Forty-Year Trends in Menopausal Hormone Therapy Use and Breast Cancer Incidence Among Postmenopausal Black and White Women

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After reports from the Women's Health Initiative randomized trial evaluating estrogen plus progestin, there was a sudden, substantial, and sustained decrease in all categories of menopausal hormone therapy, and the first reduction in age-adjusted breast cancer incidence in more than 20 years was seen in 2003-2004 among US women 50 years of age or older. Subsequent trends in breast cancer incidence have been described, but most reports have not focused on the postmenopausal age group or fully engaged the potential influence of reduced hormone therapy on breast cancer incidence trends by race/ethnicity. To address this gap, this commentary examines trends for annual age-adjusted breast cancer incidence over a 40-year period from 1975 to 2015 for white and black women on the basis of findings from the Surveillance, Epidemiology, and End Results 9 registries. Overall, the sharp decline in breast cancer incidence seen in 2003-2004 was followed in the subsequent decade by a continued low breast cancer incidence plateau in white women that has largely persisted. In contrast, a new discordance between breast cancer incidence trends in black and white women has emerged. In the 2005-2015 decade, a sustained increase in breast cancer incidence in black women has resulted in annual incidence rates comparable, for the first time, to those in white women. This commentary explores the hypothesis that the over-decade-long and discordant changes in breast cancer incidence rates in postmenopausal black and white women are, to a large extent, associated with changes in hormone therapy use in these 2 groups. ***Cancer* 2020;0:1-9**. © *2020 American Cancer Society*.

KEYWORDS: breast cancer in black women, breast cancer incidence trends, breast cancer in white women, hormone therapy trends, Women's Health Initiative.

INTRODUCTION

After the first reduction in breast cancer incidence in the United States in more than 20 years resulted in a lower age-adjusted breast cancer incidence in 2003-2004, a finding attributed to decreased menopausal hormone therapy use,[1,2] it was uncertain what the future course of breast cancer incidence would be. Over a decade later, the low-incidence plateau has largely persisted in white women, whereas a new discordance between incidence trends has emerged from a comparison of findings in black and white women. We review these developments and, using findings from the Women's Health Initiative (WHI) randomized trials evaluating hormone therapy as background, propose a complementary hypothesis.

MENOPAUSAL HORMONE THERAPY BEFORE THE WHI

Hormone therapy with conjugated equine estrogen (CEE) alone was introduced into clinical practice in 1942[3] and remains the most effective therapy for menopausal vasomotor symptoms.[4] Findings from several decades of observational studies suggested benefits from hormone therapy use, including lower risks of coronary heart disease and fracture and possibly cognitive impairment.[5] After hormone therapy was associated with higher breast cancer risk,[6,7]

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the concept emerged that hormone-related breast cancers were detected early and had a favorable prognosis.[5] Subsequently, because of the anticipated favorable risk/benefit balance, hormone therapy became increasingly common, and its use peaked in 1999 with more than 35 million US prescriptions.[8] However, despite a half-century as one of the most common medications for postmenopausal women, hormone therapy had never been evaluated in a full-scale, randomized clinical trial.

THE WHI HORMONE THERAPY TRIALS

Against that background, 2 randomized, full-scale clinical trials were initiated in 1993 by WHI investigators to provide definitive evidence regarding the risks and benefits of 2 hormone therapy regimens with respect to chronic disease risk: CEE plus medroxyprogesterone acetate (MPA; for postmenopausal women with an intact uterus) and CEE alone (for postmenopausal women with prior hysterectomy).[9,10] The trials evaluated the 2 hormone therapy preparations most commonly used in US clinical practice. The CEE plus MPA trial was stopped early in 2002 after 5.6 years (median) of intervention when overall health risks exceeded benefits with increases in cardiovascular disease and invasive breast cancer,[11] with the breast cancers diagnosed at a more advanced stage.[12,13] The WHI trial evaluating CEE alone also was stopped early after 7.2 years (median) of follow-up on the basis of increased stroke risk and no overall coronary heart disease benefit.[14] With additional follow-up, breast cancer incidence was found to be significantly reduced by CEE alone.[13,15]

