Published in final edited form as:

Cancer Epidemiol Biomarkers Prev. 2008 October ; 17(10): 2609–2618. doi:
10.1158/1055-9965.EPI-08-0385.

Conjugated Equine Estrogens and Colorectal Cancer Incidence and Survival: The Women's Health Initiative Randomized Clinical Trial

Cheryl Ritenbaugh¹, Janet L. Stanford², LieLing Wu², James M. Shikany³, Robert E. Schoen⁴, Marcia L. Stefanick⁵, Vicky Taylor², Cedric Garland⁶, Gail Frank⁷, Dorothy Lane⁸, Ellen Mason⁹, S. Gene McNeely¹⁰, Joao Ascensao¹¹, and Rowan T. Chlebowski¹² For the Women's Health Initiative Investigators

¹University of Arizona College of Medicine, Tucson, AZ

²Fred Hutchinson Cancer Research Center, Seattle, WA

³University of Alabama at Birmingham, Birmingham, AL

⁴University of Pittsburgh, Pittsburgh, PA

⁵Stanford University, Palo Alto, CA

⁶University of California, San Diego, CA

⁷University of California, Irvine, CA

State University of New York, Stony Brook, NY

⁹John H. Stroger Jr. Hospital of Cook County, Chicago, IL

¹⁰Wayne State University, Detroit, MI

¹¹V.A. Medical Center and George Washington University, Washington DC

¹²Los Angeles Biomedical Research Institute at Harbor-UCLA (LABioMed), Torrance, CA

Abstract

Background—In separate Women's Health Initiative randomized trials, combined hormone therapy with estrogen plus progestin reduced colorectal cancer incidence but estrogen alone in women with hysterectomy did not. We now analyze features of the colorectal cancers that developed and examine survival of women following colorectal cancer diagnosis in the latter trial.

Participants and Methods—10,739 postmenopausal women who were 50 to 79 years of age and had undergone hysterectomy were randomized to conjugated equine estrogens (0.625 mg/day) or matching placebo. Colorectal cancer incidence was a component of the study's monitoring global index but was not a primary study endpoint. Colorectal cancers were verified by central medical record and pathology report review. Bowel exam frequency was not protocol defined but information on their use was collected.

Results—After a median 7.1 years, there were 58 invasive colorectal cancers in the hormone group and 53 in the placebo group (hazard ratio [HR] 1.12, 95% Confidence Interval [CI] 0.77–1.63). Tumor size, stage, and grade were comparable in the two randomization groups. Bowel exam frequency was also comparable in the two groups. The cumulative mortality following colorectal cancer diagnosis

among women in the conjugated equine estrogen group was 34 % compared to 30 % in the placebo group (HR 1.34, 95% CI 0.58–3.19).

Conclusions—In contrast to the preponderance of observational studies, conjugated equine estrogens in a randomized clinical trial did not reduce colorectal cancer incidence nor improve survival after diagnosis.

Keywords

Conjugated equine estrogen; colorectal cancer incidence; colorectal cancer survival after diagnosis; Women's Health Initiative; colorectal cancer screening

INTRODUCTION

Colorectal cancer is the second leading cause of cancer death in the United States (1). Interventions including calcium (2), celecoxib (3), aspirin (4), sulindac (5,6), and the bile acid ursodiol (7), have all reduced colorectal polyp recurrence in various high-risk populations. However, only combined estrogen plus progestin use has been shown to reduce colorectal cancer incidence in a randomized trial setting (8,9).

In prospective cohort studies, which have generally not distinguished combined estrogen plus progestin from estrogen alone use, postmenopausal hormone therapy has been consistently associated with reduced colorectal cancer risk (10,11,12,13,14). In addition, both significantly improved colorectal cancer-specific survival (15), and overall survival (15,16), has been seen in women using postmenopausal hormone therapy when their colorectal cancer was diagnosed. These observational study findings received some support from the WHI randomized trial evaluating combined hormone therapy with conjugated equine estrogen (CEE) plus medroxyprogesterone acetate (MPA) where a statistically significant 44% decrease in colorectal cancer incidence in the combined hormone therapy compared to placebo groups was seen (9).

In the original report of the WHI randomized, placebo-controlled trial, CEE alone did not reduce colorectal cancer incidence compared to placebo (17). The current report provides details of the colorectal cancer screening procedures, characteristics of the diagnosed colorectal cancers, additional subgroup analyses, and additional follow-up information including survival following colorectal cancer diagnosis in the WHI randomized trial comparing CEE alone to placebo.

METHODS

Study design

The WHI trial of CEE alone enrolled 10,739 women with prior hysterectomy at 40 clinical centers in the U.S. between 1993 and 1998 under protocols approved by the Institutional Review Boards at each institution (18). Recruitment was predominantly done through mass mailings. Eligibility criteria included ages between 50 to 79 years, postmenopausal status, and providing written informed consent. Women were eligible if they had undergone a prior hysterectomy, with or without oophorectomy. Exclusion criteria included a personal history of breast cancer, medical conditions likely to result in death in the next three years, or colorectal cancer within the past 10 years. Women currently using postmenopausal hormones were eligible after a 3-month washout period.

The trial was a randomized, double-blind, placebo-controlled trial of CEE (0.625 mg/day) administered in a single tablet (Premarin®, Wyeth Ayerst, Collegeville, PA) compared with

an identical-appearing placebo. Randomization was determined by the WHI Clinical Coordinating Center (CCC) and implemented at local centers with a distributed data base that maintained blinding of participants and staff to randomization allocation throughout the trial.

Women in the hormone trial also could participate on study entry in the Dietary Modification (DM) trial or could enter a randomized trial of calcium and vitamin D (CaD) at the first or second annual clinic visit. Approximately 20% and 60% joined the DM and CaD trials, respectively.

Follow-up

Follow-up procedures have been described previously (19,18). Participants were contacted after six weeks to assess symptoms and promote adherence, at six month intervals for clinical outcomes assessment, and annually for clinic visits. For potential colorectal cancer diagnoses, medical records and pathology reports were reviewed by locally trained physician adjudicators (blind to group assignment) to identify cases; cases underwent a second blind adjudication at the clinical coordinating center and tumor characteristics were coded using the Surveillance, Epidemiology, and End Results (SEER) program guidelines (20). Proximal colon lesions included those in the cecum, ascending colon (right colon), hepatic flexure and transverse colon. Distal colon lesions included those in the splenic flexure, descending colon (left colon), sigmoid and rectosigmoid junction.

