Colorectal Cancer in Relation to Postmenopausal Estrogen and Estrogen Plus Progestin in the Women’s Health Initiative Clinical Trial and Observational Study

Ross L. Prentice,1 Mary Pettinger,1 Shirley A.A. Beresford,2 Jean Wactawski-Wende,3 F. Allan Hubbell,4 Marcia L. Stefanick,5 and Rowan T. Chlebowski6

1Public Health Sciences Division, Fred Hutchinson Cancer Research Center and 2Department of Epidemiology, University of Washington, Seattle, Washington; 3Department of Social and Preventive Medicine, University at Buffalo, Buffalo, New York; 4Department of Medicine, University of California, Irvine, California; 5Stanford Prevention Research Center, Palo Alto, California; and 6Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, California

Abstract

Background: Colorectal cancer incidence was reduced among women assigned to active treatment in the Women’s Health Initiative (WHI) estrogen plus progestin-randomized trial, but the interpretation was obscured by an associated later stage of diagnosis. In contrast, the estrogen-alone trial showed no incidence reduction or differential stage at diagnosis. Here, data from the WHI observational study are considered, in conjunction with colorectal cancer mortality data from the hormone therapy trials, in an attempt to clarify postmenopausal hormone therapy effects.

Participants and Methods: Postmenopausal women ages 50 to 79 years at WHI enrollment. Estrogen-alone analyses include 21,552 and 10,739 women who were postmenopausal hormone therapy effects.

Results: Hazard ratios (95% confidence intervals) from the WHI observational study were 0.80 (0.53-1.20) for estrogen and 1.15 (0.74-1.79) for estrogen plus progestin, with, respectively, 168 and 175 women diagnosed with colorectal cancer. Delayed diagnosis with estrogen plus progestin is not evident in the observational study. No protective effect on colorectal cancer mortality in the estrogen plus progestin trial is seen over an 8-year intervention and follow-up period.

Conclusion: Hazard ratio patterns in the WHI clinical trial and observational study do not provide strong evidence of a clinically important colorectal cancer benefit with either estrogen-alone or estrogen plus progestin over 7 to 8 years of treatment and follow-up. (Cancer Epidemiol Biomarkers Prev 2009;18(5):1531–7)

Introduction

Colorectal cancer was included in a “global index” to summarize health benefits and risks in the Women’s Health Initiative (WHI) randomized controlled trials of daily 0.625 conjugated equine estrogens (CEE) versus placebo among 10,739 women who were post hysterectomy, and this same estrogen preparation plus daily 2.5 mg of medroxyprogesterone acetate (CEE/MPA) among 16,608 postmenopausal women with a uterus (1, 2). The CEE/MPA trial was stopped early in 2002 when it was judged that overall health risks exceeded benefits (3). The (invasive) colorectal hazard ratio (HR) for the active treatment over a 5.6-year average intervention period was 0.56 with a 95% confidence interval (CI) of 0.38 to 0.81 (4). However, the interpretation of this finding was substantially obscured by the fact that “colorectal cancers in women who took estrogen plus progestin were diagnosed at a more advanced stage than those in women who took placebo” (4). The CEE trial had health benefits and risks that were approximately balanced (5) but was also stopped early, in 2004, in part because of an elevation in stroke. The colorectal cancer HR over the 7.1-year average follow-up period in the CEE trial was 1.12 with 95% CI of 0.77 to 1.63, and there was no suggestion of an effect of CEE on diagnosis (6).

Observational studies have mostly reported an inverse association with colorectal cancer incidence for either estrogen or estrogen plus progestin (7-9), although some studies (10-12) have reported lower colorectal cancer incidence among users of estrogen plus progestin but not among estrogen-alone users.

