singapore
[c] Department of Surgery, National University Health System, Singapore
[d] Geneva Cancer Registry, Geneva University, Geneva, Switzerland
[e] Oncology Center, Universitair Ziekenhuis Brussel, Belgium
[f] Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden

ARTICLE INFO

Article history:
Received 29 June 2009
Received in revised form 21 July 2009
Accepted 21 July 2009

Keywords:
Breast cancer
Incidence
Hormone replacement therapy

ABSTRACT

Even though a link between hormone replacement therapy (HRT) and breast cancer has been well documented in the epidemiological literature since the 1980s, it was not until publication of the results of the Women's Health Initiative (WHI) study in 2002 and the Million Women Study in 2003 that women and doctors started reconsidering the use of HRT and sales of HRT started to drop. This paper evaluates the impact of the publication of these two landmark studies on the expected and observed changes in the incidence of breast cancer.

Between 2001–2002 and 2005–2006, sharp and significant reductions in the incidence of breast cancer of up to 22% were reported in many US and European populations, temporally consistent with the drop in usage of HRT. Declines in the rates of breast cancer were strongest for 50–60-year-old women (those most likely to be current users of HRT), affected mainly ER+ and PR+ cancers (those most strongly associated with HRT use), and were largest among women with the highest pre-decline prevalence of HRT use and the sharpest decline in its use.

A considerable amount of scientific evidence supports the hypothesis that the decline in the incidence of breast cancer is in large part attributable to the sudden drop in HRT use following publication of the WHI and Million Women studies. Nevertheless, the problem of how to advise women contemplating HRT use today remains. Medical relief will remain necessary for many women with menopausal complaints, and so new therapeutic options need to be explored.

Contents

* Corresponding author at: Department of Epidemiology and Public Health, Yong Loo Lin School of Medicine, 16 Medical Drive, Singapore 117597, Singapore. Tel.: +65 6516 8414; fax: +65 6779 1489.
E-mail address: ephhmv@nus.edu.sg (H.M. Verkooijen).

0378-5122/$ – see front matter © 2009 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.maturitas.2009.07.015

1. Introduction

In 2002, after decades of controversy, hormone replacement therapy (HRT) was declared to increase the risk of breast cancer, while itself offering limited health benefits. The HRT saga started in the 1930s, when estrogen replacement therapy was introduced as a treatment to relieve vasomotor symptoms associated with menopause. After early reports indicated that the use of estrogen alone was associated with a 5-fold increase of endometrial cancer [1], progestagens were added to control this problem. Although increased risks of venous thrombo-embolic events were observed, reported benefits for heart disease, bone, and general well-being led proponents to advocate the use of HRT, as it was said to make a woman not only 'forever feminine' and 'much more pleasant to live with' [2] but also live longer. In the 1970s its use was extended from the typical 1–2 years for control of menopausal symptoms to 5–10 years or longer to achieve these assumed benefits. In the 1980s and 1990s, there was a tremendous rise in the use of HRT in many countries [3–7].

Even though a link between HRT and breast cancer has been well documented in the epidemiological literature since the 1980s [5,8], it was not until publication of the results of the Women's Health Initiative (WHI) study in 2002 [9] and the Million Women Study in 2003 [10] that women and doctors started reconsidering the use of HRT and as a consequence sales of HRT started to drop sharply [11].

This paper evaluates the impact of the publication of these two landmark studies on the expected and observed changes in the incidence of breast cancer, in particular in terms of age distribution and histological subtype.

2. Hormone replacement therapy and breast cancer: the facts

2.1. HRT use is associated with an increased risk of breast cancer

After some short publications had reported inconsistent findings on a possible association between HRT and breast cancer risk, a report from the Nurses' Health Study was the first large study to find a significantly increased risk of breast cancer both for estrogen-only HRT (RR = 1.32) and for combined HRT (estrogen plus progestagen) (RR = 1.41) [12]. Subsequently, a comprehensive overview of all the available case-control and cohort data from 51 studies, involving 17,949 women with breast cancer and 35,916 controls, showed that the increased risk of breast cancer was confined to current and recent use of HRT [8]. Among these current and recent users, breast cancer risks increased with duration of use and reached a 56% relative increase after more than 15 years of use. The excess risk was reduced after cessation of use of HRT and largely disappeared after about 5 years.