Complex patterns of hormone therapy influence on breast cancer risk subsequently emerged in the 2 WHI trials. In the first 2 years of the CEE plus MPA trial, an apparent decrease in breast cancer incidence was ultimately attributed to interference with mammographic detection.[12,16] Subsequently, year-to-year increases in breast cancer incidence emerged throughout the 5.6 years of intervention, with an associated increase in breast cancer mortality.[17] In the immediate postintervention period, there was a substantial drop in breast cancer incidence in the CEE plus MPA group. However, the overall hazard ratio remained above 1, and a sustained significantly higher breast cancer risk persisted for more than a decade after CEE plus MPA use ended with no evidence of risk modulation over time.[13,18,19] As a result, 5.6 years of CEE plus MPA use resulted in long-term increased risk after the cessation of CEE plus MPA therapy.

In the CEE-alone trial, the hazard ratio for breast cancer incidence for CEE alone was lower than 1 throughout the 7.2-year intervention period,[15,20] and this continued through postintervention follow-up.[13,19] The significant reduction in breast cancer incidence has been attributed to CEE-induced apoptosis[21,22] or anti-estrogenic properties unique to CEE.[23,24] For black women, the reduction in breast cancer incidence with CEE alone (hazard ratio, 0.47; 95% CI, 0.26-0.82) was possibly greater than that seen in white women (interaction $P = .09$),[25] with the largest benefit seen in black women with ≥80% African ancestry (trend $P = .04$ for effect modification by ancestry).[25,26]

To summarize, in a randomized clinical trial, CEE plus MPA increased breast cancer incidence, with the increased risk persisting through the postintervention follow-up. In a randomized clinical trial, the use of CEE alone for women with prior hysterectomy decreased breast cancer incidence, with the decreased risk persisting through the postintervention follow-up.

In the long-term follow-up of the WHI hormone therapy trials, except for younger postmenopausal women with prior hysterectomy using CEE alone, no overall health benefit emerged for hormone therapy for primary prevention of chronic conditions of postmenopausal women.[19,27,28] However, the effects of CEE plus MPA and CEE alone on breast cancer incidence and mortality continue to be of public health significance.

CLINICAL IMPACT OF FINDINGS FROM THE WHI HORMONE THERAPY TRIAL

After the presentation of CEE plus MPA trial findings in July 2002[11] and a report of adverse effects on breast cancer in June 2003,[12] there was a rapid and substantial decline in all categories of menopausal hormone therapy use. The decline was particularly steep for combined CEE and MPA use. In comparison with January to June 2002, prescriptions for combined CEE and MPA use in the United States decreased by 66%.[29] In the same time frame, a substantial decrease in breast cancer incidence was seen in the United States in women 50 years old or older from the Surveillance, Epidemiology, and End Results (SEER) program. On the basis of these findings, Ravdin et al[1] hypothesized that the breast cancer decrease resulted from the concurrent decrease in CEE plus MPA use.

The relationship between the decrease in CEE plus MPA use and the decrease in breast cancer incidence remained controversial, with a reduction in mammography a commonly explored alternative.[30,31] Subsequently, investigators from the WHI CEE plus MPA randomized trial reported that, after an abrupt interruption of study pills, the breast cancer incidence sharply declined over the

subsequent 2 years against a background of unchanging mammography.[18] However, it was uncertain what the longer term effect of the discontinuation of CEE plus MPA on breast cancer incidence would be.