The WHI observational study provides an opportunity to further explore the effects of these preparations on colorectal cancer, and to compare both incidence associations, and tumor characteristics between the WHI clinical trial and observational study, for CEE and CEE/MPA. The observational study is a prospective cohort study among 93,676 postmenopausal women in the 50 to 79 years age range, who were drawn from the same

Requests for reprints: Ross L. Prentice, Director, Public Health Sciences Division, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, P.O. Box 1924, Seattle, WA 98109-1024. Phone: 206-667-4264; Fax: 206-667-4142. E-mail: rprentic@fhcrc.org

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populations as were clinical trial women, with much commonality in protocol and procedures.

WHI investigators have compared cardiovascular disease (13, 14) and breast cancer (15, 16) effects between the clinical trial and observational study, for both CEE and CEE/MPA. Apparently discrepant findings for these outcomes could be explained mostly by taking suitable account of time from menopause to hormone therapy initiation, time since hormone therapy initiation, and applying standard confounding control procedures. Corresponding invasive colorectal cancer analyses are considered here. Additional analyses examine HRs for subsets of colorectal cancer defined by local versus regional/distant spread, primary tumor size, or the presence of positive lymph nodes. Colorectal cancer mortality data are also examined during the intervention period in the CEE trial, and during both the intervention period and post-intervention follow-up period in the CEE/MPA trial.

Materials and Methods

Study Cohorts. The design of the WHI clinical trial and observational study has been presented (17), and overall clinical trial findings have been recently summarized (18). All women were postmenopausal, in the age range 50 to 79 y, and without a medical condition likely to result in death within 3 y, at the time of enrollment. Women with a personal history of breast cancer were excluded from the hormone therapy trials. Characteristics of the observational study cohort have been described (19).

Observational study women were included in the CEE component of this analysis if they were posthysterectomy and either taking the same daily 0.625-mg CEE preparation as studied in the clinical trial or not using any hormone therapy at the time of enrollment. Women included were also required to have known values for a list of potential confounding factors. Women with a personal history of breast cancer at baseline, or without a mammogram in the 2-y period before enrollment, were also excluded to correspond with clinical trial exclusionary criteria, giving a subcohort of 21,552 observational study women including 10,582 baseline CEE users, and 10,970 nonusers. A total of 32,084 observational study women with uterus were included using these same criteria in the corresponding CEE/MPA component of this analysis, including 6,756 women who were using the same daily CEE/MPA combination as studied in the clinical trial, and 25,328 nonusers.

Information on lifetime hormone use was obtained at baseline from clinical trial and observational study women by trained interviewers, assisted by structured questionnaires and charts displaying colored photographs of various hormone preparations.

Follow-up. Clinical outcomes were reported semiannually in the clinical trial and annually in the observational study (20). Medical record documentations of initial self-reports were obtained and diagnoses were confirmed by physician adjudicators. All colorectal cancer cases were centrally reviewed and classified using Surveillance, Epidemiology, and End Results program guidelines (21). Information on adherence to study hormone pills was obtained semiannually in the clinical trial, and information on hormone therapy use was updated annually by questionnaire in the observational study.

Statistical Analysis. Statistical methods and variable definitions are similar to previous reports of this type (13-16), for other clinical outcomes. Briefly, follow-up in the hormone therapy trials was included through the end of the respective intervention periods, whereas observational study subcohorts were followed through December 15, 2004, for CEE analyses, and through February 28, 2003, for CEE/MPA analyses to give respective average follow-up periods of 7.1 and 5.5 y, similar to the clinical trial. Women in the hormone therapy trials were required to obtain mammograms annually, or study pills were withheld. Toward ensuring comparable exposure to the medical care system, follow-up times for women were censored at the first instance of being >2 y from most recent mammogram, in both the clinical trial and observational study.

