Published in final edited form as:

Cancer Causes Control. 2011 January ; 22(1): 125–134. doi:10.1007/s10552-010-9682-7.

The Contribution of Postmenopausal Hormone Use Cessation to the Declining Incidence of Breast Cancer

Brian L. Sprague, PhD, Amy Trentham-Dietz, PhD, and Patrick L. Remington, MD, MPH

Department of Population Health Sciences and Carbone Cancer Center, University of Wisconsin, Madison, WI 53726, USA

Abstract

The striking decline in United States breast cancer incidence since 2002 has been widely attributed to a reduction in postmenopausal hormone use, yet very little analysis has been conducted to quantify the contribution of changes in hormone use to the declining trend. We used literature-based estimates of the relative risk and the changing prevalence of hormone use to estimate the impact of hormone use on the decline in breast cancer incidence between 2002 and 2003 among women aged 40–79 years old. For the base case of a 44% decline in hormone use and a relative risk for current use of 1.5, we estimated that 43% of the decline in incidence was attributable to hormone use. By exploring a range of parameter values we found that high, unlikely values of the relative risk (i.e., ≥ 2.25) and/or the percent decline in hormone use (i.e., $\geq 75\%$) would be required to account for 100% of the observed decline in breast cancer incidence. We conclude that hormone use is unlikely to account for more than half of the observed decline in breast cancer incidence between 2002 and 2003. Further efforts are needed to quantify the potential contributions of other factors, such as the plateau in screening mammography utilization.

Keywords

breast neoplasms; hormone replacement therapy; incidence; epidemiology

INTRODUCTION

For the first time in recorded history, the United States has experienced a dramatic and sustained decline in breast cancer incidence. After decades of rising incidence, this marked reversal has attracted widespread scientific and media attention [1–3]. A number of hypotheses have been proposed to account for this phenomenon, including a reduction in the number of women taking postmenopausal hormones, lower utilization of screening mammography, and a natural decline following the screening-related increase in incidence (due to depletion of the pool of prevalent cancers detectable by screening) [1,4,5]. The relative contributions of each have been widely debated and are yet to be resolved.

Prior to 1980, breast cancer incidence increased modestly, 0.5–2% per year, and responded to changes in reproductive patterns and public awareness [6,7]. As screening mammography was introduced in a widespread manner in the 1980s, the incidence of breast cancer rose rapidly (Figure 1). Consistent with an impact of screening, the increase in incidence was largely limited to *in situ* and localized tumors, rather than regional or distant disease [8,9,10]. Increases in breast cancer incidence continued until reaching a plateau in the late

1990s. National data for breast cancer incidence have revealed a decreasing pattern since 1999 (Figure 1). Incidence of invasive breast cancer in 2003–2007, the last 5 years for which national data are available, are the lowest since 1985 [10].

Epidemiologic evidence has long suggested that postmenopausal hormone therapy is associated with an increase in breast cancer risk. A meta-analysis of 51 studies in 1997 indicated that the risk of a breast cancer diagnosis increased by 2.3% for each additional year of postmenopausal hormone use [11]. In 2002, the Women's Health Initiative (WHI) published the results of their large, placebo-controlled, randomized trial of estrogen plus progestin, finding that the risks of use outweighed the benefits [12]. After approximately five years of follow-up, women assigned to the estrogen plus progestin arm were 26% (95% CI: 0–59%) more likely to develop breast cancer than women in the placebo arm.

Following the publication of this report in July 2002, there were rapid and dramatic reductions in postmenopausal hormone use in the United States [2,13–15]. Nationally, it is estimated that prescriptions for postmenopausal hormone therapy fell by 38% in the first year following publication of the WHI results [16]. Reports from a number of populations have demonstrated that the decline in breast cancer incidence since 2002 coincided with this drop in postmenopausal hormone use [2,14,17,18]. Ravdin et al. observed that breast cancer incidence in the United States fell by 6.7% in the one year following the results of the WHI [1].

Given the temporal association between trends in postmenopausal hormone use and breast cancer incidence, particularly between 2002 and 2003, it has been widely speculated that cessation of hormone use accounts for the observed decline in incidence [1,19]. Though the descriptive data for trends in breast cancer incidence according to demographic and tumor characteristics offer both support and challenges to this theory, very little quantitative analysis has been conducted. In this paper we estimate the influence of cessation of hormone use in late 2002 on the United States breast cancer incidence rate in 2003 and compare this to what was actually observed.

METHODS

Overview

We predicted the expected incidence rate in 2003 based on the observed decrease in the prevalence of hormone use in late 2002 following the publication of the WHI results. This is essentially a calculation of the attributable risk associated with hormone use. However, rather than determining the percent of cases which would be eliminated with complete absence of hormone use, we determined the change in incidence associated with the observed reduction in hormone use. Moreover, we conducted our analysis in an age-stratified fashion since changes in hormone use after the WHI have been observed to vary by age group [15]. Since the WHI found no increased risk of breast cancer in their randomized placebo-controlled trial of estrogen-alone hormone therapy [20], we will consider only the effect of cessation of estrogen plus progestin therapy.