The Women's Health Initiative, which was launched in 1991, involved a cohort study and two randomized trials of HRT – one with estrogen alone *versus* placebo in hysterectomized women, and one with combined (estrogen plus progestagen) HRT *versus* placebo for women with an intact uterus – and aimed to evaluate the effect of HRT on the risk of coronary heart disease, breast cancer, fractures, stroke, pulmonary embolism, colorectal cancer, endometrial cancer and all cause mortality in women aged 50–79 years [9]. The combined HRT trial was stopped early, because the overall health effects of HRT became significantly inferior for the treated group. Overall breast cancer risk was significantly increased in the combined HRT trial (hazard ratio [HR] = 1.24), and this risk was similar across age groups, increased with duration of use and was most apparent in women who had used HRT before entry into the trial [13]. The estrogen-only trial was stopped in 2004, after it showed no net health benefit: estrogen-only HRT increased the risk of stroke and had no beneficial effect on the risk of cardiovascular disease, although it did reduce the risk of hip fractures. Initial results suggested a *reduced* risk of breast cancer associated with estrogen-only HRT, but after additional control for other factors, in particular time from menopause to first use of postmenopausal hormone therapy, there was little indication of a reduction in breast cancer risk among hysterectomized women who initiated estrogen-only HRT after menopause [14].

In 1996, an Oxford-based group began collecting risk-factor (including HRT use) and follow-up data from 1,084,110 women in the United Kingdom aged 50–64 who attended the national breast screening programme. The initial results of this Million Women Study were reported in 2003 after a 2.6-year median follow-up, at which time 6096 breast cancers had been recorded [10]. No increased risk of breast cancer was found in previous HRT users (RR = 1.01), nor in women who had stopped using HRT only 1–5 years before the start of the study. Current HRT users, on the other hand, had a significantly increased risk, which was largest for current users of combined HRT (RR = 2.00), but also significantly increased in current users of estrogen-only HRT (RR = 1.30). The relative risk of breast cancer for current users of combined HRT ranged from 1.45 for women who had been using HRT for less than 1 year to 2.31 for women who had been using HRT for more than 10 years. The Million Women Study was the first to clearly establish that the risk of fatal breast cancer was also significantly increased in current users (RR = 1.22).

Combined HRT, which can be administered continuously or sequentially, is generally taken orally, but can also be delivered by injection, transdermal patch or implanted preparations [8,11]. Even though the estimated risk of breast cancer may vary between methods of delivery, all are associated with an increased risk of breast cancer [10,15].

2.2. Tumor characteristics associated with HRT use

In parallel to the rise in HRT use during the 1980s and 1990s, the incidence rates of invasive lobular carcinoma increased disproportionately compared with rates of ductal cancer in some populations, particularly in postmenopausal women [16–18]. This observation generated the hypothesis that HRT use is particularly associated with lobular breast cancer subtypes (pure lobular or ducto-lobular breast cancer). Several studies have now consistently shown that the use of combined HRT is associated with a significant 2–4-fold increased risk of lobular or ducto-lobular carcinoma [19–26]. In contrast, the association between combined HRT and ductal carcinoma is less consistent: i.e. some studies showed no association [20,22,23], while others showed weak associations [10,19,21,24,26].

In a Swedish cohort of 2660 postmenopausal breast cancer patients, it was confirmed that current HRT users, especially those who had been using HRT for more than 5 years, were more likely to present with low-grade tumors, lobular histology and either estrogen and progesteron receptor positive (ER+ PR+) or ER− PR+ tumors