TRENDS IN BREAST CANCER INCIDENCE FOR WHITE AND BLACK WOMEN

The substantial reduction in hormone therapy use following the reports of the WHI trial findings has been sustained. Estimates of hormone therapy use examining several data sets have found that the sharp decrease in hormone use has been sustained through 2016[32] (Table 1). According to the household component of the Medical Expenditure Panel Survey, from 2001 to 2008, total expenditures on hormone therapy decreased from $5.3 billion to $2.3 billion (a 62% reduction).[33] Results from the National Health and Nutrition Examination Survey showed that the prevalence of hormone therapy use was 22.4% in 1999 and 4.7% in 2010.[34] Other reports have supported these observations (Table 1),[29,35,36] with reductions observed across racial groups for estrogen with and without progestin.[34,37]

The background of the long-term reduction in hormone therapy use and the sharp decline in breast cancer incidence rates seen in women 50 years old or older between 2002 and 2003[1,2] has focused attention on the subsequent trajectory of breast cancer incidence and outcomes in the United States. A number of studies have examined breast cancer trends in this period, but most have not focused on postmenopausal women, and none have considered the potential influence of discordant effects of estrogen alone versus estrogen plus progestin on breast cancer incidence. On the basis of findings through 2007, DeSantis et al[37] identified no further decrease in breast cancer incidence among white women with no comparable reduction seen in black women over the same period. Toriola and Colditz,[38] on the basis of findings through 2009, described a long-term divergence with decreasing breast cancer mortality with increasing breast cancer incidence. In 2016, the convergence of incidence rates between black and white women was identified for follow-up through 2014.[39,40]

Despite the relatively low and stable age-adjusted breast cancer incidence seen from 2004 to 2015 among white women, a more common impression may be a breast cancer incidence continuing to increase on the basis of an overall increasing total incidence (not age-adjusted) in the US population. For example, the estimated annual breast cancer incidences reported by *CA: A Cancer Journal for Clinicians* were 211,240 breast

TABLE 1. Selected Reports of Hormone Therapy Use in the United States From 1999 to 2010

Lead Author	Source	Endpoint	Results
Stagnitti & Lefkowitz 2011[33]	Household component of the Medical Expenditure Panel Survey (MEPS-HS), a nationally representative longitudinal survey, 2001-2008	• Outpatient prescription drugs: ◦ Total expenditures ◦ Total N prescriptions • Total with 1 prescription	• Over 2001-2008, total expenses on hormone therapy decreased from $5.3 to $2.3 billion (62%) • Total hormone therapy prescriptions decreased from 112.2 million in 2001 to 31.8 million in 2008
Tsai 2011[35]	National Disease and Therapeutic Index, 2000-2009	• Sample survey of US office-based physicians conducted by IMS Health (approximately 1800 physicians) • Representing 340,820 patient encounters	• Hormone therapy use declined each year since 2002 • Hormone therapy decreased from 16.3 million in 2001 to 6.1 million in 2009
Jewett 2014[8]	Integrated data from NHANES, 1999-2010, and National Prescription Audit, 1970-2003 (CEE plus MPA only)	• Prevalence of CEE plus MPA use (year by year) • Cumulative sample of 8960	• Prevalence peaked at 13.5% in 1999, decreased dramatically in early 2000s • Prevalence was only 2.7% in 2010
Sprague 2012[34]	Cross-sectional data from NHANES, 1999-2010	• Prevalence of hormone therapy use (year to year) • Sample of 10,107	• A sharp decrease in all formulations occurred in 2003-2004 • Prevalence was 22.4% in 1999-2000, decreased to 4.7% in 2010
Crawford 2018[36]	Women's Health Across the Nation Survey data, 1996-2013	• MHT limitation and continuation • Sample of 3018	• MHT initiation changed from 8.6% before WHI to 2.8% after WHI in 2013 ($P < .0001$)
ClinCalc.com[32]	MEPS-HS, a nationally representative longitudinal survey, 2006-2016	• Outpatient prescription drugs, total number of prescriptions of CEEs, conjugated	• Decreased from 2006 to 2016 • Decreased from 13 million in 2016 to 4 million in 2016

Abbreviations: CEE, conjugated equine estrogen; MEPS-HS, Medical Expenditure Panel Survey–Household Survey; MHT, menopausal hormone therapy; MPA, medroxyprogesterone acetate; NHANES, National Health and Nutrition Examination Survey; WHI, Women's Health Initiative.