Colorectal cancer was not a WHI CEE primary study outcome and colorectal cancer screening was not protocol-defined; participants received bowel exams as determined by their personal health care provider. Self-administered questionnaires or structured telephone interviews were used every six months to monitor the frequencies of rectal exams, fecal occult-blood testings, sigmoidoscopies and colonoscopies (asked as one question), and barium enema exams. Participants were also asked semi-annually if they had intestinal or colon polyps diagnosed during that period.

Termination of the study

After a mean follow-up of 7.1 years, the National Heart Lung and Blood Institute stopped the trial early because of increased stroke risk, absence of coronary heart disease benefit and the low probability that interpretation of the trial would change with further information. In the original report on CEE trial outcomes, 119 total colorectal cancer cases were identified (17). The current report is based on 120 total colorectal cancers diagnosed before February 29, 2004, the date on which the participants were instructed to discontinue their study medication, and follow-up mortality data through April 1, 2005 on those women diagnosed with colorectal cancer.

Statistical Analysis

Primary results were assessed with time-to-event methods based on the intention-to-treat principle. Comparisons of rates of colorectal cancer are presented as hazard ratios (HR) with 95 percent confidence intervals (CI) and Wald z-statistic P-values from Cox regression models, stratified according to age and randomization in the WHI trials of DM, CaD, or both. Since participants in the CaD trial entered that trial one to two years after their entry into the hormone trial, stratification for CaD trial participation was time-dependent, based on the CaD randomization date. No adjustments are made for multiple analyses over time since the incidence of colorectal cancer did not influence the decision to stop the trial.

Kaplan-Meier plots were used to examine the rates of colorectal cancer over time. Effects of baseline participant characteristics, including risk factors for colorectal cancer, were assessed in Cox regression models as described above, expanded to include the designated risk factor

and randomization assignment (as the main effects) and the interaction between them. P-values for interaction were computed with likelihood-ratio tests, and models with and without the interaction term were compared. For variables measured on a continuous scale, p-values were computed on the continuous variable. Women with missing risk factor values in a given analysis were excluded from that analysis. Eighteen subgroup comparisons were performed; one would be expected to be significant at the 0.05 level by chance alone. The exploratory analyses significance levels were not adjusted for multiple comparisons. Comparisons of survival after colorectal cancer diagnosis between estrogen alone and placebo groups were based on a proportional hazards model that was stratified by age and cancer stage at diagnosis with age as a covariate. Sensitivity analyses were conducted to explore the impact of adherence on outcome, and follow-up was censored 6 months after participants first became non-adherent (defined as taking <80% of study pills).

RESULTS

There were 5310 women randomized to CEE and 5429 to placebo (total = 10,739) with follow-up during active intervention for an average of 7.1 years (maximum of 10.8 years). Recent outcomes data were available for 10,176 participants (94.8%). Fifty-four percent of the women in the hormone group and 53.5% percent in the control group stopped study medications at some point; the vast majority did not restart. In addition, 5.7% in the hormone group and 9.1% in the control group reported using postmenopausal hormones off protocol. A full consort diagram is published elsewhere (8). The two groups were well-balanced for colorectal cancer risk factors, including age, education, anthropometry, personal or family history of colorectal cancer, smoking history, use of anti-inflammatory medications, dietary patterns, use of nutritional supplements, levels of physical activity, prior postmenopausal hormone use, and prior colorectal cancer screening (Table 1).

At the termination of the study intervention, 53.8% of women had already stopped taking study medication and the discontinuation rate was closely comparable in the intervention and placebo groups. Non-protocol hormone therapy was initiated by 9.1% in the placebo group and 5.7% in the CEE group through year 6.

Among the 120 women with colorectal cancer, three in the intervention group and two in the placebo group had stage 0 (in situ) disease. There was one squamous cell carcinoma and one neuroendocrine carcinoma in the placebo group, and one malignant melanoma of the colon and one neuroendocrine carcinoma in the hormone group. All presented analyses are limited to the remaining 111 women with invasive colorectal carcinomas of epithelial origin.

By an intention-to-treat analysis, there was no difference between groups in the incidence of invasive colorectal cancer (58 in the CEE group and 53 in the placebo group) HR: 1.12, 95% CI: 0.77–1.63, $p=0.55$ (Table 2). Although fewer rectal cancers were diagnosed in the CEE group, a total of only 15 rectal cancers were observed, precluding reliable estimation of any CEE effect. Additionally, Kaplan-Meier plots by randomization group revealed no time trends of treatment effects (Figure 1). In adherence-adjusted sensitivity analysis, the HR for invasive colorectal cancer changed only slightly to 1.02 (95% CI: 0.64 – 1.64). Tumor characteristics were also comparable between treatment groups (Table 2).

Among the 18 interactions examined, history of polyp removal, height, and waist circumference differed at the 0.05 level of significance (Table 3) with more colorectal cancer seen in the CEE group among women with waist circumference < 85 cm or height < 158.7 cm. Although the interaction test was not significant, the HR of the CEE to placebo group for invasive colorectal cancer was 0.82 (95% CI: 0.34–1.98) for women 50–59 years and 0.83

(95% CI: 0.49–1.43) for women 60–69 years old at baseline compared to 2.11 (95% CI 1.06–4.21) in the 70–79 year age group.

Based on self-reports, the proportion of women who developed polyps during the trial was comparable between the two randomization groups (16.9% of hormone and 17.1% of placebo users) as was the time to first report of an identified polyp (HR 0.97, 95% CI 0.87–1.07). A higher risk of invasive colorectal cancer was associated with prior polyp removal among those in the hormone compared to the control group; however, the limited number of cases (n=9) precludes reliable estimation of effect [see Table 3].

The frequency of bowel exams, including rates of hemoccult testing, rectal exams, and sigmoidoscopy/colonoscopy was similar in the CEE and placebo groups during the study. Screening rates increased during the study, with rates of sigmoidoscopy/colonoscopy ranging from approximately 9% to 15.5% per year, and other exams (rectal or hemoccult) ranging from approximately 16% to 23%. Over the study period, 24.0% of women in the hormone group and 22.9% of the placebo group participants reported no bowel screening. Surveillance sigmoidoscopy or colonoscopy was more frequent in women with prior polyp removal than was screening use of these exams in women without such history (69% versus 44%). Screening with these tests was also more frequent in those with a colorectal cancer family history (57% versus 45%), and somewhat more frequent in women 50–59 years old, but did not differ by randomization group.

Mortality outcomes for participants who were diagnosed with colorectal cancer were compared between randomization groups. After 3.6 ± 2.7 years (mean $\pm$ standard deviation) following a colorectal cancer diagnosis, the cumulative mortality rate for women in the CEE alone group was 34% (20 of 58 dead) compared to 30% (16 of 53 dead) in the placebo group (HR 1.34, 95% CI 0.58–3.19). Kaplan-Meier plots by randomization group are provided in figure 2.