Data sources

The SEER registries—The SEER 9 (Surveillance, Epidemiology, and End Results) registries provide data on breast cancer incidence from 1975–2007 in the states of Connecticut, Iowa, New Mexico, Utah, and Hawaii, the metropolitan areas of Detroit, San Francisco-Oakland, and Atlanta, and the 13-county Seattle-Puget Sound area [10]. Incidence and population denominator data for 2002 and 2003 were obtained using SEER*Stat software (version 6.5.1, National Cancer Institute, Silver Spring, Maryland) [21].

The relative risk associated with hormone use—We examined a range of relative risk (RR) estimates, while using 1.5 as the most likely point estimate (i.e., the base case). The WHI observed a breast cancer hazard ratio of 1.26 (95% CI: 1.00–1.59%) for women assigned to estrogen plus progestin compared to women assigned to placebo [12]. When non-adherence was considered and accounted for in the analyses, the hazard ratio increased to 1.49. Observational studies suggest that risk may vary somewhat by duration and recency of use. A combined analysis of 51 epidemiologic studies of over 100,000 women found a 15% increase in breast cancer risk for less than 5 years of estrogen plus progestin use, and a 53% increase for more than 5 years of use [11]. More recently, the Million Women Study found that current users of estrogen plus progestin at baseline were two times (95% CI: 1.9–2.1) as likely to develop breast cancer [22].

The prevalence of hormone use—Nationally, it has been estimated that prescriptions for all forms of hormone therapy fell from about 7.2 million per month in June 2002 to 5.5 million in December 2002 to 4.5 million in July 2003 [16]. While data regarding the percent of women currently using estrogen plus progestin hormone therapy is not available from nationally representative surveys, a number of reports have been provided from large populations [2,13–15,17]. In perhaps the largest study with a geographically diverse sample, Buist et al. [15] presented the age-specific prevalence of estrogen plus progestin use among over 169,000 subjects aged 40–80 years who were enrolled in one of five large health maintenance organizations throughout the United States (Table 1). Overall, the prevalence of estrogen plus progestin use declined by 46% between the pre-WHI baseline period (September 1999–June 2002) and the post-WHI period (December 2002). The decline was smallest among women aged 40–44 years (27%) and largest among women aged 65–79 years (50–53%). Due to the different population age structures and the variation in hormone cessation by age, an overall 46% decline in the Buist et al. [15] study population is equivalent to a 44% decline among women aged 40–79 in the SEER registry population.

Model

The total incidence of breast cancer (I_t) can be considered an average of incidence among current users (I_u) and non-users (I_n) of postmenopausal hormones, weighted by the proportion of women in the total population (N_t) who are current users (N_u) and non-users (N_n). This can be specified for each age strata (represented by the subscript a) in any given year (subscript y) by the following equation:

$$I_{t,a,y} = \frac{I_{u,a,y} * N_{u,a,y} + I_{n,a,y} * N_{n,a,y}}{N_{t,a,y}} \quad (\text{Eq. 1})$$

Notably, this assumes that former users and never users of hormones have the same breast cancer risk, such that they can be grouped together as non-users (see Discussion for further comment on this assumption and the Appendix for a model incorporating former users). The number of users and non-users of hormone therapy can be calculated from the prevalence of hormone use ($P_{a,y}$):

$$N_{u,a,y} = P_{a,y} * N_{t,a,y} \quad \text{and} \quad N_{n,a,y} = (1 - P_{a,y}) * N_{t,a,y} \quad (\text{Eq. 2})$$

Further, breast cancer incidence among users and non-users of hormones are related to each other by the relative risk (RR), such that:

$$I_{u,a,y} = RR * I_{n,a,y} \quad (\text{Eq. 3})$$

RR is assumed to be constant year-to-year and among all age strata. Estrogen plus progestin formulations have remained largely unchanged in the United States over the recent past and there is little evidence that **RR** varies substantially according to age [11,12,22].

Given known values for the age-specific prevalence of hormone use prior to the WHI results and age-specific breast cancer incidence and population size in 2002, Equations 2 and 3 are substituted into Equation 1 and rearranged to solve for the age-specific incidence among non-users of hormones in 2002:

$$I_{n,a,2002} = \frac{I_{t,a,2002} * N_{t,a,2002}}{RR * P_{a,pre-WHI} * N_{t,a,2002} + (1 - P_{a,pre-WHI}) * N_{t,a,2002}} \quad (\text{Eq. 4})$$

The incidence rate among hormone users follows simply from Equation 3. These calculations are presented for the base case of **RR**=1.5 in Table 2.