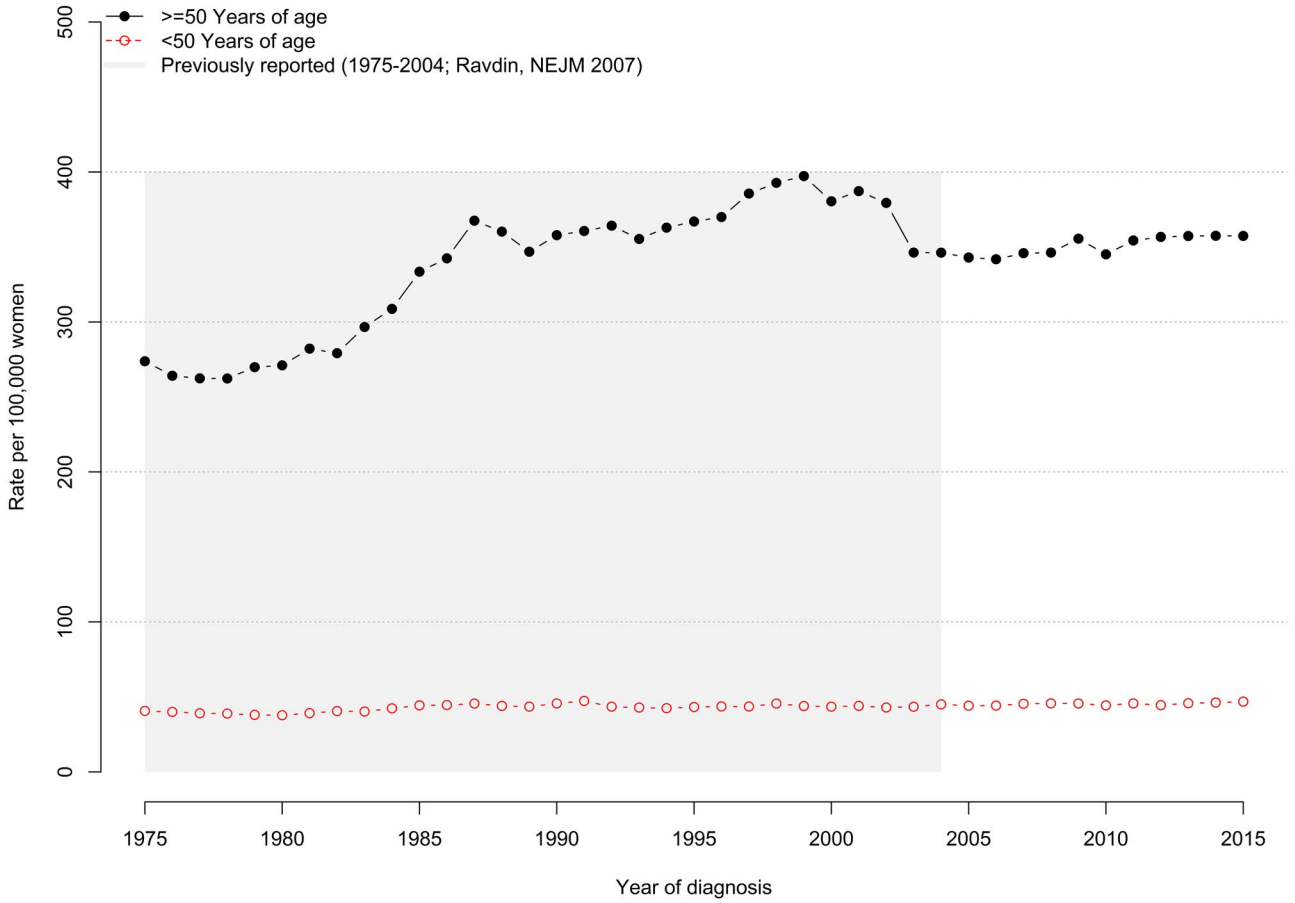

Figure 1. Annual breast cancer incidence (1975-2015) for women 50 years old or older and women younger than 50 years. The data are from 9 of the National Cancer Institute's SEER registries. The SEER sites include San Francisco, Connecticut, Detroit (metropolitan area), Hawaii, Iowa, New Mexico, Seattle–Puget Sound, Utah, and Atlanta (metropolitan area). Annual incidence rates were age-adjusted to the US standard population in the year 2000 (19 age groups; Census P25-1130 series) and were adjusted for reporting delays. SEER indicates Surveillance, Epidemiology, and End Results.

cancer cases in US women in 2005,[41] 212,920 cases in 2006,[42] 231,840 cases in 2015,[43] and 266,120 cases in 2018.[44] However, these numbers resulted from increases in the number and age of US postmenopausal women.

COMMENTARY OBJECTIVES

In this commentary, we specifically examine the potential role of changes in menopausal hormone therapy with respect to trends in breast cancer incidence over time. The disparate results for breast cancer incidence in the WHI hormone therapy trials evaluating CEE plus MPA and CEE alone are summarized, the sustained nationwide reduction in hormone therapy use is described, and a biological rationale for mediating a sustained reduction in breast cancer incidence years after the discontinuation of CEE plus MPA in white women is offered along with a rationale for the different trend in breast cancer incidence seen in black women. Although we recognize that a complex series of factors influences breast cancer incidence, we present evidence showing that the sustained reduction in hormone therapy use could largely be responsible for the sustained reduction in breast cancer incidence seen in white women and that differences in hormone therapy use among black women could make some contribution to breast cancer incidence over the same time period.

CURRENT FINDINGS

Based on findings from SEER 9, annual age-adjusted breast cancer incidence rates over a 40-year period for US women by age group are depicted in Figure 1.[45] The figure updates the findings through 2004 presented by Ravdin et al[1] (gray-shaded area of Fig. 1). The sharp