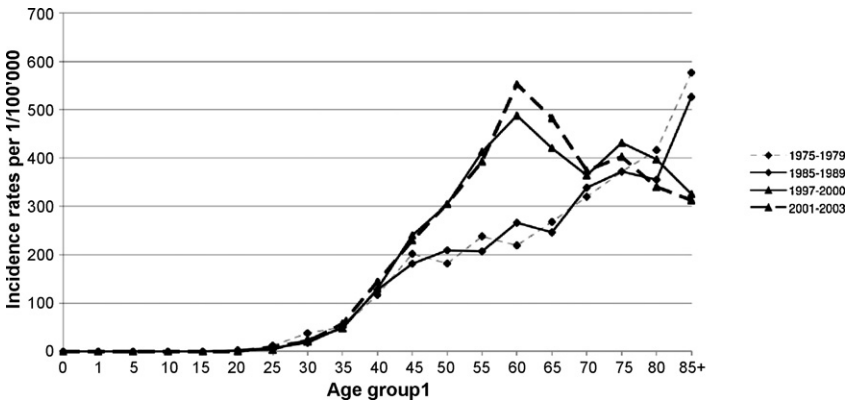

Fig. 1. Invasive breast cancer incidence rates by age and period, Geneva cancer registry 1975–2003. [From Bouchardy et al. [30].]

[27]. The Swedish investigators also showed that invasive breast cancer occurring in HRT users was associated with better survival, which was only partly explained by the favorable tumor characteristics, and may be due to some residual confounding by indication, since more-educated and health-conscious women are more likely to take HRT. Similarly, Fournier showed that the use of several types of combined HRT was more strongly related to lobular cancers than to ductal cancers, and to ER+ positive (especially ER+ PR−) than to ER− cancers [28].

2.3. HRT changes the age distribution of breast cancer

In 2003, investigators at the population-based Cancer Registry of Geneva, Switzerland (where use of HRT was among the highest in Europe [29]) observed a remarkable change in the age distribution of breast cancer rates, which they attributed to the high prevalence of HRT use [30]. In the 1980s and 1990s, the typical age–incidence curve for breast cancer in Western countries described a progressive increase of risk with age, with a slope down around the menopause age (Clemmensen's hook). However, this typical curve by age was gradually changing in Geneva (Fig. 1), as the risk of developing breast cancer was no longer increasing with age but became highest among women aged 60–64 years and declined in older women. This so-called 'incidence peak' around the age of 60–64 years was limited to early-stage disease and ER+ tumors. Some investigators attributed this shift in age-specific incidence rates to mammography screening [31]. However, in a subgroup analysis, restricted to women for whom information on HRT use and mammography screening was available, the Geneva investigators showed that the incidence peak was present only among women who had ever used HRT, regardless of whether they had undergone mammography screening or not [30]. Also, in the Netherlands, where uptake of organized screening mammography exceeds >80%, no such change in age-specific incidence, i.e. 'incidence peak', was observed [32].

2.4. The biological mechanism behind the association between HRT and breast cancer

Until now, none of the studies on the risk associated with HRT have incorporated biochemical or immunopathological data on tumoral levels of estrogen receptor expression. As a result, it is not completely clear whether the association between hormone use and breast cancer risk is due to *de novo* malignant breast tumors brought about by an increased frequency of initiating mutations or to facilitated detection of pre-existing small carcinomas growing more rapidly under HRT stimulation. Indirect evidence suggests that the latter explanation is more plausible. Assuming a median tumor doubling time of 50–100 days, and 30–35 tumor doublings needed to achieve a tumor size of 1 cm diameter, a single malignant tumor cell requires 5–10 years to grow to a clinically and/or mammographically detectable cell mass (i.e. 1 cm). [33]. All studies showing associations between HRT and breast cancer are based on far shorter observational periods, suggesting that the increased risks of breast cancer is more likely to be the result of accelerated growth with attendant earlier detection, than that of primary tumor initiation [8–10,13,14,19].

3. Incidence of breast cancer in the post WHI and Million Women era

After publication of the WHI trials and the Million Women Study, many countries have seen a sudden and steep drop in the use of HRT [6,11,29,34]. Given the lack of individual data on HRT use for most populations, causal inference is difficult and we have to rely on correlations of breast cancer rates with changes in HRT use on a population level. If the association between breast cancer risk and current use of HRT is indeed real, the following effects are to be expected as a consequence of the drop in use of HRT.