In a cross-study comparison, the colorectal cancer annual incidence rates were found to be similar in the placebo groups from the trial of CEE alone compared to the trial of CEE plus MPA (0.14% for women in the CEE alone trial versus 0.16% for women in the CEE plus MPA trials, $p=0.35$ for comparison of incidence between the two placebo groups) (1). Difference between the CEE plus MPA (9) and CEE effect on colorectal cancer were explored using a Cox regression model stratified according to cohorts, age, DM participation, history of colorectal cancer, and adjusting for covariates of ethnicity, BMI, history of polyp removal, prior colonoscopy/sigmoidoscopy, and family history of colorectal cancer. The ratio of the hazard ratios for the CEE alone compared to the CEE plus MPA trial for colorectal cancer incidence was 2.21 (95% CI: 1.29–3.81, $p=0.004$) indicating a significant difference in hormone therapy effects in the two trials.

DISCUSSION

In a randomized, double-blind, placebo-controlled trial, CEE alone for an average of 7.1 years did not influence invasive colorectal cancer incidence or survival following a colorectal cancer diagnosis in postmenopausal women. No differences were observed in the clinical characteristics of the tumors diagnosed in the CEE and placebo groups. Colorectal cancer risk factors were balanced between treatment groups, as were examinations for colorectal cancer detection.

The lack of an effect of CEE alone on colorectal cancer incidence contrasts with the results of the WHI trial of CEE plus MPA, where colorectal cancer incidence was significantly lower in the combined hormone group (9). In the randomized Heart and Estrogen/Progestin Replacement Study (HERS) fewer colorectal cancers were also seen in women randomized to the CEE and MPA compared to the placebo groups (HR 0.69, 95% CI 0.32–1.49, N.S.) (21).

Although participants in the two WHI trials, one evaluating CEE plus MPA for women with no prior hysterectomy and one evaluating CEE alone for women with prior hysterectomy, differed in several baseline characteristics (22), the colorectal cancer annual incidence rates were similar in the placebo groups for the two trials. Thus, differences in participant characteristics do not explain the discrepant findings and suggest progestin may modify the influence of estrogen on colorectal cancer. Since colorectal cancers in the WHI combined hormone therapy trial were diagnosed at a higher stage compared to those diagnosed on placebo, a differential influence on cancer detection in the two studies also cannot be excluded as an explanation.

In the predominance of observational studies, postmenopausal hormone therapy use has been consistently associated with reduced colorectal cancer risk (23,24) and improved cancer-specific and overall survival in some reports (25,15,16). However, the observational study literature regarding menopausal hormone therapy and colorectal cancer have not commonly considered use of estrogen alone and combined hormone therapy separately. Several case control studies reported that both estrogen plus progestin as well as estrogen alone were associated with lower colorectal cancer risk (12,26). A recent case control in the U.S. found an association with lower colorectal cancer risk only in women using estrogen plus progestin (OR = 0.6, 95% CI 0.5–0.9) but not those using estrogen alone (OR = 0.9, 95% CI 0.7–1.1) (13). Similarly, in a Swedish cohort (27), and in the large United Kingdom General Practice Research Database, colorectal cancer risk was lower only in women using estrogen plus progestin but not those using estrogen alone (28). Future observational studies of colorectal cancer should clearly differentiate combined hormone use from estrogen alone.

In the current randomized trial, there was no improvement in the post diagnosis survival for women with colorectal cancers in the CEE group (n=58 cases) compared to those diagnosed in the placebo group (n=53 cases) (HR 1.34, 95% CI 0.58–3.19). This result stands in contrast to the recent findings of Chan and colleagues (15) who reported that, for women in the Nurse's Health Study cohort, current users of estrogen at the time of diagnosis of colorectal cancer (n=235 cases) experienced significantly less colorectal cancer-specific mortality and less overall mortality compared to women who never used hormone therapy prior to a colorectal cancer diagnosis (multivariate HR for overall mortality was 0.74, 95% CI 0.56–0.97). In that observational study experience, 75% of the person-time represented estrogen alone use. Other reports of longer survival for women diagnosed with colorectal cancer when they were receiving menopausal hormone therapy do not provide details regarding type of hormone therapy received (19,29). Given the findings from the WHI randomized trial, current evidence does not support clinical use of estrogen to improve outcome of postmenopausal women with diagnosed colorectal cancer.

The biological effects of combined estrogen plus progestin and estrogen alone on malignant processes are complex. Use of estrogen alone increases endometrial proliferation and endometrial cancer risk while addition of progestin to estrogen largely abrogates the estrogen effects (8,30). Combined estrogen plus progestin use significantly increased breast cancer risk (31) while use of estrogen alone was associated with a non-significant reduction in breast cancer incidence (32). Combined CEE plus MPA use reduced colorectal cancer incidence in the WHI trial for women with no prior hysterectomy (9) but use of CEE alone in the currently reported trial did not influence either colorectal cancer incidence or mortality after diagnosis. Taken together, these results suggest an hypothesis that progestins modulate estrogen effects on malignancy and that their influence is organ specific. Alternatively, progestins and/or estrogens alone could simply have different effects on these three cancer types, but clinical evidence for effects related to progestin alone use are sparse.

Study subgroup analyses suggested that CEE influence on colorectal cancer may vary according to age. Alternatively, given the limited numbers of women in these subgroup analyses and that the test for interaction was not significant, chance alone may explain the age effects observed. One case-control study (33) reporting on mostly unopposed estrogen use found no association with colorectal cancer risk in younger women but hormone users aged 60–69 had a lower colorectal cancer risk relative to non-users. A nominally significant interaction among CEE alone use and colorectal cancer with both waist circumference and height was seen along with a suggestion of an interaction with BMI. However, observational studies examining BMI modification of hormone therapy association with colorectal cancer have provided conflicting results (34,16,35,36,37,38) and relationships among BMI, menopausal hormone therapy and colorectal cancer risk remain unclear.

While no effect of CEE alone on colorectal cancer incidence was seen in the current trial, several mechanisms have been proposed as potential mediators of the favorable effect of combined CEE plus MPA use on colorectal cancer previously reported⁹. These include hormone influences on bile acids,³⁹ insulin,⁴⁰ and direct effects on the intestinal epithelium.^{41,42}

Strengths of the current study include the randomized, double-blind design and the long-term follow-up of a large number of ethnically diverse participants with standardized outcome ascertainment and adjudication. The limited number of colorectal cancers is a constraint, as is the lower than anticipated adherence to study medications, which likely dilutes any true effect. Although bowel screening was not protocol-defined, the frequency of exams was comparable in the two groups.