HR estimation for colorectal cancer incidence was based on Cox regression (22), with time from WHI enrollment as the basic time variable. The baseline hazard rate was stratified on age at enrollment in 5-y intervals and on a personal history of colorectal cancer at enrollment (yes versus no) in both clinical trial and observational study analyses. Clinical trial analyses also stratify on WHI dietary modification trial randomization (intervention, control, or not randomized). Observational study analyses stratify also on prior postmenopausal hormone therapy (no versus hormone therapy before enrollment for nonusers at baseline, or before the beginning of the ongoing hormone therapy episode for baseline hormone therapy users, with a usage gap of 1 y or longer defining a new hormone therapy episode), and include baseline colorectal cancer risk factors, as listed below, in the HR regression model for confounding control (with separate regression coefficients for prior hormone therapy users and nonusers). Because of the random allocation, these factors were not included in the HR model in the clinical trial, but randomization into the calcium and vitamin D clinical trial component (active, versus placebo, or not randomized) was included as a time-dependent regression variable.

Hazard ratios among adherent women were estimated using these same modeling procedures, with follow-up times censored 6 mo after a change from baseline in hormone therapy status. For a nonuser, a status change involved the initiation of any hormone therapy. For a baseline user, a status change involved either hormone therapy discontinuation, or a change to another hormone therapy preparation.

Colorectal cancer mortality data and all-cause mortality data were also considered through the end of the active intervention periods for both clinical trials and for the CEE/MPA trial also through the end of a subsequent clinical trial follow-up period ending 3/31/05. These analyses also used Cox models, with baseline HRs stratified as in previous trial reports (3-6).

Nominal 95% CIs are presented for HRs, and all significance levels (P values) are two-sided.

Results

Table 1 shows age-adjusted colorectal cancer incidence rates in the clinical trial and observational study cohorts,
according to hormone therapy group, and prior use of hormone therapy for both CEE and CEE/MPA. Age-adjusted incidence rates do not vary strongly among the nonuser groups according to uterine status, or prior hormone therapy use but tend to be somewhat lower in the observational study than in the clinical trial. Table 2 shows invasive colorectal cancer HR estimates for CEE and CEE/MPA both from the clinical trial as previously reported, and from the observational study. The HR (95% CI) for CEE from the observational study is 0.80 (0.53-1.20) with 168 colorectal cancer cases, whereas that for CEE/MPA from the observational study is 1.15 (0.74-1.79) with 175 cases. Hence, observational study data provide little evidence overall for a colorectal cancer association with either CEE or CEE/MPA. Potential confounding factors in observational study analyses are listed in a Table 2 footnote.

Additional joint analyses of the clinical trial and observational study data were carried out to provide more detailed HR comparisons. Most hormone therapy users in the observational study were some years into their ongoing hormone therapy episode at WHI enrollment, and the observational study mostly contributes HR information well after therapy initiation. Hence, separate HRs were calculated for 0 to 2, 2 to 5, and ≥5 years from hormone therapy initiation. Table 3 shows results of these analyses, which also included product term between hormone therapy and cohort (clinical trial versus observational study) to quantitatively judge overall HR agreement between the two sources. Under this statistical model, the hormone therapy HRs in the observational study are restricted to differ from those in the clinical trial by a simple multiplicative factor, for which an estimate and 95% CI are shown in the final row of Table 3. This ratio of HR in the observational study to HR in the clinical trial would be close to unity if HRs from the 2 sources agree, but note that CEE/MPA HRs in the observational study are estimated to be 81% higher than in the clinical trial, whereas CEE HRs in the observational study are estimated to be 37% lower than in the clinical trial, although neither ratio is significantly different from one. The right side of Table 3 shows corresponding analyses among women who were adherent to their baseline hormone therapy group designation, by censoring the follow-up time 6 months after a change from baseline hormone therapy status. Among adherent women, HRs do not agree closely between the clinical trial and observational study for either hormone therapy preparation.