The hypothesis under examination is that the decline in breast cancer incidence between 2002 and 2003 was due to changes in the prevalence of hormone use. Thus it was assumed that the incidence of breast cancer among non-users and users of hormones remains constant from year to year. With constant age-specific incidence rates among non-users ($I_{n,a}$) and users ($I_{u,a}$) established, the predicted total incidence rate for 2003 can be calculated from Equation 1 using the prevalence data for hormone use following the WHI results:

$$I_{t,a,2003} = \frac{I_{u,a} * P_{a,post-WHI} * N_{t,a,2003} + I_{n,a} * (1 - P_{a,post-WHI}) * N_{t,a,2003}}{N_{t,a,2003}} \quad (\text{Eq. 5})$$

RESULTS

We used Equation 5 to predict incidence in 2003 ($I_{t,a,2003}$) for the SEER 9 population using the calculated values for $I_{n,a}$ and $I_{u,a}$, the post-WHI prevalence of hormone use from Buist et al. [15], and the population age distribution from the SEER 9 registries [21]. Table 3 shows these calculations for the base case where **RR**=1.5.

The predicted 2003 incidence rates were then compared to those observed in 2003 in the SEER 9 registries. In Figure 2 we see that in all but the 40–44 year age group the predicted decline in incidence for 2003 was less than that which was actually observed. The 65–69 year age group experienced a notably large drop in incidence compared to the other age groups, which was not evident in our predicted rates.

This data was summarized as an overall incidence rate by age-adjusting to the US 2000 Standard Population [23]. Age-adjusting the data in Table 3 produces a predicted age-adjusted rate for 2003 of 276.9 per 100,000 women aged 40–79 years old. The observed SEER 9 age-adjusted incidence among 40–79 years olds was 286.1 per 100,000 women in 2002. Thus, given a **RR**=1.5 and the changes in hormone use observed by Buist et al [15], we would expect a 3.2% $[(286.1 - 276.9) / 286.1]$ decline in incidence in 2003 due to the cessation of hormone use. The observed age-adjusted incidence rate in SEER 9 for 40–79 years olds in 2003 was in fact 264.5 per 100,000 women (a drop of 7.5% from 2002). Thus, for the base case we estimate that cessation of hormone use accounts for less than half $(3.2 / 7.5 = 43\%)$ of the observed decline in breast cancer incidence between 2002 and 2003.

Given the uncertainty in our estimates of **RR** and the change in prevalence of hormone use, we repeated this calculation for a variety of parameter estimates. Table 4 shows the

predicted 2003 incidence as a function of variation in **RR** and the overall percent decline in hormone use. For example, with **RR**=1.5 and a 75% decline in hormone use, 71% of the observed drop in incidence is attributable to cessation of hormone use.

Figure 3 displays this data graphically with a higher density of data points. With **RR**=1.5, complete (100%) cessation of hormone use would have accounted for 93% of the observed decline in incidence. As the **RR** parameter is increased, a lesser degree of cessation is required to reach 100% of the observed decline. With **RR**=3, a ~30% decrease in hormone use is required.

DISCUSSION

This analysis suggests that a 44% drop in postmenopausal hormone use following the publication of the results of the WHI would have caused a 3.2% decline in breast cancer incidence between 2002 and 2003 among women aged 40–79 years old, assuming that current hormone use is associated with a relative risk of 1.5. This would account for less than half (43%) of the observed decline in incidence experienced in the SEER 9 registries between 2002 and 2003 in this age group. Sensitivity analyses indicate that unrealistic estimates of the relative risk and decline in prevalence of hormone use would be required to predict 100% of the observed decline in incidence. For example, with a 50% decline in hormone use between 2002 and 2003, a relative risk of ~2.25 would be necessary to completely account for the observed decline in breast cancer incidence. This exceeds the risk estimates of the WHI, the Million Women Study, and a meta-analysis of 51 observational epidemiologic studies [11,12,22]. With a smaller relative risk of 1.75, approximately 75% of hormone users in 2002 would have had to quit use in 2003. This also exceeds estimates of the one year decline in prevalence of estrogen plus progestin use [2,14,15,17].

Two previous studies have used estimates of the relative risk and prevalence of hormone use to assess the influence of changing hormone use on breast cancer incidence rates. Clarke et al. [24] cite previous national studies showing that the prevalence of combined estrogen-progestin use dropped from 5.6 million women in 2001 to 2.5 million in 2003. They assume that the vast majority of use is among women 50–74 years old to extrapolate that prevalence of use changed from 17% of 50–74 year old women in 1999–2001 to 5% in 2003. With these estimates, and a **RR** of 1.5 associated with hormone use, they predict a decline in breast cancer incidence of 5.5% among women 50–74 years old. The observed decline in invasive breast cancer incidence in SEER for women aged 50–74 between 2001 and 2003 was 11.5% [21]. Therefore, cessation of hormone use would appear to explain about half of the observed decrease in incidence, similar to our results.

A recently published report by Coombs et al. [25] used estimates of hormone use prevalence in 2000 and 2005 to examine the change in the attributable fraction associated with hormone use in each year. The authors considered a range of estimates for the relative risk associated with both estrogen plus progestin and estrogen only formulations. They conclude that depending on the relative risk estimates used, the reduction in breast cancer incidence between 2000 and 2005 can be entirely or partially explained by the reduction in hormone use. A notable difference between our analyses is the time periods examined. Further declines in hormone use were experienced between 2003 and 2005 [2,17], which may lead to greater attribution of the role of hormone cessation in declining incidence for this time period. However, our analysis focused on 2002–2003, as the decline in breast cancer incidence was essentially limited to this period [21].

