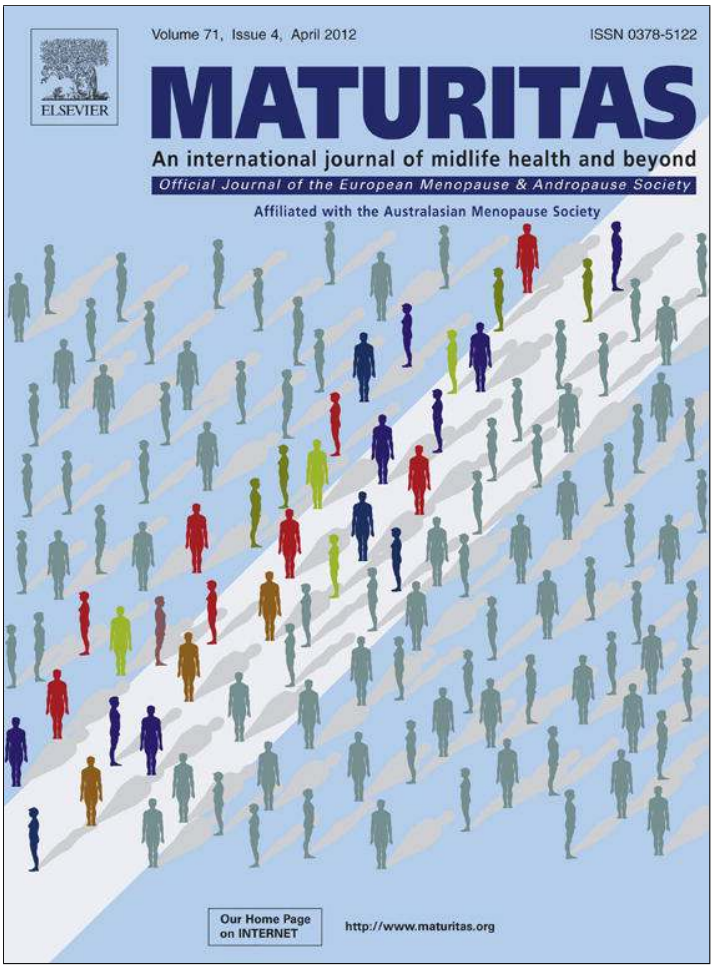

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Stopping menopausal hormone therapy: If breast cancer really decreased, why did colorectal cancer not increase?

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ABSTRACT

Objective: The Women's Health Initiative (WHI) study of postmenopausal hormone therapy (HT) found that estrogen plus progestogen therapy (EPT) decreased colorectal cancer risk. Thus, the decline in EPT use from 2002 to 2003 should have precipitated an increase in the incidence of colorectal cancer. We tested this prediction using the SEER 9 epidemiologic database.
Methods: We analyzed WHI data concerning the effects of EPT and estrogen therapy (ET) on colorectal cancer risks. We also examined HT prescription sales data, as well as SEER 9 colorectal cancer incidences from 2001 to 2004.
Results: In the WHI study, the incidence of colorectal cancer was comparable in EPT placebo-users, ET users, and ET placebo-users, but significantly lower in EPT users. Assuming that 30% of eligible women used HT in 2001, the decline in EPT sales from 2002 to 2003 of 63% should have increased the incidence of colorectal cancer by 2.8% in the overall population at risk. However, the SEER 9 colorectal cancer incidence *fell* by 5.9% in this population, which is comparable to the 6.7% decrease observed for invasive breast cancer from 2002 to 2003.
Conclusions: Declining EPT use from 2002 to 2003 should have precipitated an increase in the incidence of colorectal cancer, but the opposite trend was seen in the SEER 9 database during this time. The incidences of invasive breast cancer and colorectal cancer both declined by a similar amount from 2002 to 2003, despite the results of the WHI study predicting opposing trends for the two different types of cancer. Thus, the SEER 9 findings are fundamentally incompatible with expectations from the WHI findings. This implies that reductions in HT use from 2002 to 2003 cannot account for the contemporaneous changes in invasive breast cancer and colorectal cancer incidences. Alternative explanations must be found.