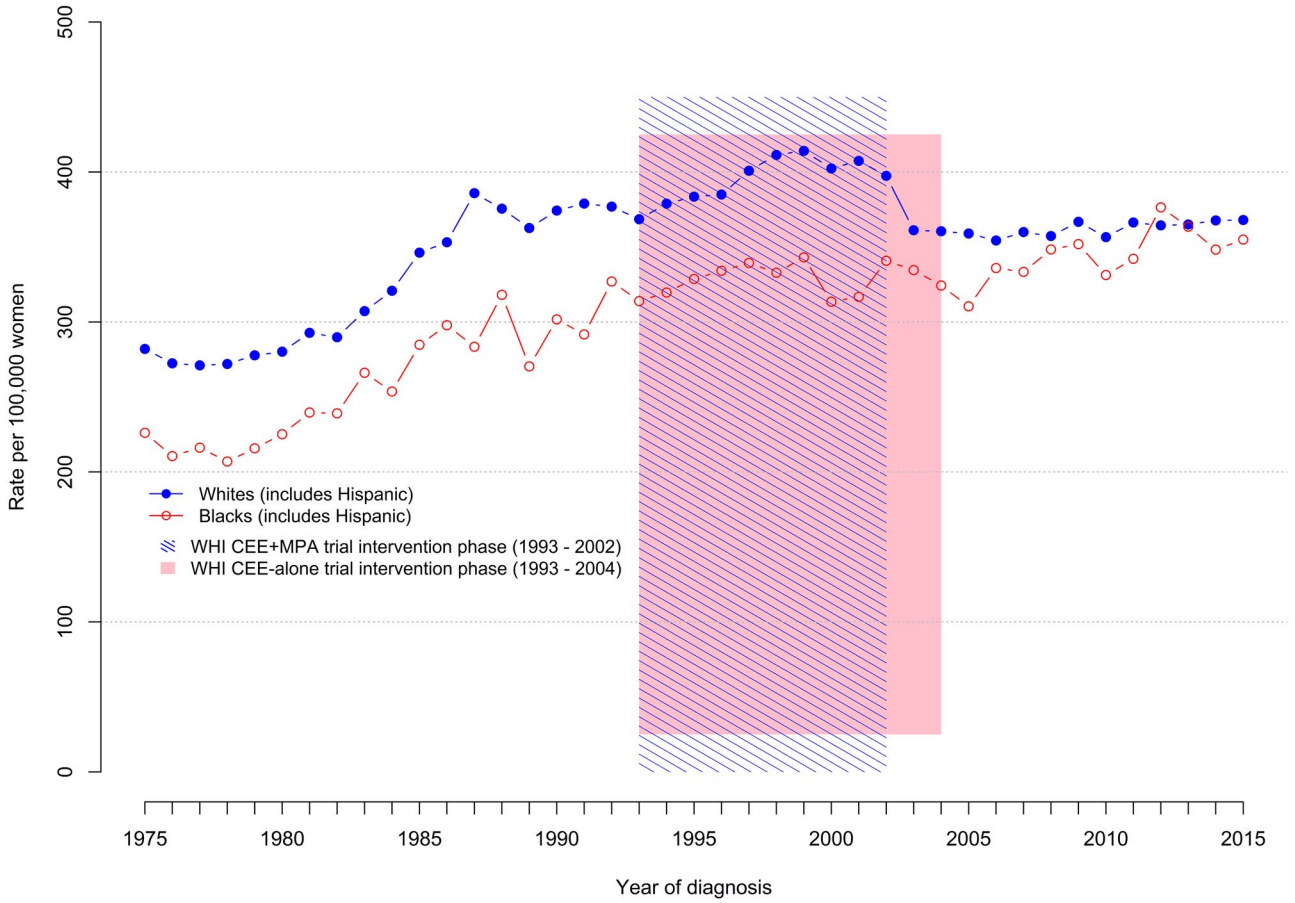

Figure 2. Annual breast cancer incidence (1975-2015) for white women and black women 50 years old or older. The data are from 9 of the National Cancer Institute's SEER registries. The SEER sites include San Francisco, Connecticut, Detroit (metropolitan area), Hawaii, Iowa, New Mexico, Seattle–Puget Sound, Utah, and Atlanta (metropolitan area). Annual incidence rates were age-adjusted to the US standard population in the year 2000 (19 age groups; Census P25-1130 series) and were adjusted for reporting delays. The blue shading depicts the 5.6-year (median) duration of intervention in the Women's Health Initiative randomized trial evaluating CEE and MPA. The pink shading depicts the 7.2-year (median) duration of intervention in the Women's Health Initiative randomized trial evaluating CEE alone. CEE indicates conjugated equine estrogen; MPA, medroxyprogesterone acetate; SEER, Surveillance, Epidemiology, and End Results.

decline in breast cancer incidence rates for women 50 years old or older seen in 2003 and 2004 has continued with only a modest increase seen over the ensuing decade, with the plateau of breast cancer incidence similar to rates last seen in the early 1990s. In contrast, the incidence rates for women younger than 50 years show no perceptible temporal trend.