Additional analyses extended the Table 3 analyses by including an interaction term between hormone therapy and baseline age in the log-HR. For CEE, a modest increase in HR with age could be detected (P = 0.02) with the CEE HR increased by a factor of 1.19 (95% CI, 1.03-1.37) for each 5-year increment in age. This interaction was also significant (P = 0.02) among adherent women, with the CEE HR increased by 1.23 (95% CI, 1.03-1.47) for each 5-year age increment. The corresponding hormone therapy by age interaction was not significant for CEE/MPA but in the same direction with HR of 1.09 (95% CI, 0.84-1.42) without adherence restriction and with HR of 1.15 (95% CI, 0.85-1.55) among adherent women, for a 5-year age increment. We also examined the possibility of an interaction of hormone therapy HRs with time from menopause to first use of hormone therapy but found little evidence of such dependency for CEE (P = 0.15), or CEE/MPA (P = 0.87) without adherence restriction, or for CEE (P = 0.29) or CEE/MPA (P = 0.54) among menopausal hormone therapy and hysterectomy status.

| Table 1. Age-adjusted incidence rates of, and numbers of women developing, invasive colorectal cancer in the WHI hormone trials and in corresponding observational study subcohorts, according to prior use of postmenopausal hormone therapy and hysterectomy status |
|---|---|---|---|---|---|---|---|
| Without uterus at enrollment | Yes | Clinical trial | Placebo | CEE | Placebo | CEE |
| No. of women | 2659 | 2541 |
| Average age (y) | 63.4 | 63.6 |
| Incidence rate | 1.21 | 1.47 |
| No. of cases | 33 | 26 |
| | Yes | Clinical trial | Placebo | CEE | Placebo | CEE |
| No. of women | 2541 |
| Average age (y) | 63.6 |
| Incidence rate | 1.47 |
| No. of cases | 26 |
| With uterus at enrollment | Yes | Clinical trial | Placebo | CEE/MPA | Placebo | CEE/MPA |
| No. of women | 2082 | 2229 |
| Average age (y) | 63.4 | 63.0 |
| Incidence rate | 1.53 | 0.70 |
| No. of cases | 17 | 8 |
| | Yes | Clinical trial | Placebo | CEE/MPA | Placebo | CEE/MPA |
| No. of women | 2229 |
| Average age (y) | 63.0 |
| Incidence rate | 0.70 |
| No. of cases | 8 |

Abbreviation: HT, hormone therapy.

*Prior HT is defined relative to WHI enrollment in the clinical trial and nonuser group in the observational study, and defined relative to the beginning of the on-going hormone therapy episode at enrollment in the observational study user groups.

CEE, conjugated equine estrogens; CEE/MPA, conjugated equine estrogens plus medroxyprogesterone acetate.

Incidence rate per 1,000 person years, adjusted to the 5-1 age distribution in the respective clinical trials.
adherent women. Additional analyses of this type with focus on women who initiate CEE or CEE/MPA soon after the menopause can be found in a study by Prentice et al. (23) for a range of clinical outcomes, including colorectal cancer.

To better understand suggested HR differences between the clinical trial and observational study, and hormone therapy effects more generally, the analyses of Table 2 were extended by calculating HRs separately according to metastatic spread, primary tumor size, and the presence of one or more positive lymph nodes. HR estimates and 95% CIs for related tumor subtypes are shown in Fig. 1 for each preparation, separately for the clinical trial and observational study. The previously noted (4) deficit of early stage tumors with CEE/MPA in the clinical trial is not evident in the observational study. In contrast, there seems to be some deficit of more advanced tumors with CEE in the observational study that, as previously noted (6), is not evident in the clinical trial.

Colorectal cancer mortality data were considered to examine whether the lower incidence in the clinical trial for women assigned to CEE/MPA translated to reduced colorectal cancer mortality. Through the end of the active intervention period (July 7, 2002) there were 10 colorectal cancer deaths in each of the CEE/MPA and placebo groups, giving a colorectal cancer mortality HR (95% CI) of 0.95 (0.40-2.28) and logrank P value of 0.49. Participating women were followed systematically through March 31, 2005 (24), by which time there were 18 colorectal cancer deaths in the CEE/MPA group and 17 in the placebo group, with HR (95% CI) of 1.00 (0.51-1.94) with logrank P of 1.00. Among the 115 women diagnosed with colorectal cancer during the intervention phase of the CEE/MPA trial, 12 had died in the CEE/MPA group and 11 in the placebo group by the end of the intervention period, giving a total mortality HR (95% CI) for CEE/MPA of 1.64 (0.70-3.83) with a P value of 0.25. Among the 182 women diagnosed with colorectal cancer through March 31, 2005, there were 23 deaths in the CEE/MPA group and 21 in the placebo group, giving a total mortality HR (95% CI) of 1.54 (0.82-2.87) and P value of 0.18.