In summary, in a randomized, placebo-controlled clinical trial in 10,749 postmenopausal women, use of CEE alone did not reduce colorectal cancer incidence or improve the post diagnosis survival of women with this disease.

REFERENCES

1. Jemal A, Siegel R, Ward E, et al. Cancer Statistics, 2007. *Ca Cancer J Clin* 2007;57:43–66. [PubMed: 17237035]
2. Baron JA, Beach M, Mandel JS, et al. Calcium supplements for the prevention of colorectal adenomas. *N Engl J Med* 1999;340:101–107. [PubMed: 9887161]
3. Steinbach G, Lynch PM, Phillips RKS, et al. The effect of celecoxib, a cyclooxygenase 2 inhibitor, in familial adenomatous polyposis. *N Engl J Med* 2000;342:1946–1952. [PubMed: 10874062]
4. Sandler RS, Halabi S, Baron JA, et al. A randomized trial of aspirin to prevent colorectal adenomas in patients with previous colorectal cancer. *N Engl J Med* 2003;348:883–890. [Erratum, *N Engl J Med* 2003;348: 1939.]. [PubMed: 12621132]
5. Labayle D, Fischer D, Vielh P, et al. Sulindac causes regression of rectal polyps in familial adenomatous polyposis. *Gastroenterology* 1991;101:635–639. [PubMed: 1650315]
6. Giardiello FM, Hamilton SR, Krush AJ, et al. Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. *N Engl J Med* 1993;328:1313–1316. [PubMed: 8385741]
7. Alberts DS, Martinez ME, Hess LM, et al. Phase III trial of ursodeoxycholic acid to prevent colorectal adenoma recurrence. *J Natl Cancer Inst* 2005;97(11):846–853. [PubMed: 15928305]
8. Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;200(3):321–333.
9. Chlebowski RT, Wactawski-Wende J, Ritenbaugh C, et al. Estrogen plus progestin and colorectal cancer in postmenopausal women. *N Engl J Med* 2004;350(10):991–1004. [PubMed: 14999111]
10. McMichael AJ, Potter JD. Reproduction, endogenous and exogenous sex hormones, and colon cancer: a review and hypothesis. *J Natl Cancer Inst* 1980;65:1201–1207. [PubMed: 7001123]

11. La Vecchia C, Gallus S, Fernandez E. Hormone replacement therapy and colorectal cancer: an update. *J Br Menopause Soc* 2006;12(4):139–142. [PubMed: 17178013]
12. Newcomb PA, Storer BE. Postmenopausal hormone use and risk of large-bowel cancer. *J Natl Cancer Inst* 1995;87:1067–1071. [Erratum, *J Natl Cancer Inst* 1995;87:1416.]. [PubMed: 7616598]
13. Newcomb PA, Zheng Y, Chia VM, et al. Estrogen plus progestin use, microsatellite instability and the risk of colorectal cancer in women. *Cancer Res* 2007;67(15):7534–7539. [PubMed: 17671225]
14. Herbert-Croteau N. A meta-analysis of hormone replacement therapy and colon cancer in women. *Cancer Epidemiology, Biomarkers and Prevention* 1998;7:653–659.
15. Chan JA, Meyerhardt JA, Chan AT, Giovannucci EL, Colditz GA, Fuchs CS. Hormone replacement therapy and survival after colorectal cancer diagnosis. *J Clin Oncol* 2006;24(36):5680–5686. [PubMed: 17179103]
16. Slattery MT, Ballard-Barbash R, Edwards S, Caan BJ, Potter JD. Body mass index and colon cancer: an evaluation of the modifying effects of estrogen. *Cancer Causes and Control* 2003;14:75–84. [PubMed: 12708728]
17. The WHI Steering Committee. Effects of conjugated equine estrogens in postmenopausal women with hysterectomy: The Women's Health Initiative randomized controlled trial. *JAMA* 2004;291:1701–1712. [PubMed: 15082697]
18. The Women's Health Initiative Study Group. Design of the Women's Health Initiative clinical trial and observational study. *Control Clin Trials* 1998;19:61–103. [PubMed: 9492970]
19. Mandelson MT, Miglioretti D, Newcomb PA, Harrison R, Potter JD. Hormone replacement therapy in relation to survival in women diagnosed with colon cancer. *Cancer Causes and Control* 2003;14:979–984. [PubMed: 14750537]
20. National Cancer Institute. About SEER. [verified March 28, 2005]. Available at <http://www.seer.cancer.gov/.Accessibility>
21. Hulley S, Furberg C, Barrett-Connor E, et al. Noncardiovascular disease outcomes during 6.8 years of hormone therapy. Heart and Estrogen/Progestin Replacement Study Follow-up (HERS II). *JAMA* 2002;288(1):58–66. [PubMed: 12090863]
22. Stefanick ML, Hsai J, Barad D, Johnson SJ, Cochrane B, Liu J. The Women's Health Initiative postmenopausal Hormone Trials: Overview and Baseline Characteristics of Participants. *Annals Epidemiol* 2003;13 Suppl 1(9):S78–S86.
23. Janne PA, Mayer R. Chemoprevention of colorectal cancer. *N Engl J Med* 2000;342:1960–1968. [PubMed: 10874065]
24. Grodstein F, Newcomb PA, Stampfer MJ. Postmenopausal hormone therapy and the risk of colorectal cancer: a review and meta-analysis. *Am J Med* 1999;106:574–582. [PubMed: 10335731]
25. Calle EE, Miracle-McMahill HL, Thun MJ, Heath CW Jr. Estrogen replacement therapy and risk of fatal colon cancer in a prospective cohort of postmenopausal women. *J Natl Cancer Inst* 1995;87:517–523. [PubMed: 7707438]
26. Campbell PT, Newcomb P, Gallinger S, Cotterchio M, McLaughlin JR. Exogenous hormones and colorectal cancer risk in Canada: Associations stratified by clinically defined familial risk of cancer. *Cancer Causes Control* 2007;18(7):723–733. [PubMed: 17549595]
27. Persson I, Yuen J, Bergkvist L, Schairer C. Cancer incidence and mortality in women receiving estrogen and estrogen-progestin replacement therapy – long-term follow-up of a Swedish cohort. *Int J Cancer* 1996;67:327–332. [PubMed: 8707404]
28. Tannen RL, Weiner MG, Xie D, Barnhart K. Estrogen affects postmenopausal women differently than estrogen plus progestin replacement therapy. *Hum Reprod.* 2007 March 8; [Epub ahead of print].
29. Slattery ML, Anderson K, Sanowitz W, et al. Hormone replacement therapy and improved survival among postmenopausal women diagnosed with colon cancer (USA). *Cancer Causes Control* 1999;10:467–473. [PubMed: 10530618]
30. The Writing Group for the PEPI Trial. Effects of hormone replacement therapy on endometrial histology in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. *JAMA* 1996;275(5):370–375. [PubMed: 8569016]
31. Chlebowski RT, Hendrix SL, Langer RD, et al. Influence of estrogen plus progestin on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative Randomized Trial. *JAMA* 2003;289(24):3243–3253. [PubMed: 12824205]