1. An overall decrease in the incidence of breast cancer, mainly in women aged 50–60 years, who are most likely to be current users of HRT. This decrease would be most pronounced in populations with the highest prevalence and longest duration of combined HRT use.
2. A drop in the incidence of lobular breast cancer, which is sharper than the incidence reduction in ductal breast cancer. Similarly, a drop in ER+ and/or PR+ and low-grade breast cancer would be more pronounced than a drop in ER− and/or PR− and high-grade breast cancer.
3. A (partial) reversal of the changed age-specific incidence pattern, i.e. the previously discussed 'incidence peak', would be expected.

No studies have been published on the last point, that is, regarding a possible reversal of the age-specific incidence patterns of breast cancer (the 'incidence peak' as a consequence of HRT use). In the following sections, we discuss the first two effects.

3.1. Decline in the incidence of breast cancer

The first signals of an effect of publication of the results from the WHI and Million Women Study on breast cancer risk were presented in short reports in 2006–2007 [35–37]. Clarke et al. were the first to publish ecological data which showed a 10% decline in the incidence of breast cancer between 2001 and 2003 [36]. This decline was temporally consistent with a substantial reduction in the use

Table 1
Observational studies on changes in the incidence rates of breast cancer following publication of the WHI and Million Women Study.

Authors	Year	Study population	Period	Country	Peak prevalence of current HRT use (year)	Decline in HRT use	Decline in breast cancer incidence (age group)
Clarke et al. [36]	2006	Clinical	2001–2003	US	18.5% (2001)	−68%[a]	−10%
		Population-based	2001–2003	US	–	–	−11%
Ravdin et al. [37]	2007	Population-based	2001–2004	US	–	−38%[b]	−8.6% (predominantly >50 years)
Kerlikowske et al. [38]	2007	Screened population	2000–2003	US	35% (2000)	−34%[c]	−5%
Robbins and Clarke [39]	2007	Population-based	2001–2004	US	16.5% (2001)	−67%[d]	−8.8%
					22.7% (2001)	−73%[d]	−13.9%
					25.8% (2001)	−74%[d]	−22.6%
Glass et al. [40]	2007	Clinical	2000–2006	US	21.8% (1999)	−79%[e]	−18% (>45 years)
Katalinic and Rawal [43]	2008	Population-based	2001–2004	Germany	46.3% (2001)	−8.0% per year	−6.7% per year
Canfell et al. [41]	2008	Population-based	2001–2003	Australia	21% (2001)	−40%[b]	−6.7% (>49 years)
Vankrunkelsven et al. [34]	2009	Population-based	2002–2004	Belgium	27% (2002)	−41%	−9.5% (50–69 years)
Parkin [6]	2009	Population-based	1999–2006	UK	25% (2000–2001)	−64%[f]	0.8% per year (50–59 years)
Seradour et al. [48]	2009	National Health Fund Affiliates	2003–2006	France	–	−62%[g]	−12.9% (55–59 years)
							−7.7% (60–64 years)

HRT = Hormone replacement therapy; US = United States; UK = United Kingdom.
[a] Based on prevalence of HRT use among Kaiser Permanente Northern California members (i.e. women filling at least two prescriptions were considered HRT users).
[b] Based on number of dispersed HRT prescriptions.
[c] Based on self-reported use of HRT in 2002–2003.
[d] Based on data from California Health Interview survey, and classified use as low, moderate and high according to absolute decline in HRT use.
[e] Based on prevalence of HRT use among Kaiser Permanente Northwest members (i.e. women filling at least one prescription were considered HRT users).
[f] Obtained from General Practice Research Database, combined HRT, women 45–69 years.
[g] Based on reimbursement databank of National Health Fund between 2001 and 2006 (at least two prescriptions per year).