1. Introduction

The Women's Health Initiative (WHI) was a study of postmenopausal women aged 50–79 years in the United States. It included two interventional hormone therapy (HT[1]) trials that were prospective, randomized, double-blind, and placebo-controlled. One trial investigated 16,608 non-hysterectomized women who used combined estrogen plus progestogen therapy (EPT) from 1997 to 2002 [1]. The incidence of invasive breast cancer among these women who used EPT was 24% greater than among placebo users (HR[2] 1.24; 95% CI 1.01–1.54) [2], representing

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[1] In this article, the generic term "hormone therapy" (HT) refers to all forms of postmenopausal estrogen therapy, including those with the addition of a progestogen (estrogen plus progestogen therapy, or EPT, typically used only in non-hysterectomized women) and those without a progestogen (estrogen therapy, or ET, typically used in hysterectomized women).

[2] The increases and decreases in risk that we report here represent percent deviations from a hazard ratio (HR) of 1.0, which denotes an equivalent risk. A hazard ratio represents a risk ratio for an event occurring over a prescribed time frame. In a HR, as in a relative risk (RR), the risk of an event occurring in one group (in this case, the "hormone exposed" group) is compared to the risk of the same event occurring in another group (in this case, the "hormone unexposed" group) in a ratio of the type:

$$\text{HR (or RR)} = \frac{P_1}{P_0}$$

where P_1 is the probability of the event occurring to the members in the exposed group, and P_0 is the probability of the event occurring to the members in the unexposed group. For the results of the WHI, the HR can be used to estimate the RR, because the relative risks appear constant over the study interval that was

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approximately 8 additional cases per 10,000 women-years of EPT exposure [1]. The second trial investigated 10,739 hysterectomized women who used estrogen therapy (ET) without the concomitant use of a progestogen from 1993 to 2004 [3]. For these women, the overall incidence of invasive breast cancer was decreased by 20% compared to placebo (HR 0.80; 95% CI 0.62–1.04), and by 33% in the subgroup of women who were adherent to 80% or more of their medication (HR 0.67; 95% CI 0.47–0.97) [4]. For the women who were randomized to ET and then followed for a mean of 10.7 years after discontinuation, the breast cancer incidence remained 23% lower compared to those randomized to placebo (HR 0.77; 95% CI 0.62–0.95), indicating a persistent benefit with regard to breast cancer risk [5].

The initial WHI breast cancer findings from the EPT trial were highly publicized following their publication in July 2002 [6]. Their announcement precipitated a steep decline in the sales of the two most commonly prescribed forms of menopausal HT in the United States, namely Conjugated Equine Estrogens (CEE; an ET formulation marketed under the trade name Premarin®) and CEE + Medroxyprogesterone Acetate (an EPT formulation marketed under the trade name Prempro®) [7]. These are the same two HT products that were investigated in the WHI interventional hormone trials and they comprised the bulk of prescriptions filled for all forms of ET and EPT in the United States from 2001 to 2004 [7]. During this same period, the National Cancer Institute's Surveillance Epidemiology and End Results (SEER 9) database recorded a decrease in the incidence of breast cancer in the United States [8]. The annual age-adjusted rate declined by 8.6% from 2001 to 2004, with the largest drop (6.7%) occurring from 2002 to 2003 [9]. This decrease was evident primarily in women 50 years of age and older. The coincidental timing of the decrease in HT sales and the decrease in breast cancer incidence led some researchers to postulate a causal link between the two events [8,9].

If cancer rates are responsive at least partly to HT use, then all cancers that occur more often in HT users should have decreased in frequency after HT sales fell in 2002–2003, while all cancers for which HT use is protective should have increased. To test this hypothesis, we examined colorectal cancer, which was studied as a pre-specified endpoint in both of the WHI interventional HT trials [1,3]. As Fig. 1 illustrates, the WHI findings for colorectal cancer are opposite to those for invasive breast cancer: compared to placebo, EPT increased the incidence of invasive breast cancer by 24%, but decreased the incidence of colorectal cancer by 37%. This latter finding represents an absolute decrease in colorectal cancer risk of approximately 6 cases per 10,000 women-years of EPT exposure [1]. A subsequent re-calculation of the incidence of colorectal cancer based on the final adjudicated data after a mean of 5.6 years of use showed a statistically significantly decrease of 44% for EPT users as compared to those women randomized to placebo (HR 0.56; 95% CI 0.38–0.81) [10]. A qualitative difference between breast and colorectal cancer is also evident in the WHI findings for ET users, who had a 20% reduced incidence of invasive breast cancer compared to those women taking placebo, but an 8% increased incidence of colorectal cancer (neither of these point estimates being a statistically significant difference for the intent-to-treat population) [3].