32. Stefanick M, Anderson GL, Margolis KL, et al. Effects of conjugated equine estrogens on breast cancer and mammography in postmenopausal women with hysterectomy: The Women's Health Initiative Randomized Trial. *JAMA* 2006;295(14):1647–1657. [PubMed: 16609086]
33. Rabeneck L, Davila J, Thompson M, El-Serag. Outcomes in elderly patients following surgery for colorectal cancer in the Veterans Affairs health care system. *Al Ther* 2004;20(10):1115–1124.
34. Prihartono N, Palmer JR, Louik C, Shapiro S, Rosenberg L. A case-control study of use of postmenopausal female hormone supplements in relation to the risk of large bowel cancer. *Cancer Epidemiology, Biomarkers & Prevention* 2000;9:443–447.
35. Pischon T, Lahmann PH, Boeing H, et al. Body size and risk of colon and rectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC). *J Natl Cancer Inst* 2006;98(13):920–931. [PubMed: 16818856]
36. Wang Y, Jacobs EJ, Teras LR, et al. Lack of evidence for effect modification by estrogen of association between body mass index and colorectal cancer risk among postmenopausal women. *Cancer Causes Control* 2007;18(8):793–799. [PubMed: 17619155]
37. Hoffmeister M, Raum E, Winter J, Chang-Claude J, Brenner H. Hormone replacement therapy, body mass, and the risk of colorectal cancer among postmenopausal women from Germany. *Br J Cancer* 2007;97(11):1486–1492. [PubMed: 17987040]
38. Lin J, Zhang SM, Cook NR, Rexrode KM, Lee IM, Buring JE. Body mass index and risk of colorectal cancer in women (United States). *Cancer Causes Control* 2004;15(6):581–589. [PubMed: 15280637]
39. Giardiello FM, Hamilton SR, Krush AJ, et al. Treatment of colonic and rectal adenomas with sulindac in familial adenomatous polyposis. *N Engl J Med* 1993;328(18):1313–1316. [PubMed: 8385741]
40. Saydeh SH, Platz EA, Rifai N, Pollak MN, Brancati FL, Helzlsouer KJ. Association of markers of insulin and glucose control with subsequent colorectal cancer risk. *Cancer Epidemiol Biomarkers Prev* 2003;12:412–418. [PubMed: 12750235]
41. Thomas ML, Xu X, Norfleet AM, Watson CS. The presence of functional estrogen receptors in intestinal epithelial cells. *Endocrinology* 1993;132:426–430. [PubMed: 8419141]
42. Witte D, Chirala M, Younes A, Li Y, Younes M. Estrogen receptor beta is expressed in human colorectal adenocarcinoma. *Hum Pathol* 2001;32(9):940–944. [PubMed: 11567223]

WHI INVESTIGATORS

Program Office

(National Heart, Lung, and Blood Institute, Bethesda, Maryland) Barbara Alving, Jacques Rossouw, Linda Pottern, Shari Ludlam, Joan McGowan, Nancy Geller, Leslie Ford.

Clinical Coordinating Center

(Fred Hutchinson Cancer Research Center, Seattle, WA) Ross Prentice, Garnet Anderson, Andrea LaCroix, Ruth Patterson, Anne McTiernan, Barbara Cochrane, Julie Hunt, Lesley Tinker, Charles Kooperberg, Martin McIntosh, C. Y. Wang, Chu Chen, Deborah Bowen, Alan Kristal, Janet Stanford, Nicole Urban, Noel Weiss, Emily White; (Wake Forest University School of Medicine, Winston-Salem, NC) Sally Shumaker, Ronald Prineas, Michelle Naughton; (Medical Research Laboratories, Highland Heights, KY) Evan Stein, Peter Laskarzewski; (San Francisco Coordinating Center, San Francisco, CA) Steven R. Cummings, Michael Nevitt, Lisa Palermo; (University of Minnesota, Minneapolis, MN) Lisa Harnack; (Fisher BioServices, Rockville, MD) Frank Cammarata, Steve Lindenfelter; (University of Washington, Seattle, WA) Bruce Psaty, Susan Heckbert.

Clinical Centers

(Albert Einstein College of Medicine, Bronx, NY) Sylvia Wassertheil-Smoller, William Frishman, Judith Wylie-Rosett, David Barad, Ruth Freeman; (Baylor College of Medicine, Houston, TX) Jennifer Hays, Ronald Young, Jill Anderson, Sandy Lithgow, Paul Bray;