Postmenopausal Hormone Use as an Explanation for Recent Breast Cancer Incidence Trends

Postmenopausal hormones as a promoter of carcinogenesis—Our results likely overestimate the contribution of cessation of hormone use to the decline in breast cancer incidence because of the assumption that former users immediately acquire the baseline risk of never users. It has been argued that if postmenopausal hormones fuel breast cancer growth, cessation of use may quickly lead to fewer tumors reaching a detectable size on a mammogram, thereby leading to an immediate impact on breast cancer detection. However, epidemiologic evidence indicates that risk of breast cancer is similarly elevated among current users of postmenopausal hormones ($RR=1.46$ vs. never users) and past users who have not used hormones within the past two years ($RR=1.44$ vs. never users) [26]. Risk of breast cancer appears to remain elevated for up to five years following cessation [11,26,27]. We wished to estimate the maximum predicted effect of cessation of hormone use on breast cancer incidence and therefore assumed that former users immediately assumed the risk of never users. In contrast, if former users had an intermediate relative risk of breast cancer (e.g., $RR=1.25$ instead of $RR=1$), the predicted overall incidence in the total population in 2003 would be higher. Comprehensive modeling of this issue would require estimates of the percent of women who were current, former, and never users before and after the WHI results, as well as the distribution of years of hormone use and time since last use (as these likely influence risk level). In the absence of this data, we roughly estimated the impact of elevated risk in former users in a simplified sub-analysis (see Appendix). Former-user status was assigned to the segment of the modeled population which made up the difference between the pre- and post-WHI hormone use prevalence estimates. For a base case with a 44% decline in hormone use, $RR=1.5$ for current users, and $RR=1.25$ for former users, the model predicts a 1.6% decline in incidence in 2003 to 281.5 per 100,000. Hormone use cessation would then account for just 21% of the observed 7.5% drop in breast cancer incidence.

Postmenopausal hormone use in relation to tumor characteristics—Changes in breast cancer tumor characteristics during this time period do not completely support the hypothesis that changes in hormone use accounted for most or all of the trends in incidence. Postmenopausal hormone use is primarily associated with an increased risk of ER-positive tumors. For example, in a prospective cohort of over 370,000 women, long term users of estrogen plus progestin were at a 72% increased risk of ER-positive breast cancer compared to never users, with no increase in risk of ER-negative tumors [28]. To directly estimate the impact of changes in hormone use on ER-positive breast cancer incidence, we applied our mathematical model to ER-positive breast incidence rates available from SEER [21]. The age-adjusted incidence rate of ER positive breast cancer in 2002 was 199.1 per 100,000 among 40–79 year old women. In 2003, this declined by 8.9% to 181.4 per 100,000. For a case with $RR=1.75$ and a 44% decline in hormone use, the model predicted a 4.7% decline in ER-positive breast cancer incidence in 2003 (189.8 per 100,000), which would account for 53% of the observed decline. These results suggest that the change in hormone use cannot account for all of the decline in breast cancer incidence, even when restricted to ER-positive cancers.

Notably, there was also a decline in ER-negative breast cancer between 2002 and 2003. SEER data indicates that incidence of ER-negative breast cancer declined by 4.1% from 51.6 per 100,000 in 2002 to 49.5 per 100,000 in 2003 [21]. With no elevated risk for ER-negative breast cancer associated with hormone use, we would have expected no change in ER-negative breast cancer incidence. This suggests a role for other factors in addition to changes in hormone use.

The relation between postmenopausal hormone use and breast cancer is stronger for tumors of lobular compared to ductal histology [29–31]. This is likely related to the fact that lobular tumors more often express ER [32]. Thus, if discontinuation of postmenopausal hormone use is driving the recent decline in breast cancer incidence, one would expect a more dramatic decline in lobular compared to ductal cancers. The decline in breast cancer incidence since 1999, however, has been similar among both ductal (13% drop) and lobular (10% drop) invasive carcinomas [33].

The majority of epidemiologic studies indicate that use of postmenopausal hormones is associated with 1.2–2.4 fold increased risk of *in situ* breast cancer [34–37]. This is similar in magnitude to the risk estimates observed for invasive breast cancer. While overall incidence rates of *in situ* breast cancer were relatively stable between 2000 and 2003 [4], there was a 5.3% decline in incidence among 40–79 year old women between 2002 and 2003 (from 77.7 to 73.6 per 100,000 women) [21]. We re-ran our model to consider the impact of changes in hormone use on *in situ* rates. With a 44% decline in hormone use and a RR of 1.5 for *in situ* breast cancer, the model predicts a 3.2% decline in *in situ* breast cancer incidence to 75.2 per 100,000 in 2003. This would account for 60% of the observed decline in incidence.