of combined HRT and was present in both clinical and population-based groups (Table 1) [36]. Next, Ravdin et al. used data from the Surveillance, Epidemiology, and End Results (SEER) registries to show that the age-adjusted incidence rate of breast cancer in women in the United States fell sharply (by 8.6%) between 2001 and 2004 [37]. In addition, they showed that the decrease was evident only in women who were 50 years or older and was more pronounced for ER+ than in ER− cancers. The authors concluded that the decrease in incidence seemed to be temporally related to the first report of the WHI and the ensuing drop in the use of HRT among postmenopausal women in the United States [37]. A multitude of studies reporting decreasing breast cancer rates followed [6,34,38–43], all reporting sudden and steep declines in the use of HRT around 2002–2003, accompanied by declines in rates of breast cancer (Table 1). Robbins and Clarke investigated the magnitude of the decline in the incidence of breast cancer in relation to the reduction in HRT use [39]. Between 2001 and 2004, the incidence rate declined by 8.8% in areas with the smallest reductions in HRT use, by 13.9% in areas with intermediate reductions and by 22.6% in areas with the largest reductions in HRT use (Table 1), thus providing further support for the hypothesis that changes in the prevalence of HRT use were responsible for declines in the incidence of breast cancer.

Robust evidence of a strong impact of discontinuation of HRT on the incidence of breast cancer was reported by Chlebowski et al., who analyzed trends in breast cancer risks in the WHI randomized trial and cohort participants before and after the early termination of the study [44]. During the course of the trial, women in the intervention arm (combined HRT) had a higher risk of breast cancer, in terms of both hazard ratios and incidence rates, than those in the placebo group. These excess risks increased as duration of exposure increased, and suddenly and steeply decreased in the post-intervention period. Similarly, in the observational group, the incidence of breast cancer was initially twice as high in the group taking HRT than in non-users, but this difference in incidence decreased rapidly in the 2 years following termination of the study, closely following the reduction in use of combined HRT. In this period, the frequency of mammography use was unchanged [44].

3.2. Breast cancer trends by histological subtype, estrogen receptor status and grade

Since HRT is most strongly associated with (ducto)-lobular, ER+ and/or PR+ and low-grade breast cancer [19–28], one would expect larger declines in the incidence of these subtypes of breast cancer as a result of the sudden drop in HRT use. Hausauer et al. found that absolute declines in HRT use among US women older than 50 years were most dramatic among Whites, followed by Asians, less pronounced among Hispanics and least among African-Americans [45]. They also found substantial ethnic variation in the recent incidence trends for breast cancer among these women. Overall, incidence rates declined in all ethnic groups, except in African-American women. Consistent with the evidence that HRT acts as a 'fertilizer' of hormone-sensitive tumors, drops in the rates of ER+/PR+, but not ER−/PR−, tumors occurred in White and Asian/Pacific Islander women (who had the *a priori* highest prevalence of HRT use) [45]. In contrast, *increases* in the incidence rates of ER−/PR− and stable rates of ER+/PR+ tumors were observed in the Hispanic and African-American women. The authors also reported larger declines among Whites for (ducto)-lobular than for ductal cancers, further supporting an important impact of HRT on reductions in breast cancer rates. Because there were too few cases, this association could not be assessed in other subgroups.

Jemal et al. evaluated trends in tumor characteristics of breast cancer using SEER data between 1975 and 2003 and observed two distinct incidence patterns. Firstly, there was a downturn in incidence rates in all age groups above 45 years, which is consistent with the saturation in screening mammography. In addition, however, they observed sharp drops in incidence rates for ER+ (−9.1%) and PR+ (−9.1%) tumors between 2002 and 2003, in particularly for women aged 50–69 years [46]. In contrast, the incidence rates for ER− tumors significantly decreased by 1.1% per year from 1990 to 2003 and the incidence rates of PR− tumors continued to increase by 1.2% per year between 1990 and 2003. They concluded that, in addition to the effect of saturation of screening mammography, the sharp decrease in incidence among 50–69-year-olds might reflect the early benefit of reduced use of HRT.