As these findings illustrate, the WHI interventional hormone trials described opposing changes in the incidence of invasive breast cancer and colorectal cancer resulting from exposure to menopausal HT, most dramatically in the case of EPT [1–5,10]. In this study, we sought to determine whether similar opposing trends were found in the observational data reported by the SEER 9 epidemiologic database over the time when HT sales declined precipitously [11]. To accomplish this, we used the findings of the WHI interventional hormone trials to model the effects of the changes in HT use on invasive breast cancer and colorectal cancer incidences in the relevant overall population of the United States. The cancer incidences predicted by this model were compared to the actual incidences reported by the SEER 9 database. Our aim was to determine if changes in HT use could account for the cancer incidence trends that were evident in the SEER 9 database between July 2002 (when the first WHI results were published) and 2004 [12].

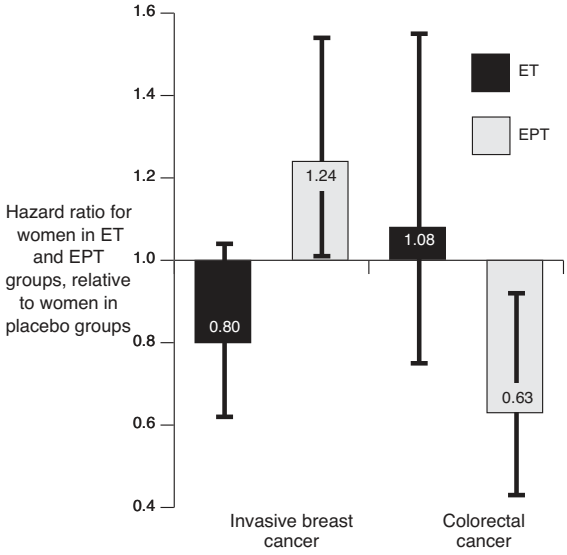

Fig. 1. Hazard ratios and 95% CIs for invasive breast cancer and colorectal cancer among women in the ET (black) and EPT (grey) user groups of the WHI interventional hormone trials, relative to women in the corresponding WHI placebo groups.

2. Materials and methods

2.1. Estimation of cancer risks from the WHI studies

We analyzed previously published WHI data concerning the effects of postmenopausal EPT and ET on the incidence of colorectal cancer [2,4]. Life table analyses incorporating the Wilcoxon Gehan test were used to compare the incidences of colorectal cancer among EPT and ET user and placebo groups. Groups that did not differ significantly were combined; the hazard ratio for cancer in the combined group was then estimated using a Cox proportional hazards regression.

2.2. Estimation of EPT and ET usage

Based on previously published estimates, we assumed that 30% of eligible postmenopausal women used HT products in 2001 [13]. We also assumed that the ratio of postmenopausal HT users to prescription units sold is the same for ET as for EPT menopausal therapies. These assumptions allowed us to use prescription drug data for EPT and ET sales in the United States [7] to determine the percentage of postmenopausal women who used ET, the percentage who used EPT, and the percentage who did not use any form of HT in 2001. The percentages for 2002–2004 were estimated by assuming that each 1% drop in ET or EPT prescription unit sales reflected a corresponding 1% decrease in the absolute percentage of postmenopausal women using that product (and, thus, a

investigated (i.e., the risk functions are linear over time). Because of this linearity, the RR can be considered constant and equal to the HR over any time span up to the duration of the WHI studies. In addition, since the baseline probabilities of the events of interest (breast cancer and colorectal cancer) are much less than 10% (on the order of 1-in-1000), the HR and RR are also approximated by the associated odds ratio (OR) for the occurrence of the events [19–21].

Table 1
Annualized risk of colorectal cancer in the four study groups of the WHI interventional hormone studies.

Group	Annualized risk of colorectal cancer	p-value for difference
EPT placebo	0.17%	0.96
ET placebo	0.15%	
ET users	0.13%	
Above three groups combined	0.15%	0.01
EPT users	0.10%	

EPT = estrogen + progestogen (Prempro®) therapy; ET = estrogen (Premarin®) therapy.

commensurate increase in the percentage of postmenopausal women who did not use any HT products).