Thus, the temporal correlation between discontinuation of hormone use and the decline in breast cancer incidence is suggestive of a causative role, yet a number of characteristics of the decline in breast cancer incidence indicate that other factors are contributing to this trend.

Alternative Explanations for the Observed Decrease in Breast Cancer Incidence

Recent decreases in the utilization of screening mammography—Although changes in breast cancer screening can affect the incidence of breast cancer, it does not appear that recent changes in mammography utilization can account for the large decline in incidence observed between 2002 and 2003. The widespread adoption of screening mammography was associated with dramatic increases in breast cancer incidence throughout the 1980s [8]. The National Health Interview Survey indicates that the percent of women 50 years and older having a mammogram within the past two years rose from 27.3% in 1987 to 73.7% in 2000 [38]. Since 2000, this rate has declined somewhat: to 72.4% in 2003 and 68.2% in 2005. Comparable declines were observed among all age groups above 50 years old. Similarly, the Behavioral Risk Factor Surveillance System (BRFSS) has estimated that the percent of women 40 years and older reporting having had a mammogram in the past two years declined from 76.4% in 2000 to 74.6% in 2005 [39]. The decline in breast cancer incidence across all age groups above the age of 45 years is consistent with a period effect due to a decline in screening across all age groups since 2000. However, a decline of 2–5% in screening rates is unlikely to completely account for the >10% decline in breast cancer incidence observed since 1999. Additionally, declines in breast cancer incidence have been observed in populations which have maintained high screening rates [2,17]. There is some evidence that cessation of postmenopausal hormone use is associated with a decline in mammography use, which could further complicate attempts to clarify the contribution of each to changes in breast cancer incidence. In a study of Kaiser Permanente members, mammography utilization declined among women who quit using hormones between 2002 and 2003, whereas screening among never users was relatively unchanged [40]. However, the magnitude of the decline in mammography use (~10%) among former users was relatively small, making it unclear whether this would have a large impact on incidence rates.

Anticipated decline in breast cancer incidence resulting from screening—It has been hypothesized that the observed decline in breast cancer incidence may have

resulted from a depletion of the pool of prevalent cancers detectable by screening. As discussed above, mammography utilization increased dramatically throughout the 1980s, finally reaching a plateau in the late 1990s. During this period of intense screening, the prevalent pool of disease was likely vastly depleted as cases of breast cancer diagnosed by mammography were essentially pulled from the future. That is, cases that would have been detected at a regional or distant stage in the future were instead detected years earlier at a localized or *in situ* stage. Now as a plateau in screening mammography utilization has been reached, there is a reduced pool of undiagnosed prevalent cases to detect and an absence of advanced cases; thus, incidence can be expected to be lower [4,33]. This phenomenon is visible by examining trends in prostate cancer incidence; prostate cancer incidence increased by over 100% between 1985 and 1992 from 116 to 237 per 100,000 males per year with the introduction of widespread prostate-specific antigen (PSA) screening [10]. Following this dramatic peak, incidence declined sharply by 1995 to ~170 per 100,000 males.

Other contributions to breast cancer incidence—Changes in a variety of risk factors other than postmenopausal hormone use are likely influencing breast cancer incidence trends. The prevalence of obesity, a known risk factor for postmenopausal breast cancer, has risen dramatically in the United States over the past two decades [38]. However, there was relatively little change during the time period examined here (2002–2003); the percent of adult females who were overweight was essentially stable between 1999–2002 (61.6%) and 2003–2006 (61.3%).

Tamoxifen has been shown to be effective in reducing breast cancer incidence risk [41]. However, tamoxifen use remains rare among women without breast cancer and has not changed dramatically over the past decade. In a study of Kaiser Permanente Northwest members, tamoxifen use among women aged 45–59 years and women older than 60 years remained stable at about 1% and 2%, respectively, between 1994 and 2006 [17].

Limitations

Our analysis was designed to estimate the maximum predicted impact of changes in hormone use on breast cancer incidence. Notably, Equation 1 assumes that breast cancer risk among former users immediately recedes to the risk of never users. This is almost certainly not the case, as epidemiologic evidence suggests that breast cancer risk remains elevated for 2–5 years following cessation [11]. If risk is indeed elevated among former users, the predicted impact of cessation on breast cancer incidence in 2003 would be attenuated, causing the contour lines in Figure 3 to shift towards the upper right hand corner. Our simple sub-analysis suggests that if former users are assigned a relative risk of 1.25, cessation of hormone use would account for only 21% of the observed decline in invasive breast cancer incidence.

We have also assumed that incidence among users and non-users of hormones remains constant year-to-year, such that changes in total incidence are due only to changes in the prevalence of hormone use. This assumption may not be valid if changes in other risk factors or screening practices have occurred in this population. However, the magnitude of change in both other risk factors and screening rates between 2002 and 2003 appears quite small compared to changes in hormone use.