4. Other explanations for the decline in the incidence of breast cancer

Some investigators have proposed other explanations for this decline in the incidence of breast cancer [37,38], a saturation in the rate of uptake of mammography screening or a general decline in its use being one of them. In the US, there was a decline in mammography uptake between 2000 and 2005 [47] and it is indeed quite likely that this explains part of the reduction in the incidence breast cancer. Moreover, the decline in HRT was not large enough to explain the entire decrease in the incidence of breast cancer [47]. In the Kaiser Permanente data set, for example, the reduction in mammography use was about 2–7%, and it is very unlikely that this is a major explanation of the much larger reductions in breast cancer rates [36]. In addition, follow-up data from the WHI study provide further evidence against changes in mammography use being an explanation for the observed reduction in the incidence of breast cancer, since the 2% difference in frequency of mammography use between 2002 and 2003 for women using HRT is insufficient to account for the 43% reduction in the incidence of breast cancer [44]. The observed sharp drop in breast cancer incidence in France between 2000 and 2006, despite a 30% increase in mammography screening rates in the 50–74-year-olds, is further supportive of a role for HRT in breast carcinogenesis [48]. A decline in screening as a reason for a reduction in the detection of breast cancers should have affected ER+ and ER− tumors equally, while in fact a predominant effect was observed for ER+ tumors [49].

Others have argued that, since its introduction in the 1980s, mammography screening has led to more frequent detection and surgical removal of ductal carcinoma in situ (DCIS), explaining (some of) the decrease in the incidence of invasive breast cancer some 15–20 years later [50]. However, early treatment of DCIS is unlikely to completely explain the sharp and sudden drop in breast cancer incidence within a very short time frame.

Changes in lifestyle factors, such as increases in physical activity, reduction of alcohol intake, reduction of body mass index – all known to affect the risk of breast cancer – could explain some of the decline [51]. However, since these factors have only a modest influence on the incidence of breast cancer, enormous changes in the proportions of women changing their lifestyle in these ways would be needed to create this effect.

5. Future directions

There is a considerable amount of scientific evidence to support the hypothesis that a large part of the decline in the incidence of breast cancer between 2002 and 2005 can be attributed to the sudden drop in HRT use following publication of results from the WHI and Million Women studies. These reductions in incidence are temporally consistent with the drop in HRT use, the reductions were greatest among 50–60-year-old women (those most likely to be current users of HRT), sharpest for ER+ and PR+ cancers (most strongly related to HRT use), and most pronounced among women with the highest pre-decline prevalence of HRT use and the strongest drop in use.

The use of HRT has provided us with a deepened understanding of the etiology of breast cancer, as we have been able to observe clear associations with tumor biology and modifications of risk of disease by duration of use. However, there are still many gaps in the understanding of the association of HRT and breast cancer and the issue remains of how best to advise women contemplating HRT use. Many women with menopausal complaints do need medical relief. Right now, there are still about 10 million HRT users worldwide; hence, the possible public health consequences of HRT are still considerable. Clearly, it is important to ensure that patients are aware of the risks and benefits of HRT. The US Food and Drug Administration (FDA) recommends that women who choose to use HRT take the lowest beneficial dose for the shortest period of time [52].

New therapeutic options need to be explored. A French study has indicated that it is the progestagen component of combined HRT that has a particularly important influence on the risk of breast cancer and suggests that combined HRT regimens containing progesterone or dydrogesterone may be less harmful in this respect than those containing other progestagens [28]. Additional research may reveal whether there is genetic predisposition to the effect of HRT on breast cancer risk, in terms of metabolism of sex hormones and individual enzymatic capacity, and whether women who develop breast cancer under HRT can be identified by pretreatment tests.

Contributors

Helena M Verkooijen participated in study design, literature review, interpretation of results and manuscript writing, Christine Bouchardy, Elisabetta Rapiti and Vincent Vinh-Hung assisted in literature review, interpretation of results and critical evaluation of the manuscript Mikael Hartman helped in study design, interpretation of results and writing of manuscript.

Conflict of interest

All authors state that they have no conflict of interest.

Provenance

Commissioned and externally peer reviewed.