2.3. Prediction of cancer rates in the United States

We assumed, as others have done [8,9], that when women stop using an HT product, their risk of cancer shifts without delay from the risk associated with the use of that product to the risk associated with the non-use of that product. We then predicted the overall incidence of colorectal cancer in the United States in the population at risk for each year by weighting the cancer risks associated with ET use, with EPT use, and with the non-use of HT by the corresponding percentage of postmenopausal women in each of the three HT use categories. Finally, we compared this overall rate to the incidence reported in the publicly available SEER 9 database for women aged 50 years and older [11].

3. Results

In re-analyzing the findings of the WHI interventional hormone studies, we found that the annualized risk of colorectal cancer did not differ significantly between the EPT placebo group, the ET placebo group, and ET users ($p = 0.96$); thus, we were able to combine the data from these three groups (Table 1). This combined group of postmenopausal women who did not use EPT had an annualized risk of colorectal cancer that was significantly higher ($p = 0.01$) than the annualized risk for EPT users (HR 1.60; 95% CI 1.15–2.23).

Sales of both ET and EPT products began slowing during the second half of 2002. They declined precipitously in 2003 and remained low in 2004 (Fig. 2) [7]. The prescription data indicate that EPT product use fell much more than ET product use; the ratio of ET sales to EPT sales was 2.32 to 1 in 2001, but increased to 4.78 to 1 in 2004 (Fig. 3). In 2001, 69.8% of all HT prescription unit sales were for ET products, while the remaining 30.2% were for EPT products. Since only 30% of the eligible population of postmenopausal women used HT products in 2001 [13], this meant that 69.8% × 30% = 20.9% of postmenopausal women used ET products in that year. Similarly, 30.2% × 30% = 9.1% of postmenopausal women used EPT products in 2001, while the remaining 70% of postmenopausal women did not use any HT products. The percentages and ET to EPT sales ratios for all years from 2001 to 2004 are shown in Fig. 3.

The predicted annualized incidence of colorectal cancer for postmenopausal women in the United States was 0.145% in 2001. This was determined from a weighted combination of the risks associated with the three categories of HT product use: a 0.15% annualized risk that applied to the 20.9% of postmenopausal women who used ET products in 2001; a 0.10% annualized risk that applied to the 9.1% of postmenopausal women who used EPT products in 2001; and a 0.15% annualized risk that applied to the 70% of postmenopausal women who used no HT products in 2001. As Fig. 4 illustrates, the incidence of colorectal cancer was predicted from the WHI study results to rise annually until 2004. The greatest increase (2.8%) was expected between 2002 and 2003, when the majority of women discontinued using their menopausal EPT products, thereby foregoing the protective prophylactic effect that EPT provided for colorectal cancer.

The actual incidence of colorectal cancer among women age 50 and older was markedly different (Fig. 4). The SEER 9 database recorded a 5.9% decline in colorectal cancer incidence among these women from 2002 to 2003. But, the WHI study findings predicted fewer cases of colorectal cancer than were actually reported in 2001 and 2002 (dark grey region in left of Fig. 4), and more cases of colorectal cancer than were actually reported in 2003 and 2004 (light grey region in right of Fig. 4). Thus, the incidence of colorectal cancer predicted by the WHI study findings is at odds with the actual incidence reported by the SEER 9 database.

4. Discussion

Our finding of a discrepancy in the incidences of colorectal cancer between those predicted from the WHI study findings and those reported in the SEER 9 database mirrors an earlier discrepancy we