Conclusions

A dramatic decline in breast cancer incidence since 2002 has been observed among women over 45 years old. With a model designed to assess the maximum effect of hormone cessation, we estimated that only 43% of the decline in incidence between 2002 and 2003 could be attributed to the decline in hormone use. More sophisticated analyses are necessary

to elucidate the influence of screening mammography on breast cancer incidence trends. Simulation modeling may be an ideal tool for assessing these multiple and complex influences on breast cancer rates [42]. A better understanding of the contributions of each component to the declines observed in breast cancer incidence is needed so that predictions of future rates can be made. By quantifying the impact of various contributors to breast cancer rates, we can plan accordingly so that the decrease in rates can be continued and, ideally, accelerated.

Acknowledgments

FUNDING: This work was supported by the National Institutes of Health (CA067264). Dr. Sprague is supported by a Cancer Prevention Research Fellowship from the Prevent Cancer Foundation and the American Society of Preventive Oncology.

We are grateful to Dr. Polly Newcomb for her advice and support and Dr. Diana Buist for providing access to her published data.

ABBREVIATIONS

WHI	Women's Health Initiative
RR	relative risk
SEER	Surveillance Epidemiology and End Results
ER	estrogen receptor

References

1. 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(16):1670–1674. [PubMed: 17442911]
2. 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(17):1335–1339. [PubMed: 17698950]
3. Kolata, G. Reversing trend, big drop is seen in breast cancer. *The New York Times*; Dec 15, 2006
4. 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(3):R28. [PubMed: 17477859]
5. Robbins AS, Clarke CA. Re. Declines in invasive breast cancer and use of postmenopausal hormone therapy in a screening mammography population. *J Natl Cancer Inst* 2007;99(23):1815. author reply 1816–1817. [PubMed: 18042938]
6. Harris JR, Lippman ME, Veronesi U, Willett W. Breast cancer (1). *N Engl J Med* 1992;327(5):319–328. [PubMed: 1620171]
7. Holford TR, Cronin KA, Mariotto AB, Feuer EJ. Chapter 4: changing patterns in breast cancer incidence trends. *J Natl Cancer Inst Monogr* 2006;(36):19–25. [PubMed: 17032890]
8. Miller BA, Feuer EJ, Hankey BF. Recent incidence trends for breast cancer in women and the relevance of early detection: an update. *CA Cancer J Clin* 1993;43(1):27–41. [PubMed: 8422603]
9. Chu KC, Tarone RE, Kessler LG, et al. Recent trends in U.S. breast cancer incidence, survival, and mortality rates. *J Natl Cancer Inst* 1996;88(21):1571–1579. [PubMed: 8901855]
10. Altekruse, SF.; Kosary, CL.; Krapcho, M., et al. SEER Cancer Statistics Review, 1975–2007. Bethesda, MD: National Cancer Institute; 2010. http://seer.cancer.gov/csr/1975_2007/, based on November 2009 SEER data submission, posted to the SEER web site
11. 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(9084):1047–1059. [PubMed: 10213546]

12. 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(3):321–333. [PubMed: 12117397]
13. Haas JS, Kaplan CP, Gerstenberger EP, Kerlikowske K. Changes in the use of postmenopausal hormone therapy after the publication of clinical trial results. *Ann Intern Med* 2004;140(3):184–188. [PubMed: 14757616]
14. Clarke CA, Glaser SL, Uratsu CS, et al. Recent declines in hormone therapy utilization and breast cancer incidence: clinical and population-based evidence. *J Clin Oncol* 2006;24(33):e49–50. [PubMed: 17114650]
15. Buist DS, Newton KM, Miglioretti DL, et al. Hormone therapy prescribing patterns in the United States. *Obstet Gynecol* 2004;104(5 Pt 1):1042–1050. [PubMed: 15516400]
16. Hersh AL, Stefanick ML, Stafford RS. National use of postmenopausal hormone therapy: annual trends and response to recent evidence. *JAMA* 2004;291(1):47–53. [PubMed: 14709575]
17. Glass AG, Lacey JV Jr, 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(15):1152–1161. [PubMed: 17652280]
18. 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(23):3437–3439. [PubMed: 17592152]
19. Colditz GA. Decline in breast cancer incidence due to removal of promoter: combination estrogen plus progestin. *Breast Cancer Res* 2007;9(4):108. [PubMed: 17666116]
20. Anderson GL, Limacher M, Assaf AR, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004;291(14):1701–1712. [PubMed: 15082697]
21. National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch; SEER*Stat Database: Incidence - SEER 9 Regs Research Data, Nov 2009 Sub (1973–2007) <Katrina/Rita Population Adjustment> - Linked to County Attributes - Total U.S., 1969–2007 Counties. released April 2010; based on the November 2009 submission (www.seer.cancer.gov)
22. Beral V. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 2003;362(9382):419–427. [PubMed: 12927427]
23. Standard Populations (Millions) for Age-Adjustment. [Accessed April 2007]. Available at: <http://seer.cancer.gov/stdpopulations/>[<http://seer.cancer.gov/stdpopulations/>]
24. Clarke CA, Glaser SL. Declines in breast cancer after the WHI: apparent impact of hormone therapy. *Cancer Causes Control* 2007;18(8):847–852. [PubMed: 17619153]
25. Coombs NJ, Cronin KA, Taylor RJ, Freedman AN, Boyages J. The impact of changes in hormone therapy on breast cancer incidence in the US population. *Cancer Causes Control* 2010;21(1):83–90. [PubMed: 19795215]
26. 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(24):1589–1593. [PubMed: 7753136]
27. Schairer C, Lubin J, Troisi R, et al. Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. *JAMA* 2000;283(4):485–491. [PubMed: 10659874]
28. Kerlikowske K, Miglioretti DL, Ballard-Barbash R, et al. Prognostic characteristics of breast cancer among postmenopausal hormone users in a screened population. *J Clin Oncol* 2003;21(23):4314–4321. [PubMed: 14645420]
29. 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(11):2570–2577. [PubMed: 10861435]
30. 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(7):593–600. [PubMed: 12101105]
31. 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(12):2455–2464. [PubMed: 12467057]