References

[1] Weiss NS, Szekely DR, Austin DF. Increasing incidence of endometrial cancer in the United States. N Engl J Med 1976;294:1259–62.
[2] Wilson RA, Wilson TA. The basic philosophy of estrogen maintenance. J Am Geriatr Soc 1972;20:521–3.
[3] Nagel G, Lahmann PH, Schulz M, Boeing H, Linseisen J. Use of hormone replacement therapy (HRT) among women aged 45–64 years in the German EPIC-cohorts. Maturitas 2007;56:436–46.
[4] Schaad MA, Bonjour JP, Rizzoli R. Evaluation of hormone replacement therapy use by the sales figures. Maturitas 2000;34:185–91.
[5] Krieger N. Hormone therapy and the rise and perhaps fall of US breast cancer incidence rates: critical reflections. Int J Epidemiol 2008;37:627–37.
[6] 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.
[7] Wysowski DK, Golden L, Burke L. Use of menopausal estrogens and medroxyprogesterone in the United States, 1982–1992. Obstet Gynecol 1995;85:6–10.
[8] Collaborative Group on Hormonal Factors in Breast Cancer. 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;350:1047–59.
[9] Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321–33.
[10] Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet 2003;362:419–27.
[11] Hersh AL, Stefanick ML, Stafford RS. National use of postmenopausal hormone therapy: annual trends and response to recent evidence. JAMA 2004;291:47–53.
[12] Colditz GA, Hankinson SE, Hunter DJ, et al. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. N Engl J Med 1995;332:1589–93.
[13] Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. JAMA 2003;289:3243–53.
[14] Prentice RL, Chlebowski RT, Stefanick ML, et al. Conjugated equine estrogens and breast cancer risk in the Women's Health Initiative clinical trial and observational study. Am J Epidemiol 2008;167:1407–15.
[15] Colditz GA. Estrogen, estrogen plus progestin therapy, and risk of breast cancer. Clin Cancer Res 2005;11:909s–17s.