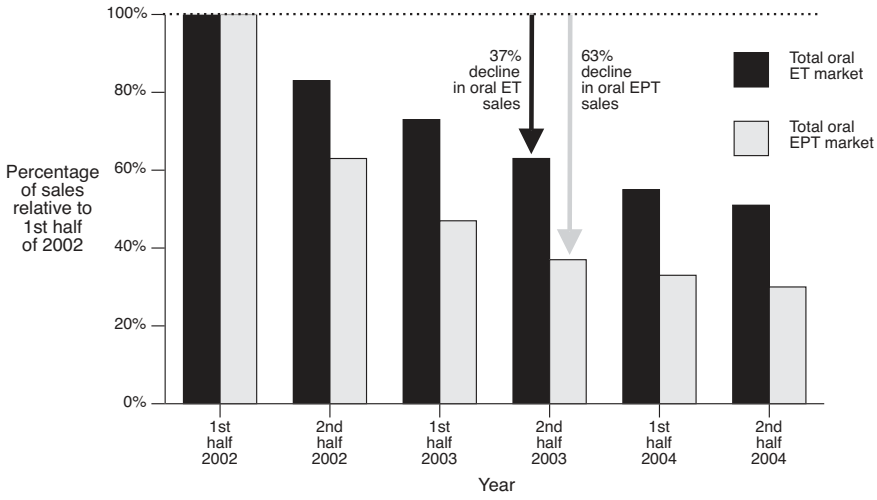

Fig. 2. Total oral ET and oral EPT markets (as reflected by total prescription unit sales) for 2002 through 2004, relative to sales during the first half of 2002. By the second half of 2002, sales of ET products were reduced by 37% (black arrow) and sales of EPT products were reduced by 63% (grey arrow) relative to sales in the first half of 2002 (dotted line). Oral ET and EPT products comprised the great majority of all HT sales from 2002 to 2004 [14].

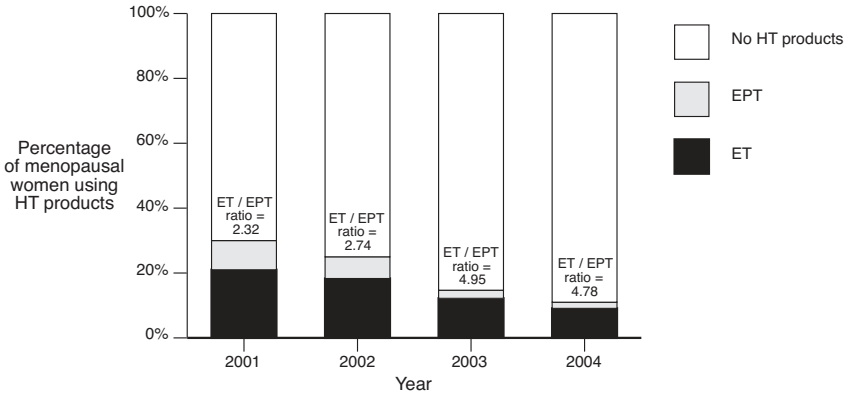

Fig. 3. Percentage of eligible women using ET products (black), EPT products (grey), and no HT products (white) by year, and the ratio of ET to EPT users. All data are as estimated from prescription unit sales data and assume a 30% HT utilization rate in 2001 [13].

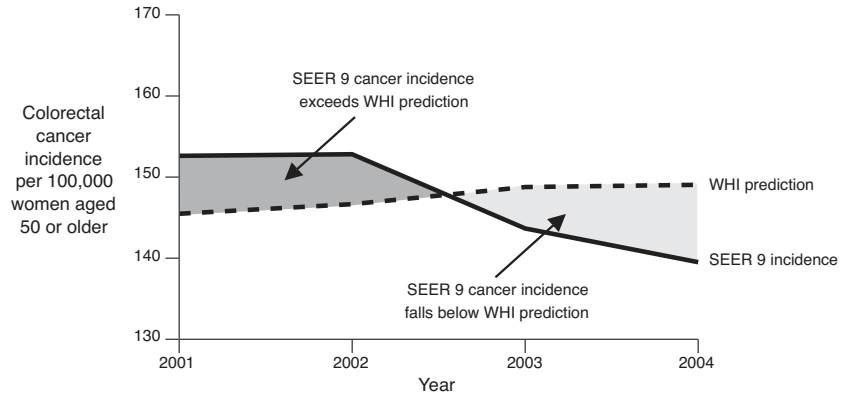

Fig. 4. Colorectal cancer incidence from 2001 to 2004 as predicted from the WHI interventional hormone trial findings (broken line), and the actual incidence as reported in the SEER 9 database for women aged 50 years and older in the general population (solid line).

reported for invasive breast cancer [14]. In that study, we found that the differential effects of EPT versus ET on the incidence of breast cancer from the WHI interventional hormone studies – assuming that there is an instantaneous effect – predicted essentially no change in the incidence of invasive breast cancer from 2001 to 2004. However, the SEER 9 database showed a dramatic reduction of 6.7% in breast cancer incidence from 2002 to 2003 (Fig. 5) [9,14].