32. Stierer M, Rosen H, Weber R, et al. Immunohistochemical and biochemical measurement of estrogen and progesterone receptors in primary breast cancer. Correlation of histopathology and prognostic factors. *Ann Surg* 1993;218(1):13–21. [PubMed: 8328824]
33. Li CI, Daling JR. Changes in breast cancer incidence rates in the United States by histologic subtype and race/ethnicity, 1995 to 2004. *Cancer Epidemiol Biomarkers Prev* 2007;16(12):2773–2780. [PubMed: 18086787]
34. Longnecker MP, Bernstein L, Paganini-Hill A, Enger SM, Ross RK. Risk factors for in situ breast cancer. *Cancer Epidemiol Biomarkers Prev* 1996;5(12):961–965. [PubMed: 8959317]
35. Claus EB, Stowe M, Carter D. Breast carcinoma in situ: risk factors and screening patterns. *J Natl Cancer Inst* 2001;93(23):1811–1817. [PubMed: 11734598]
36. Ross RK, Paganini-Hill A, Wan PC, Pike MC. Effect of hormone replacement therapy on breast cancer risk: estrogen versus estrogen plus progestin. *J Natl Cancer Inst* 2000;92(4):328–332. [PubMed: 10675382]
37. Reeves GK, Beral V, Green J, Gathani T, Bull D. Hormonal therapy for menopause and breast-cancer risk by histological type: a cohort study and meta-analysis. *Lancet Oncol* 2006;7(11):910–918. [PubMed: 17081916]
38. National Center for Health Statistics: Health, United States, 2008 with chartbook.
39. CDC. Use of mammograms among women aged >40 years - United States, 2000–2005. *MMWR* 2007;56:49–51. [PubMed: 17251897]
40. Caan B, Habel L, Quesenberry C, Kushi L, Herrinton L. Re: Declines in invasive breast cancer and use of postmenopausal hormone therapy in a screening mammography population. *J Natl Cancer Inst* 2008;100(8):597–598. author reply 599. [PubMed: 18398101]
41. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst* 1998;90(18):1371–1388. [PubMed: 9747868]
42. Feuer EJ. Modeling the impact of adjuvant therapy and screening mammography on U.S. breast cancer mortality between 1975 and 2000: introduction to the problem. *J Natl Cancer Inst Monogr* 2006;(36):2–6. [PubMed: 17032887]
43. Surveillance Epidemiology and End Results (SEER) Program: SEER*Stat Database. [released April 2009; based on the November 2008 submission] (www.seer.cancer.gov)

APPENDIX

To incorporate elevated risk (compared to never users) among women who quit using hormones after the WHI results, a few simple modifications to the model were made.

For the post-WHI period, Equation 2 in the main model was replaced by the following relations:

$$\begin{aligned} N_{c,a,2003} &= P_{a,\text{post-WHI}} \times N_{t,a,2003} \\ N_{f,a,2003} &= (P_{a,\text{pre-WHI}} - P_{a,\text{post-WHI}}) \times N_{t,a,2003} \\ N_{n,a,2003} &= (1 - P_{a,\text{pre-WHI}}) \times N_{t,a,2003} \end{aligned}$$

where N_c , N_f , and N_n are the number of current, former and never users, respectively. Breast cancer incidence among these groups are related to each other by the relative risk (**RR**):

$$I_{c,a} = RR_c \times I_{n,a} \quad \text{and} \quad I_{f,a} = RR_f \times I_{n,a}$$

Equation 5 in the main model was then replaced with the following equation for incidence in 2003:

$$I_{t,a,2003} = \frac{I_{c,a} * P_{a,post-WHL} * N_{t,a,2003} + I_{f,a} * (P_{a,pre-WHL} - P_{a,post-WHL}) * N_{t,a,2003} + I_{n,a} * (1 - P_{a,pre-WHL}) * N_{t,a,2003}}{N_{t,a,2003}}$$

Figure 1. Female breast cancer incidence, 1975–2007

Female breast cancer incidence in SEER 9 registries (all ages), invasive vs. *in situ*, 1975–2007 [21].