Corresponding colorectal cancer mortality data from the CEE trial were also considered. Through the end of the intervention period (2/29/2004), there were 16 colorectal cancer deaths in the active arm and 17 in the placebo, with corresponding HR (95% CI) of 0.99 (0.50-1.96) and logrank P value of 0.99. Among 111 women diagnosed with colorectal cancer, there were 16 deaths in each of the intervention groups, with all-cause mortality HR (95% CI) of 0.75 (0.34-1.70) and logrank P value of 0.49.

### Discussion

The data analyses presented here were undertaken to further the interpretation of a reduced colorectal cancer incidence with CEE/MPA, and lack of evidence of any

| Table 2. Numbers of women diagnosed with colorectal cancer, HR estimates and 95% CIs from the WHI postmenopausal hormone therapy trial and observational study for CEE and for CEE plus MPA |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                  | CEE Nonuser     | HR* (95% CI)    | CEE/MPA Nonuser | HR* (95% CI)    |
| Clinical trial   | 58              | 1.12 (0.77-1.63) | 43              | 0.80 (0.53-1.20) |
| Observational study | 70              | 0.54 (0.13-2.19) | 31              | 0.56 (0.38-0.81) |

*HRs in the clinical trial are from a Cox regression stratified by age group at enrollment, dietary modification trial randomization, and prior colorectal cancer, with assignment to the calcium and vitamin D trial as a time-dependent covariate. HRs in the observational study from a Cox regression model stratified by age group at enrollment, prior colorectal cancer, and prior postmenopausal hormone therapy, and adjusted for age (linear), body mass index, education, cigarette smoking, alcohol consumption, bilateral oophorectomy, type and duration of prior hormone therapy, family history of colorectal cancer, waist circumference, height, history of polyp removal, dietary selenium intake, nonsteroidal anti-inflammatory drug use, and prior oral contraceptive use. HR regression coefficients were estimated separately for prior postmenopausal hormone therapy users and nonusers.

| Table 3. Colorectal cancer hazard ratio estimates for CEE and CEE/MPA from combined analysis of WHI hormone therapy trial and observational study data |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Years from hormone therapy initiation | No prior hormone therapy | Prior hormone therapy |
|                  | CEE             | CEE/MPA         | CEE             | CEE/MPA         |
|                  | HR* (95% CI)    | HR* (95% CI)    | HR* (95% CI)    | HR* (95% CI)    |
|                  |                 |                 |                 |                 |
| <2               | 1.03 (0.43-2.47)| 0.90 (0.44-1.83)| 1.10 (0.45-2.67)| 0.89 (0.39-2.04)|
| 2-5              | 1.20 (0.47-3.06)| 0.62 (0.35-1.09)| 1.45 (0.42-5.06)| 0.73 (0.35-1.54)|
| >5               | 0.98 (0.47-2.03)| 0.62 (0.27-1.46)| 1.83 (0.51-6.50)| 0.65 (0.22-1.88)|
|                  |                 |                 |                 |                 |
| Ratio of HR in OS to HR in CT |                 |                 |                 |                 |
|                  | 0.63 (0.30-1.34)| 1.81 (0.82-4.00)| 0.35 (0.10-1.23)| 1.62 (0.61-4.33)|

Abbreviations: OS, observational study; CT, clinical trial.