Based on the current study's findings, we conclude that the incidences of invasive breast cancer and colorectal cancer among postmenopausal women who participated in the WHI's prospective, randomized, and controlled interventional hormone trials are fundamentally incompatible with the trends that have been reported by the National Cancer Institute's SEER 9 observational database from 2002 to 2003. The WHI studies indicate that estrogen plus progestogen exposure increases the risk of invasive breast cancer and decreases the risk of colorectal cancer [1–5]. If these findings are correct and if the effects on cancer incidence occur contemporaneously with the change in HT usage (as has been purported previously by other authors, including Ravdin et al. [8,9]), then the 63% decline in EPT product use among menopausal women in the United States from 2002 to 2003 should have decreased the

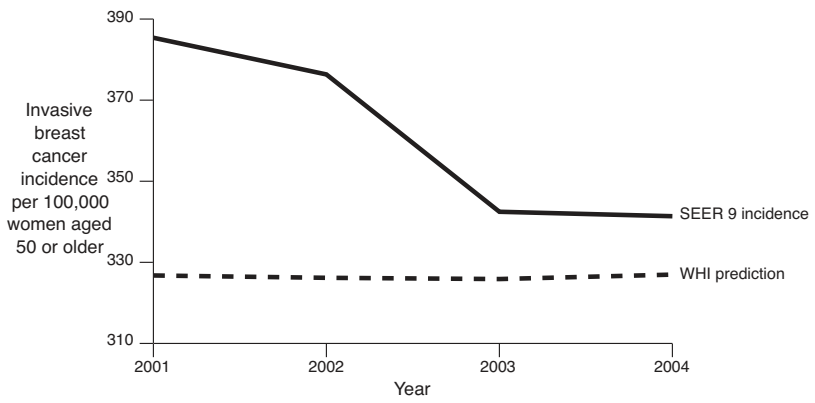

Fig. 5. Invasive breast cancer incidence from 2001 to 2004 as predicted from the WHI interventional hormone trial findings (broken line), and the actual incidence as reported in the SEER 9 database for women aged 50 years and older in the general population (solid line).

incidence of invasive breast cancer and increased the incidence of colorectal cancer. By contrast, the WHI studies indicate that postmenopausal exposure to estrogen in the absence of progestogen decreases the risk of invasive breast cancer (by 33% in those women who are ≥80% adherent to their therapy) and has no effect on the risk of colorectal cancer [1–5,10]. These findings imply that the 37% decline in ET product use from the first half of 2002 to the second half of 2003 should have increased the incidence of invasive breast cancer and had no impact on the incidence of colorectal cancer. When the opposing effects of EPT and ET use are considered collectively and in light of their different sales patterns, the overall prediction is for the incidence of invasive breast cancer in postmenopausal women to have remained constant from 2002 to 2003 [14], while the incidence of colorectal cancer should have increased during the same period. However, this is not what was observed in the population-based SEER 9 database, where the incidences of *both* cancers decreased in a nearly identical manner from 2002 to 2003: The incidence of invasive breast cancer decreased by 6.7% from 2002 to 2003, while the incidence of colorectal cancer decreased by 5.9% during that same period.

These results suggest that the SEER 9 observational findings are fundamentally incompatible with the results of the WHI interventional hormone studies – at least over the period of interest – and strongly imply that changes in menopausal HT usage patterns were not primarily responsible for the changes in the SEER 9 cancer incidences that occurred from 2002 to 2003.

We do not find this conclusion surprising. The very rapid decrease in the incidences of invasive breast cancer and colorectal cancer in the population monitored by the SEER 9 database began only 6 months after the initial publication of the WHI results. Even if one were to completely ignore the WHI findings and imagine that EPT use and ET use both increase the risk of breast and colorectal cancer, the close temporal proximity of the decline in HT sales and the decline in the cancer incidences argues against a causal relationship between the two events [15]. The minimum progression time for an initial breast cancer cell to become a clinically detectable lesion of ∼1 cm is at least 5 years, with a comparably long delay for colorectal neoplasia to develop into an invasive colorectal cancer [16]. Thus, it is highly implausible to assume that exposure to any agent that incites or protects against these types of cancers would have a measurable effect on the incidences of the clinically detectable manifestations of these diseases before several years had elapsed.