(Brigham and Women's Hospital, Harvard Medical School, Boston, MA) JoAnn Manson, J. Michael Gaziano, Claudia Chae, Kathryn Rexrode, Caren Solomon (Brown University, Providence, RI) Annlouise R. Assaf, Carol Wheeler, Charles Eaton, Michelle Cyr; (Emory University, Atlanta, GA) Lawrence Phillips, Margaret Pedersen, Ora Strickland, Margaret Huber, Vivian Porter; (Fred Hutchinson Cancer Research Center, Seattle, WA) Shirley A.A. Beresford, Vicky M. Taylor, Nancy F. Woods, Maureen Henderson, Robyn Andersen; (George Washington University, Washington, DC) Judith Hsia, Nancy Gaba, Joao Ascensao; (Harbor-UCLA Research and Education Institute, Torrance, CA) Rowan Chlebowski, Robert Detrano, Anita Nelson, Michele Geller; (Kaiser Permanente Center for Health Research, Portland, OR) Evelyn Whitlock, Victor Stevens, Njeri Karanja; (Kaiser Permanente Division of Research, Oakland, CA) Bette Caan, Stephen Sidney, Geri Bailey Jane Hirata; (Medical College of Wisconsin, Milwaukee, WI) Jane Morley Kotchen, Vanessa Barnabei, Theodore A. Kotchen, Mary Ann C. Gilligan, Joan Neuner; (MedStar Research Institute/Howard University, Washington, DC) Barbara V. Howard, Lucile Adams-Campbell, Lawrence Lessin, Monique Rainford, Gabriel Uwaifo; (Northwestern University, Chicago/Evanston, IL) Linda Van Horn, Philip Greenland, Janardan Khandekar, Kiang Liu, Carol Rosenberg; (Rush University Medical Center, Chicago, IL) Henry Black, Lynda Powell, Ellen Mason; Martha Gulati; (Stanford Prevention Research Center, Stanford, CA) Marcia L. Stefanick, Mark A. Hlatky, Bertha Chen, Randall S. Stafford, Sally Mackey; (State University of New York at Stony Brook, Stony Brook, NY) Dorothy Lane, Iris Granek, William Lawson, Gabriel San Roman, Catherine Messina; (The Ohio State University, Columbus, OH) Rebecca Jackson, Randall Harris, Electra Paskett, W. Jerry Mysiw, Michael Blumenfeld; (University of Alabama at Birmingham, Birmingham, AL) Cora E. Lewis, Albert Oberman, James M. Shikany, Monika Safford, Mona Fouad; (University of Arizona, Tucson/Phoenix, AZ) Cyndi Thomson, Tamsen Bassford, Marcia Ko, Ana Maria Lopez, Cheryl Ritenbaugh; (University at Buffalo, Buffalo, NY) Jean Wactawski-Wende, Maurizio Trevisan, Ellen Smit, Susan Graham, June Chang; (University of California at Davis, Sacramento, CA) John Robbins, S. Yasmeen; (University of California at Irvine, CA) F. Allan Hubbell, Gail Frank, Nathan Wong, Nancy Greep, Bradley Monk; (University of California at Los Angeles, Los Angeles, CA) Howard Judd, David Heber, Robert Elashoff; (University of California at San Diego, LaJolla/Chula Vista, CA) Robert D. Langer, Michael H. Criqui, Gregory T. Talavera, Cedric F. Garland, Matthew A. Allison; (University of Cincinnati, Cincinnati, OH) Margery Gass, Suzanne Wernke; (University of Florida, Gainesville/Jacksonville, FL) Marian Limacher, Michael Perri, Andrew Kaunitz, R. Stan Williams, Yvonne Brinson; ¹ (University of Hawaii, Honolulu, HI) J. David Curb, Helen Petrovitch, Beatriz Rodriguez, Kamal Masaki, Santosh Sharma; (University of Iowa, Iowa City/Davenport, IA) Robert Wallace, James Torner, Susan Johnson, Linda Snetselaar, Jennifer Robinson; (University of Massachusetts/Fallon Clinic, Worcester, MA) Judith Ockene, Milagros Rosal, Ira Ockene, Robert Yood, Patricia Aronson; (University of Medicine and Dentistry of New Jersey, Newark, NJ) Norman Lasser, Baljinder Singh, Vera Lasser, John Kostis, Peter McGovern; (University of Miami, Miami, FL) Mary Jo O'Sullivan, Linda Parker, Timothy DeSantis, Diann Fernandez, Pat Caralis; (University of Minnesota, Minneapolis, MN) Karen L. Margolis, Richard H. Grimm, Mary F. Perron, Cynthia Bjerk, Sarah Kempainen; (University of Nevada, Reno, NV) Robert Brunner, William Graettinger, Vicki Oujevolk, Michael Bloch; (University of North Carolina, Chapel Hill, NC) Gerardo Heiss, Pamela Haines, David Ontjes, Carla Sueta, Ellen Wells; (University of Pittsburgh, Pittsburgh, PA) Lewis Kuller, Jane Cauley, N. Carole Milas; (University of Tennessee Health Science Center, Memphis, TN) Karen C. Johnson, Suzanne Satterfield, Raymond W. Ke, Stephanie Connelly, Fran Tyllavsky; (University of Texas Health Science Center, San Antonio, TX) Robert Brzyski, Robert Schenken, Jose Trabal, Mercedes Rodriguez-Sifuentes, Charles Mouton; (University of Wisconsin, Madison, WI) Gloria E. Sarto, Douglas Laube, Patrick McBride, Julie Mares-Perlman, Barbara Loevinger; (Wake Forest University School of Medicine, Winston-Salem, NC) Denise Bonds, Greg Burke, Robin Crouse, Mara Vitolins, Scott Washburn; (Wayne State

University School of Medicine/Hutzel Hospital, Detroit, MI) Susan Hendrix, Michael Simon, Gene McNeeley.

Former Principal Investigators and Project Officers

Baylor College of Medicine, John Foreyt, Ph.D., Emory University, Dallas Hall, M.D., George Washington University, Valery Miller, M.D., Kaiser, Oakland, Robert Hiatt, M.D., Kaiser, Portland, Barbara Valanis, Dr.Ph., National Cancer Institute, Bethesda, Maryland, Carolyn Clifford², University of California, Irvine, Frank Meyskens, Jr., M.D., University of Cincinnati, James Liu, M.D., Nelson Watts, University of Miami, Marianna Baum, Ph.D., University of Minnesota, Richard Grimm, M.D., University of Nevada, Sandra Daugherty, M.D. ², University of North Carolina, Chapel Hill, David Sheps, M.D., Barbara Hulka, M.D., University of Tennessee, Memphis, William Applegate, M.D., University of Wisconsin, Catherine Allen, Ph.D. ² ²deceased

Figure 1.
Invasive Colorectal Cancer Incidence by Randomization Group

Figure 2.
Survival Following Diagnosis of Invasive Colorectal Cancer By Randomization Group

Table 1

Characteristics of Participants in the WHI CEE Trial at Baseline by Group Assignment

Characteristic	CEE N (%)		Placebo N (%)	
Age at Screening				
50–59	1637	(30.8)	1673	(30.8)
60–69	2387	(45.0)	2465	(45.4)
70–79	1286	(24.2)	1291	(23.8)
Ethnicity				
White	4007	(75.5)	4075	(75.1)
Black	782	(14.7)	835	(15.4)
Hispanic	322	(6.1)	333	(6.1)
American Indian	41	(0.8)	34	(0.6)
Asian/Pacific Islander	86	(1.6)	78	(1.4)
Unknown	72	(1.4)	74	(1.4)
Education				
0–8 years	181	(3.4)	148	(2.7)
Some high school	354	(6.7)	370	(6.9)
High school diploma/GED	1233	(23.5)	1188	(22.1)
School after high school	2271	(43.2)	2350	(43.7)
College degree or higher	1216	(23.1)	1327	(24.7)
First-Degree Relative with Colorectal Cancer				
None	3904	(85.3)	4017	(85.2)
1	575	(12.6)	591	(12.5)
2 or more	98	(2.1)	109	(2.3)
History of Polyps Removal				
No	4323	(90.4)	4336	(90.3)
Yes	460	(9.6)	466	(9.7)
History of Ulcerative Colitis or Crohn's Disease				
No	5145	(98.6)	5268	(98.8)
Yes	74	(1.4)	64	(1.2)
History of Colorectal Cancer				
No	5233	(99.7)	5339	(99.6)
Yes	16	(0.3)	24	(0.4)
History of Diabetes				
No	4806	(90.5)	4906	(90.4)
Yes	502	(9.5)	519	(9.6)
BMI				
<25	1110	(21.0)	1096	(20.3)
25 - <30	1795	(34.0)	1912	(35.5)
>=30	2376	(45.0)	2383	(44.2)
Waist Circumference. > 88 cm				