*From Cox regression analyses with stratification and adjustment variables as in Table 2 footnotes, based on combined clinical trial and observational study analyses that include an interaction between hormone therapy HR and cohort (CT vs OS) that produces the ratio of hormone therapy HR in the OS to that in the CT shown at the bottom of the Table.
CEE effect on colorectal cancer incidence in the WHI clinical trial. The CEE/MPA finding was obscured (4) by a later stage diagnosis in the active treatment versus the placebo group, allowing the possibility that the treatment itself, or some aspect of the trial protocol, led to a delayed colorectal cancer diagnosis in the CEE/MPA group. This concern is heightened by the WHI Observational Study findings herein presented, which provide no suggestion of a lower risk among women using the same CEE/MPA preparation as studied in the clinical trial compared with nonusers of postmenopausal hormones, and little suggestion of a different extent of disease at diagnosis between CEE/MPA users and nonusers. Furthermore, the reduced incidence in the active treatment group in the CEE/MPA trial is shown here to have not led to any suggestion of colorectal cancer mortality benefit during an average 8-year intervention and follow-up period. It is important to note, however, that an even longer time period may be required to observe a mortality benefit from an actual reduction in the incidence of small, localized colorectal cancers.

It is interesting to speculate on reasons for later stage diagnoses with CEE/MPA in the clinical trial but not in the observational study. One possible difference is that colorectal tumors among CEE/MPA users in the observational study tended to be diagnosed many years after treatment initiation, compared with mostly within the first few years of use in the clinical trial. Hence, a limited-time response of colorectal tissue to CEE/MPA initiation having potential to impede the detection of small tumors, could affect clinical trial and observational study findings differentially. However, we see little evidence of time trends in HRs in either the clinical trial or observational study, although numbers of colorectal cancer events is small for this type of analysis (data not shown).

Another possibility relates to vaginal bleeding: Women assigned to CEE/MPA in the WHI trial experienced persistent vaginal bleeding to a greater extent than expected, and followed a protocol designed to manage bleeding while allowing them to continue with study hormones to the extent practical. We reanalyzed the CEE/MPA trial data while including an interaction term between randomization assignment and vaginal bleeding as a time-dependent variable. The colorectal cancer HR for CEE/MPA among women with bleeding was 0.54 with a 95% CI of 0.27 to 1.10, whereas that for women without bleeding was 0.57 with 95% CI of 0.38 to 0.86, so that this trial feature does not help to explain any diagnostic delay in the CEE/MPA trial. Hence, in summary, collective WHI data suggest that either the observed lower incidence was due to a comparatively delayed colorectal cancer detection in the CEE/MPA group perhaps as a result...

Figure 1. Colorectal cancer HRs and 95% CIs from WHI clinical trial and observational study for CEE and for CEE plus MPA, according to three aspects of extent of disease at diagnosis.
of attributing symptoms to hormone therapy use, in spite of intervention blinding, resulting in delayed evaluation; or simply as a chance occurrence. Alternatively, CEE/MPA results could reflect an actual reduction in localized, small tumors that apparently do not imply a colorectal cancer mortality benefit over an average 8-year intervention and follow-up period.

The CEE clinical trial did not suggest an effect on colorectal cancer incidence or on diagnosis (6). The observational study also does not suggest an effect of CEE on incidence overall, although there is some evidence for a deficit of larger, more advanced tumors at diagnosis among women using CEE. This is the direction of bias that would be expected if hormone therapy users in the community are under greater health surveillance than nonusers. Efforts to control such bias, here through imposing mammography use requirements before and after WHI enrollment, may not be sufficient for complete avoidance of bias from this source. The CEE trial does not provide evidence of any effect on colorectal cancer mortality over its 7.1-year average follow-up period. Hence, our summary interpretation is that collective WHI data provide little evidence for an effect of CEE on colorectal cancer incidence.

In summary, HR patterns in the WHI clinical trial and observational study do not provide strong evidence of a clinically important colorectal cancer benefit with CEE or CEE/MPA over an average 7- to 8-year treatment and follow-up period.

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References


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