In addition, there is evidence within the SEER 9 database itself that argues against attributing a change in cancer incidence to a change in HT usage: the incidences of several other cancers also decreased from 2002 to 2003 and by approximately the same magnitude as invasive breast cancer and colorectal cancer. Many of these other cancers (such as male breast cancer) have no purported relationship to the use of menopausal HT. This pattern suggests that there is some other factor underlying the change in SEER 9 cancer incidences that is independent of changes in menopausal HT use. For instance, between 2002 and 2003 there was a well-described overall "accounting change" relating to the coding and handling of data within the SEER 9 database itself (which was re-coded to ICD-O-2 and ICD-O-3 on January 27, 2003) [17]. Accounting changes such as these provide a much more plausible explanation for the global changes seen in the incidence rates for multiple types of cancers than changes in HT usage [17].

Based on the WHI's EPT interventional trial results, some previous authors have contended that at least some fraction of breast cancers are either (a) "caused" by menopausal EPT (de novo) or that (b) menopausal EPT "accelerates" the clinical recognition of pre-existing breast cancers. The latter effect may occur if EPT (but not ET) (i) precipitates the more rapid growth of breast cancers per se or if it (ii) enhances the ability of screening tests (such as mammography) to identify these lesions, thereby making them more readily detectable. However, the key findings of the WHI EPT trial cannot be ignored: that the incidence of colorectal cancer was found to decrease as a result of exposure to the same medication (EPT) within the very same study.

Although SEER data are collected for the entire U.S. population and not just for postmenopausal women who discontinued using HT, our analysis was performed by parsing out effects based on the fraction of the at-risk population (women 50 years of age and older) who used the two different types of HT (EPT vs. ET), both before and after the initial publication of the WHI results in 2002 (Fig. 3). This allowed us to control for the proportions of the overall population of women ≥50 years of age who used these different types of HT as a function of time. This approach had the effect of controlling for the confounding effects of the two different types of HT's on both invasive breast cancer and colorectal cancer. To the best of our knowledge, this approach has not been undertaken by the other authors who have previously contended that there is a connection between the decrease in the invasive breast cancer incidence within the SEER 9 database from 2002 to 2003 and the concurrent decrease in HT use by postmenopausal women in the United States.

Two additional issues about the current study should be noted. The first is that although breast cancer and colorectal cancer are both malignancies with substantial latency periods of at least several years prior to clinical detection, they are nevertheless different types of cancer. Thus, differential timing of the effects of postmenopausal HT on the two cancers may potentially provide some degree of explanation for the discrepant results that we have identified for the two cancers. Specifically, if we assume that EPT does not simply alter the ability to detect colorectal cancer (which is very unlikely, given that colonoscopy and surgery are the most common methods by which it is identified), it must reduce its de novo incidence. Given the long latency between the initiation of colorectal cancer and its clinical detection, if EPT exposure reduces its initiation, the increase in incidence after discontinuation of treatment should not likely be recognized for several years. This issue is analogous to the one previously outlined for breast cancer, which likewise suggests that any reduction in breast cancer incidence arising from EPT discontinuation should not likely be realized for many years.

Lastly, despite all of these considerations, the possibility must always be entertained that the incidence of colon cancer may have declined from 2002 to 2004 for reasons having nothing to do with postmenopausal HT (such as changes in population screening, compliance with colonoscopies, etc.). However, this would seem unlikely to occur in isolation, as it is entirely analogous to what might also have occurred with respect to breast cancer: namely that the incidence of invasive breast cancer might have actually decreased from 2002 to 2004 for reasons completely unrelated to anything that has been considered previously. Nevertheless, if this occurred, it could provide at least a partial explanation for the decline in colorectal cancer incidence that was noted in the SEER database during this period.

In summary, the findings of our current study show that changes in postmenopausal HT use from 2002 to 2003 cannot be invoked as the explanation for the changes in cancer incidences that occurred in the SEER 9 database during the same time period without precipitating an overt contradiction between the effects seen for colorectal cancer versus invasive breast cancer in the WHI studies. Thus, alternative explanations must be found for the widespread decline in cancer rates that have been seen in the SEER 9 database.