	CEE N (%)		Placebo N (%)	
No	2304	(43.5)	2342	(43.3)
Yes	2994	(56.5)	3071	(56.7)
Height (cm) > 161.3 cm				
No	2633	(49.6)	2718	(50.1)
Yes	2654	(50.0)	2688	(49.5)
Physical Activity (METs per week)				
None	1081	(22.2)	1043	(21.3)
>0 - 3.75	1089	(22.3)	1142	(23.3)
>3.75 - 8.75	914	(18.7)	895	(18.3)
>8.75 - 17.5	968	(19.8)	958	(19.5)
>17.5	828	(17.0)	866	(17.7)
NSAID Use				
No	3601	(67.8)	3689	(68.0)
Yes	1709	(32.2)	1740	(32.1)
Ibuprofen Use				
No	4702	(88.5)	4798	(88.4)
Yes	608	(11.5)	631	(11.6)
Aspirin Use (> = 100 mg)				
No	4413	(83.1)	4498	(82.9)
Yes	897	(16.9)	931	(17.2)
Acetaminophen Use				
No	4566	(86.0)	4654	(85.7)
Yes	744	(14.0)	775	(14.3)
Total Energy (kcal)				
<=1119	1211	(23.9)	1197	(23.1)
>1119 - 1414.5	980	(19.3)	1056	(20.4)
>1414.5 - 1715	957	(18.9)	939	(18.1)
>1715 - 2129.5	907	(17.9)	926	(17.9)
> 2129.5	1021	(20.1)	1056	(20.4)
Percent Energy from Fat				
<=27	867	(17.1)	868	(16.8)
>27 - 32.5	920	(18.1)	964	(18.6)
>32.5 - 37	1069	(21.1)	1098	(21.2)
>37 - 41.5	1067	(21.0)	1050	(20.3)
>41.5	1153	(22.7)	1194	(23.1)
Selenium (mcg/day)				
<= 74.4	1813	(35.7)	1872	(36.2)
74.5 - 106.3	1596	(31.4)	1638	(31.7)
>= 106.4	1667	(32.8)	1664	(32.2)
Red Meat (servings/day)				
0.000 - < 0.364	1278	(25.2)	1286	(24.9)
0.364 - < 0.649	1272	(25.1)	1290	(25.0)

	CEE N (%)		Placebo N (%)	
0.649 - < 1.070	1262	(25.9)	1293	(25.0)
>= 1.070	1260	(24.8)	1301	(25.2)
Fruit & Vegetables (servings/day)				
0.0 - <= 3.0	2214	(43.6)	2223	(43.0)
3.0 - <= 6.0	2166	(42.7)	2195	(42.4)
6.0 - <=9.0	606	(11.9)	625	(12.1)
> 9.0	92	(1.8)	132	(2.6)
Alcohol Intake				
None	1995	(38.0)	2007	(37.2)
<1 drink/wk	1768	(33.7)	1815	(33.7)
>= 1 drink/wk	1484	(28.3)	1566	(29.1)
Multi-Vitamin Use				
No	3618	(68.1)	3683	(67.8)
Yes	1692	(31.9)	1746	(32.2)
Calcium Supplement Use (mg/day)				
None	3074	(57.9)	3041	(56.0)
<=200	887	(16.7)	918	(16.9)
>200 – 662	745	(14.0)	812	(15.0)
>662	604	(11.4)	658	(12.1)
Vitamin D Supplement Use (mcg/day)				
None	3290	(62.0)	3328	(61.3)
<=10	1696	(31.9)	1770	(32.6)
>10	324	(6.1)	331	(6.1)
Smoking				
Never smoked	2723	(51.9)	2705	(50.4)
Past smoker	1986	(37.8)	2089	(38.9)
Current Smoker	542	(10.3)	571	(10.6)
Oral Contraceptive Use, Duration				
Non-User	3257	(61.4)	3377	(62.2)
< 5 Years	1207	(22.8)	1198	(22.1)
5 - < 10 Years	472	(8.9)	441	(8.1)
>= 10 Years	369	(7.0)	411	(7.6)
Prior Menopausal Hormone Use				
Non-User	2769	(52.1)	2770	(51.0)
< 5 Years	1352	(25.5)	1412	(26.0)
5 - < 10 Years	469	(8.8)	515	(9.5)
>= 10 Years	720	(13.6)	732	(13.5)
Prior Estrogen (E)-alone Use				
Non-User	2872	(54.1)	2891	(53.3)
< 5 Years	1317	(24.8)	1368	(25.2)
5 - < 10 Years	448	(8.4)	494	(9.1)
>= 10 Years	673	(12.7)	676	(12.5)

	CEE N (%)		Placebo N (%)	
Prior E+Progestin Use				
Non-User	5093	(95.9)	5178	(95.4)
< 5 Years	144	(2.7)	158	(2.9)
5 - < 10 Years	42	(0.8)	56	(1.0)
>= 10 Years	31	(0.6)	37	(0.7)
Recency of HRT Use				
Non User	2769	(52.2)	2770	(51.1)
Past, < 5 Yrs	566	(10.7)	586	(10.8)
Past, 5 – 10 Yrs	257	(4.8)	271	(5.0)
Past, > 10 Yrs	1048	(19.7)	1091	(20.1)
Current	669	(12.6)	708	(13.0)
Bilateral Oophorectomy				
No	2973	(60.5)	2917	(58.0)
Yes	1938	(39.5)	2111	(42.0)
Prior Colonoscopy/sigmoidoscopy/flex sig				
None	2606	(54.0)	2609	(53.7)
<5 years ago	1216	(25.2)	1228	(25.3)
>= 5 years ago	1008	(20.9)	1024	(21.1)

* From Chi-square test.