Annual age-adjusted breast cancer incidence rates over a 40-year period for white and black women 50 years old or older are depicted in Figure 2. Here, the blue rectangle spans the 5.6 years of the WHI CEE plus MPA trial intervention period, whereas the pink rectangle spans the 7.2 years of the longer WHI CEE-alone trial intervention period. The sharp drop in breast cancer in white women followed the sudden reduction in the use of estrogen plus progestin after the publication of findings at the end of the CEE plus MPA intervention. In consideration of the sustained lower breast cancer incidence, by one estimate, in comparison with 2002, there have been 126,000 fewer breast cancer cases through 2012 in the United States that otherwise would have occurred had the WHI hormone therapy trials not been conducted.[46] With breast cancer incidence rates through 2015 continuing to be substantially lower than those seen in 2002, likely upwards of 200,000 fewer breast cancer cases have been diagnosed through that date. In consideration of these findings, decision model analyses suggest that the WHI CEE plus MPA trial made high-value use of public funds with a substantial return on investment.[47]

In contrast to findings in white women, an initial decrease in breast cancer incidence in 2003-2004 among black women and a corresponding decrease after the CEE-alone trial were not sustained. Instead, increases in breast cancer incidence subsequently developed (Fig. 2). As a result, breast cancer incidence in black women is now closely comparable to that in white women.[37,39] This relative increase in breast cancer incidence, together with the increased proportion of poor-prognosis breast cancers in black women,[47,48] exacerbates the disparity regarding breast cancer adverse outcomes in black women. The lengthier period of declining incidence observed among blacks (2003-2005; Fig. 2) coincides with a delayed decline in hormone use.[34]

FACTORS MEDIATING THE TREND IN BREAST CANCER INCIDENCE FOR WHITE WOMEN

From 2003-2004 through at least 2016, in US women, the use of estrogen plus progestin has remained at a low level,[32] and the mammogram screening frequency has not substantially changed.[49] Although obesity has continued to increase in white women, the frequency of women with obesity was already high, and the percentage of obese white women has become only modestly higher in the most recent decade.[50] Consequently, changes in these factors do not provide an explanation for the sustained lower breast cancer incidence seen. Although additional factors may be involved, the sustained reduction in hormone therapy use, which began in 2003-2004,[29] can provide a first-order explanation for this finding.

In US white women, the rapid decrease in breast cancers, in parallel with the reduction in the use of estrogen plus progestin, has been attributed to the sudden change in the hormonal environment as a therapeutic intervention for subclinical breast cancers.[1,18] This hypothesis has support from the clinic. In anecdotal reports, breast cancer regressions after the discontinuation of hormonal therapy have been described,[51] with a rapid reduction in breast cancer proliferation seen after the cessation of hormone therapy.[52] In the randomized, placebo-controlled Breast Cancer Prevention Trial, reduced breast cancers were seen in the tamoxifen group within months of study initiation,[53] whereas oophorectomy, with a sudden reduction in estrogen levels, is an established breast cancer therapy.[54] The decrease in breast cancer incidence in 2003-2004 was seen predominantly in white women because estrogen plus progestin was commonly used by white women at that time.

With respect to potential mediating mechanisms of the influence of estrogen plus progestin on breast cancer, CEE plus MPA rapidly and substantially increases breast mammographic density.[55] In an ancillary nested case-control study within the WHI randomized trial, a 1-year change in mammographic density after CEE plus MPA predicted all the subsequent increase in breast cancer incidence.[56]

To understand the sustained, long-term lower breast cancer incidence in white women in the last decade following the decrease in hormone therapy use, the sustained increase in year-to-year breast cancer incidence seen after the stopping of combined hormone therapy use should be considered.[13] In preclinical models, progestins have been demonstrated to promote mammary tumors mediated through mitogenic signals stimulating mammary epithelium.[57] In the same setting, estrogen plus progestin, but not estrogen alone, increases the number of mammary stem and progenitor cells.[58] Thus, the persistent increase in breast cancer risk following discontinuation of estrogen plus progestin use could result from progestin-mediated clonal expansion of breast stem cells resulting in a long-term increase in breast cancer risk.[58] The substantial and sustained decrease in estrogen plus progestin use beginning in 2003-2004 then could have resulted in the removal from the population of a large number of white women who would otherwise have experienced a long-term increase in breast cancer risk.