This conclusion should make all medical practitioners take pause: Potential cause-and-effect relationships based on weak and inconsistent associations between "hormone therapies" of various types and the incidence of different kinds of cancers in

postmenopausal women should never be regarded as conclusive [18]. More definitive research in the field of hormonal exposures in postmenopausal women – especially with regard to estrogens and progestogens – is necessary before any such claims, either of harm or of benefit, can be accepted as properly founded.

Contributors

Gerard Nahum conceptualized this study and assisted in analyzing the data as well as writing and editing the paper. Harold Stanislaw performed the data analyses and assisted in writing and editing the paper. James Simon assisted in writing and editing the paper.

Competing interests

Dr. Nahum is Vice President of Global Clinical Development for Primary Care and Women's Healthcare at Bayer HealthCare Pharmaceuticals in Montville, New Jersey, where he also served previously as the Senior Director of Medical Affairs for Women's Healthcare in the United States. Prior to that, he was a Medical Officer in the Office of New Drugs at the U.S. Food and Drug Administration in Rockville, Maryland and an Associate Professor of Obstetrics and Gynecology at the Duke University School of Medicine in Durham, North Carolina. Bayer HealthCare Pharmaceuticals (and its predecessor organization, Berlex Laboratories) manufactures and distributes hormonal products for the management of menopausal symptoms and menopause-associated conditions, including the treatment of moderate-to-severe vasomotor symptoms associated with the menopause, vulvar and vaginal atrophy associated with the menopause, and prevention of postmenopausal osteoporosis.

Dr. Stanislaw is Professor and prior Chairman in the Department of Psychology, California State University, Stanislaus and has nothing to disclose.

Dr. James A. Simon in the past 12 months has served as a consultant or on the advisory boards of: Abbott Laboratories (Abbott Park, IL), Agile Therapeutics, Inc. (Princeton, NJ), Amgen Inc. (Thousand Oaks, CA), Ascend Therapeutics (Herndon, VA), Azur Pharma, Inc. (Fitzwilliam Square, Dublin), BioSante (Lincolnshire, IL), Boehringer Ingelheim (Ingelheim, Germany), Depomed, Inc. (Menlo Park, CA), Fabre-Kramer (Houston, TX), Laboratoire HRA Pharma (Paris, France), Meditrina Pharmaceuticals (Ann Arbor, MI), Merck (Whitehouse Station, NJ), Merrion Pharmaceuticals (Wilmington, NC), NDA Partners LLC (Lakewood Ranch, FL), Novo Nordisk (Bagsvrerd, Denmark), Novogyne (East Hanover, NJ), Pfizer Inc. (New York, NY), Shionogi Inc. (Florham Park, NJ), Slate Pharmaceuticals Inc. (Durham, NC), Teva Pharmaceutical Industries Ltd. (Jerusalem, Israel), Trovis Pharmaceuticals, LLC (Newton, MA), Warner Chilcott (Rockaway, NJ), and Watson Pharmaceutical Inc. (Corona, CA). He has received grant/research support from BioSante (Lincolnshire, IL), Boehringer Ingelheim (Ingelheim, Germany), EndoCeutics Inc. (Quebec, Quebec), Novo Nordisk (Bagsvrerd, Denmark), Novogyne (East Hanover, NJ), Palatin Technologies (Cranbury, NJ), Teva Pharmaceutical Industries Ltd. (Jerusalem, Israel), Warner Chilcott (Rockaway, NJ), and Watson Pharmaceutical Inc. (Corona, CA) in the past 12 months. He has also served on the speakers bureaus of: Amgen Inc. (Thousand Oaks, CA), Ascend Therapeutics (Herndon, VA), Bayer (Leverkusen, Germany), Boehringer Ingelheim (Ingelheim, Germany), Merck (Whitehouse Station, NJ), Novartis (Basel, Switzerland), Novo Nordisk (Bagsvrerd, Denmark), Novogyne (East Hanover, NJ), Teva Pharmaceutical Industries Ltd. (Jerusalem, Israel), and Warner Chilcott (Rockaway, NJ) in the past 12 months.

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Ethical approval

This study did not involve human participants; the research consisted entirely of mathematical analyses of previously published, publicly available data. No ethical approval was required.

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