[16] Li CI, Anderson BO, Porter P, Holt SK, Daling JR, Moe RE. Changing incidence rate of invasive lobular breast carcinoma among older women. Cancer 2000;88:2561–9.
[17] Verkooijen HM, Fioretta G, Vlastos G, et al. Important increase of invasive lobular breast cancer incidence in Geneva, Switzerland. Int J Cancer 2003;104:778–81.
[18] Levi F, Te VC, Randimbison L, La Vecchia C. Increase in lobular breast cancer incidence in Switzerland. Int J Cancer 2003;107:164–5.
[19] Tjonneland A, Christensen J, Thomsen BL, et al. Hormone replacement therapy in relation to breast carcinoma incidence rate ratios: a prospective Danish cohort study. Cancer 2004;100:2328–37.
[20] Li CI, Weiss NS, Stanford JL, Daling JR. Hormone replacement therapy in relation to risk of lobular and ductal breast carcinoma in middle-aged women. Cancer 2000;88:2570–7.
[21] Li CI, Malone KE, Porter PL, et al. Relationship between long durations and different regimens of hormone therapy and risk of breast cancer. JAMA 2003;289:3254–63.
[22] Chen CL, Weiss NS, Newcomb P, Barlow W, White E. Hormone replacement therapy in relation to breast cancer. JAMA 2002;287:734–41.
[23] Daling JR, Malone KE, Doody DR, et al. Relation of regimens of combined hormone replacement therapy to lobular, ductal, and other histologic types of breast carcinoma. Cancer 2002;95:2455–64.
[24] Newcomb PA, Titus-Ernstoff L, Egan KM, et al. Postmenopausal estrogen and progestin use in relation to breast cancer risk. Cancer Epidemiol Biomarkers Prev 2002;11:593–600.
[25] Banks E, Reeves G, Beral V, et al. Influence of personal characteristics of individual women on sensitivity and specificity of mammography in the Million Women Study. BMJ 2004;329:477.
[26] Slanger TE, Chang-Claude JC, Obi N, et al. Menopausal hormone therapy and risk of clinical breast cancer subtypes. Cancer Epidemiol Biomarkers Prev 2009;18:1188–96.
[27] Rosenberg LU, Granath F, Dickman PW, et al. Menopausal hormone therapy in relation to breast cancer characteristics and prognosis: a cohort study. Breast Cancer Res 2008;10:R78.
[28] Fournier A, Fabre A, Mesrine S, Boutron-Ruault MC, Berrino F, Clavel-Chapelon F. Use of different postmenopausal hormone therapies and risk of histology- and hormone receptor-defined invasive breast cancer. J Clin Oncol 2008;26:1260–8.
[29] Morabia A, Costanza MC. Recent reversal of trends in hormone therapy use in a European population. Menopause 2006;13:111–5.
[30] Bouchardy C, Morabia A, Verkooijen HM, Fioretta G, Wespi Y, Schafer P. Remarkable change in age-specific breast cancer incidence in the Swiss canton of Geneva and its possible relation with the use of hormone replacement therapy. BMC Cancer 2006;6:78.
[31] Hemminki K, Rawal R, Bermejo JL. Mammographic screening is dramatically changing age-incidence data for breast cancer. J Clin Oncol 2004;22:4652–3.
[32] Verkooijen HM, Koot VC, Fioretta G, et al. Hormone replacement therapy, mammography screening and changing age-specific incidence rates of breast cancer: an ecological study comparing two European populations. Breast Cancer Res Treat 2008;107:389–95.
[33] Dietel M, Lewis MA, Shapiro S. Hormone replacement therapy: pathobiological aspects of hormone-sensitive cancers in women relevant to epidemiological studies on HRT: a mini-review. Hum Reprod 2005;20:2052–60.
[34] Vankrunkelsven P, Kellen E, Lousbergh D, et al. Reduction in hormone replacement therapy use and declining breast cancer incidence in the Belgian province of Limburg. Breast Cancer Res Treat 2009 [Epub ahead of print].
[35] McNeil C. Breast cancer decline mirrors fall in hormone use, spurs both debate and research. J Natl Cancer Inst 2007;99:266–7.
[36] Clarke CA, Glaser SL, Uratsu CS, Selby JV, Kushi LH, Herrinton LJ. Recent declines in hormone therapy utilization and breast cancer incidence: clinical and population-based evidence. J Clin Oncol 2006;24:e49–50.
[37] 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.
[38] Kerlikowske K, Miglioretti DL, Buist DS, 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.
[39] Robbins AS, Clarke CA. Regional changes in hormone therapy use and breast cancer incidence in California from 2001 to 2004. J Clin Oncol 2007;25:3437–9.
[40] Glass AG, Lacey Jr JV, Carreon JD, Hoover RN. Breast cancer incidence, 1980–2006: combined roles of menopausal hormone therapy, screening mammography, and estrogen receptor status. J Natl Cancer Inst 2007;99:1152–61.
[41] 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.
[42] Kumle M. Declining breast cancer incidence and decreased HRT use. Lancet 2008;372:608–10.
[43] 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.
[44] Chlebowski RT, Kuller LH, Prentice RL, et al. Breast cancer after use of estrogen plus progestin in postmenopausal women. N Engl J Med 2009;360:573–87.
[45] Hausauer AK, Keegan TH, Chang ET, Clarke CA. Recent breast cancer trends among Asian/Pacific Islander, Hispanic, and African-American women in the US: changes by tumor subtype. Breast Cancer Res 2007;9:R90.
[46] Jemal A, Ward E, Thun MJ. Recent trends in breast cancer incidence rates by age and tumor characteristics among U.S. women. Breast Cancer Res 2007;9:R28.
[47] Breen N, Cronin A, Meissner HI, et al. Reported drop in mammography: is this cause for concern? Cancer 2007;109:2405–9.
[48] Seradour B, Allemand H, Weill A, Ricordeau P. Changes by age in breast cancer incidence, mammography screening and hormone therapy use in France from 2000 to 2006. Bull Cancer 2009;96:E1–6.
[49] Thorat MA. What caused the decline in US breast cancer incidence? Nat Clin Pract Oncol 2008;5:314–5.
[50] Cady B, Chung MA, Michaelson JS. A decline in breast-cancer incidence. N Engl J Med 2007;357:511.
[51] Veronesi U, Boyle P, Goldhirsch A, Orecchia R, Viale G. Breast cancer. Lancet 2005;365:1727–41.
[52] For Women. FDA—Protecting the health of women: 2009. Available from: http://www.fda.gov/ForConsumers/byAudience/ForWomen/default.htm.