Figure 2. Comparing the observed decline in invasive breast cancer to that predicted by cessation of hormone use

Predicted age-specific breast cancer incidence in 2003 (dotted line), assuming a 44% decline in postmenopausal hormone use from 2002 and a relative risk of 1.5 associated with hormone use. The observed age-specific incidence in 2002 (solid line) and 2003 (dashed line) from the SEER 9 registries show that the predicted drop in incidence was less than that observed.

Figure 3. Percent of observed decline in incidence attributable to cessation of hormone use

This contour plot displays the percent of the observed decline in breast cancer incidence between 2002 and 2003 among women aged 40–79 years old that can be attributed to cessation of postmenopausal hormone use, depending on the relative risk associated with hormone use and the percent decline in hormone use experienced between 2002 and 2003.

TABLE 1

Prevalence of estrogen plus progestin use before (September 1999–2002) and after (December 2002) the publication of the Women's Health Initiative results, by age.

Age group (years)	Prevalence of estrogen-progestin use ^a	
	Pre-WHI ^b (%)	Post-WHI ^b (%)
40–44	1.5	1.1
45–49	7.5	4.4
50–54	22.7	12.7
55–59	28.5	16.4
60–64	22.6	12.1
65–69	14.7	7.3
70–74	10.4	4.9
75–79	6.8	3.2

WHI, Women's Health Initiative.

^aData source: Buist et al. [15]

^bThe Pre-WHI period refers to September 1999–June 2002 and the Post-WHI period refers to December 2002.

TABLE 2

Calculation of the incidence of breast cancer among non-users and users of postmenopausal hormones according to age group for the SEER 9 population in 2002, assuming a relative risk of 1.5 for current hormone use.

Age group (years)	SEER 9 Population, 2002 ^a	SEER 9 Incidence ^c , 2002 ^a	Pre-WHI prevalence of hormone use ^b (%)	Calculated incidence ^c among non-users, 2002	Calculated incidence ^c among users, 2002
40-44	1,115,344	118.4	1.5	117.5	176.3
45-49	1,048,454	191.3	7.5	184.4	276.6
50-54	927,035	253.2	22.7	227.4	341.1
55-59	733,440	331.5	28.5	290.2	435.2
60-64	533,796	407.1	22.6	365.8	548.7
65-69	443,642	441.6	14.7	411.4	617.0
70-74	418,541	447.7	10.4	425.6	638.4
75-79	386,158	481.9	6.8	466.1	699.1

SEER, Surveillance Epidemiology and End Results.

^aObtained from SEER*Stat [43].

^bObtained from Buist et al. [15] The Pre-WHI period refers to September 1999-June 2002.

^cAll incidence rates presented per 100,000 females.

TABLE 3

Prediction of 2003 breast cancer incidence for the SEER 9 population in 2003, assuming a relative risk of 1.5 for current hormone use.

Age group (years)	SEER 9 Population, 2003 ^a	Post-WHI prevalence of hormone use ^b (%)	Calculated incidence ^c among non-users, 2003	Calculated incidence ^c among users, 2003	Predicted total incidence ^c , 2003
40-44	1,115,314	1.1	117.5	176.3	118.2
45-49	1,067,891	4.4	184.4	276.6	188.4
50-54	944,120	12.7	227.4	341.1	241.8
55-59	770,378	16.4	290.2	435.2	313.9
60-64	566,796	12.1	365.8	548.7	387.9
65-69	452,104	7.3	411.4	617.0	426.4
70-74	413,054	4.9	425.6	638.4	436.0
75-79	383,974	3.2	466.1	699.1	473.5

^aObtained from SEER*Stat [43].

^bObtained from Buist et al. [15] The Post-WHI period refers to December 2002

^cAll incidence rates presented per 100,000 females.

TABLE 4

Percent of the observed decline in overall breast cancer incidence between 2002 and 2003 among women 40–79 years old attributable to cessation of hormone use, according to parameter values for the relative risk of hormone use and percent decline in prevalence of hormone use.

RR	% Decline in hormone use, Pre- vs. Post-WHI	Predicted total incidence ^a , 2003	Predicted % decline from 2002 to 2003	Observed % decline from 2002 to 2003	% of observed decline attributable to cessation of hormone use
1.25	25	283.3	1.0	7.5	13
1.25	50	280.7	1.9	7.5	25
1.25	75	278.2	2.8	7.5	37
1.50	25	280.6	1.9	7.5	25
1.50	50	275.8	3.6	7.5	48
1.50	75	270.9	5.3	7.5	71
2.00	25	276.0	3.5	7.5	47
2.00	50	267.1	6.6	7.5	88
2.00	75	258.2	9.8	7.5	131 ^b

RR, relative risk of breast cancer among hormone users compared to non-users.

^a All incidence rates presented per 100,000 females.

^b Values greater than 100% indicate that we would have expected a larger decline in incidence than that which was actually observed.