FACTORS MEDIATING THE TREND IN BREAST CANCER INCIDENCE FOR BLACK WOMEN

Several factors contributed to the discordant findings in black women, in comparison with white women, regarding breast cancer incidence in the 2005-2015 decade. During this period, annual mammography screening was comparable to that seen in white women,[59] and the rate of obesity showed a substantial increase in black women as it rose from 39% in 1999-2002 to 58% in 2009-2012[50,60]; this was similar to the proportional increase in obesity seen in white women.[60] However, because the proportion of women with severe obesity, a factor associated with higher breast cancer risk,[61] has been greater in black women in comparison with white women,[62] this difference could have made some contribution to the increase in breast cancer incidence in black women over the past decade.

Changes in hormone therapy use may also affect differences in breast cancer incidence in black and white women. Although hormone therapy use decreased in both white and black women,[33-34,37] the prevalence of

estrogen plus progestin use before 2002 in blacks was only a fraction of that reported in whites.[33-34,37,63] Also, decreases in black women may have been delayed.[34] In 2001, the percentage of adult women with at least 1 hormone therapy prescription was 5.4% for white women and 0.4% for black women.[33] Therefore, the reduction in 2008 to 0.1% use in black women[34,37] would have comparatively less influence on breast cancer incidence, and black women would not have experienced a sustained reduction in breast cancer incidence similar to that seen in white women. In addition, although the discontinuation of hormone therapy was sudden in white women, the discontinuation of hormone therapy in black women took place more slowly over several years.[34] Consequently, reductions in breast cancer incidence related to discontinuing hormone therapy in black women would be parsed over several years. Finally, hysterectomy is more common in black women,[64,65] as is the use of estrogen alone. For example, DeSantis et al[37] reported relatively similar use of estrogen alone among black women 50 years old or older with hysterectomy in 2000 in comparison with whites (11.5% vs 18.6%), whereas the prevalence of estrogen plus progestin between black and white women without hysterectomy was more discordant (4.2% vs 13.8%), with less use of estrogen plus progesstin among black women. Because CEE alone in the WHI clinical trial was associated with a reduction in breast cancer incidence, especially in black women with more African ancestry,[25,26] and all categories of menopausal hormone therapy use were reduced after the WHI reports,[8,29] a larger fraction of black women may also have lost a protective benefit from the use of estrogen alone with respect to breast cancer risk.

COMMENTARY LIMITATIONS AND FUTURE DIRECTIONS

The major focus of the current commentary is the effects of the WHI hormone therapy trial reports on secular hormone therapy use in postmenopausal women and resulting time trend changes in total invasive breast cancer incidence. As a result, our commentary does not address the issue of time trends in breast cancer subtypes, perhaps most importantly estrogen receptor (ER)–negative breast cancers. We briefly outline current findings in this area and identify areas needing ongoing investigation. According to SEER data findings, divergent ER-specific breast cancer time trends have been seen with a steady decrease of nearly 2% per year in ER-negative incidence rates since 1992,[66] with trends not substantially influenced by the reduction in hormone therapy use.[66,67] Although it is known that risk factor associations differ by ER subtype,[68] the basis for the ongoing reduction in ER-negative cancer has not been established. Because poor-prognosis, triple-negative (ER-negative, PR-negative, HER2-negative) breast cancers are more commonly diagnosed in black women,[47,48] time trends in breast cancer subtypes have implications for potential changes in the known black/white disparity regarding breast cancer outcomes. Although most recent findings have identified a relatively stable breast cancer risk in white women with increasing breast cancer risk in black women, modeling that incorporates Hispanic and non-Hispanic status projects breast cancer rates slowly increasing for non-Hispanic white women and slowly decreasing for non-Hispanic black women.[69] Ongoing vigilance is needed to further define these potentially important relationships.

In conclusion, changes in hormone therapy use in postmenopausal women provide a plausible explanation for a substantial component of the sustained lower breast cancer incidence seen in white women since 2003 and contribute to the discordant findings among black women, for whom, in contrast, increases in breast cancer incidence rates were seen over the 2005-2015 decade.

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