Table 2
Incidence (Annualized Rate) and Characteristics of Colorectal Cancer, According to Hormone Treatment Group

Tumor Characteristics	CEE		Placebo		Hazard Ratio	(95% CI)	P Value
	N	% (rate)	N	% (rate)			
	(N=5310)		(N=5429)				
Invasive colorectal cancer	58	(0.15)	53	(0.14)	1.12	(0.77 – 1.63)	0.55
Colon cancer	53	(0.14)	43	(0.11)	1.26	(0.84 – 1.88)	0.26
Rectal cancer	5	(0.01)	10	(0.03)	0.53	(0.18 – 1.56)	0.25
Histology							
Adenocarcinoma	51	(0.14%)	50	(0.13%)	1.04	(0.71 – 1.54)	0.83
Mucinous & serous	7	(0.02%)	3	(0.01%)	2.44	(0.63 – 9.43)	0.20
Tumor grade							
Missing	2	(0.01%)	2	(0.01%)	ND		
Well differentiated	10	(0.03%)	4	(0.01%)	2.53	(0.79 – 8.07)	0.12
Moderately differentiated	36	(0.10%)	37	(0.10%)	1.00	(0.63 – 1.58)	0.99
Poorly differentiated/Anaplastic	10	(0.03%)	10	(0.03%)	1.03	(0.43 – 2.49)	0.94
Stage of disease							
Localized	19	(0.05%)	19	(0.05%)	1.02	(0.54 – 1.93)	0.95
Regional	34	(0.09%)	24	(0.06%)	1.46	(0.87 – 2.47)	0.15
Distant	5	(0.01%)	10	(0.03%)	0.50	(0.17 – 1.46)	0.21
Lymph node involvement							
missing	7	(0.02%)	7	(0.02%)	ND		
No	29	(0.08%)	27	(0.07%)	1.09	(0.64 – 1.84)	0.76

Tumor Characteristics	CEE		Placebo		Hazard Ratio	(95% CI)	P Value
	N	% (rate)	N	% (rate)			
Yes	22	(0.06%)	19	(0.05%)	1.20	(0.65 – 2.21)	0.57
Cancer location							
Proximal	27	(0.07%)	24	(0.06%)	1.17	(0.67 – 2.03)	0.58
Distal	26	(0.07%)	18	(0.05%)	1.45	(0.79 – 2.64)	0.23
Unknown	0	(0.00%)	1	(<.01%)	ND		
Rectum	5	(0.01%)	10	(0.03%)	0.53	(0.18 – 1.56)	0.25
Tumor size, cm							
	38	(4.1 ± 2.0)	37	(4.0 ± 2.4)			
Missing	20	(0.05%)	17	(0.04%)	ND		
< 3.0	8	(0.02%)	11	(0.03%)	0.78	(0.31 – 1.94)	0.59
3.0 – 3.9	6	(0.02%)	10	(0.03%)	0.62	(0.22 – 1.70)	0.35
4.0 – 5.9	15	(0.04%)	7	(0.02%)	2.15	(0.88 – 5.27)	0.10
>= 6.0	9	(0.02%)	8	(0.02%)	1.18	(0.46 – 3.07)	0.73
Number + lymph nodes							
	49	(1.6 ± 3.3)	44	(0.9 ± 1.8)			
Missing	10	(0.03%)	9	(0.02%)	ND		
None	26	(0.07%)	25	(0.06%)	1.05	(0.61 – 1.82)	0.86
1 – 2	10	(0.03%)	16	(0.04%)	0.65	(0.30 – 1.44)	0.29
>= 3	12	(0.03%)	3	(0.01%)	4.06	(1.15 – 14.40)	0.03

* Cox regression models stratified according to age groups, DM participation and prior colorectal cancer. CaD participation is adjusted as a time-dependent covariate.

Table 3

Incidence (Annualized Rate) of Invasive Colorectal Cancer, According to Baseline Characteristics and Treatment Group

Variable	CEE alone	Placebo	Hazard Ratio ¹ 95% CI	P-value for Interaction ²
<i>no. of women (annualized %)</i>				
Overall	58 (0.15%)	53 (0.14%)	1.12 (0.77,1.63)	
Age at enrollment				0.08
50–59 yr	9 (0.07%)	11 (0.09%)	0.82 (0.34,1.98)	
60–69 yr	24 (0.14%)	30 (0.17%)	0.83 (0.49,1.43)	
70–79 yr	25 (0.29%)	12 (0.13%)	2.11 (1.06,4.21)	
Race or ethnic group				0.40
White	46 (0.16%)	39 (0.13%)	1.20 (0.79,1.85)	
Black	5 (0.09%)	6 (0.10%)	0.92 (0.28,3.02)	
Hispanic	4 (0.18%)	5 (0.22%)	0.66 (0.17,2.56)	
American Indians	1 (0.36%)	0 (0.00%)	ND	
Asian or Pacific Islander	2 (0.36%)	1 (0.18%)	1.04 (0.06,16.60)	
Unknown/Other	0 (0.00%)	2 (0.39%)	ND	
History of polyp removal				0.00³
No	40 (0.13%)	46 (0.15%)	0.87 (0.57,1.33)	
Yes	9 (0.29%)	0 (0.00%)	ND	
Family history of colorectal cancer				0.10
No	41 (0.15%)	45 (0.16%)	0.94 (0.62,1.44)	
Yes	13 (0.23%)	6 (0.10%)	2.16 (0.82,5.72)	
Body mass index				0.09
<25	18 (0.23%)	9 (0.11%)	2.02 (0.91,4.50)	
25–29	19 (0.15%)	18 (0.13%)	1.11 (0.58,2.11)	
>30	21 (0.12%)	26 (0.15%)	0.80 (0.45,1.42)	
Height (cm)				0.03
96.0 – 158.6	26 (0.21%)	12 (0.10%)	2.12 (1.07,4.19)	
158.7 – 163.9	18 (0.15%)	15 (0.12%)	1.27 (0.64,2.52)	
164.0 – 188.3	14 (0.11%)	26 (0.20%)	0.57 (0.29,1.10)	
Waist circumference (cm)				0.03
37.0 – 84.9	22 (0.17%)	11 (0.09%)	2.03 (0.98,4.19)	
85.0 – 96.9	18 (0.15%)	17 (0.13%)	1.14 (0.59,2.22)	
97.0 – 191.6	18 (0.14%)	25 (0.20%)	0.68 (0.37,1.25)	
Smoking status				0.92
Never	33 (0.17%)	28 (0.14%)	1.14 (0.69,1.89)	
Past	20 (0.14%)	19 (0.12%)	1.14 (0.61,2.15)	
Current	5 (0.13%)	6 (0.15%)	0.94 (0.28,3.12)	
Alcohol intake				0.29
None	20 (0.14%)	20 (0.14%)	1.03 (0.55,1.91)	

Variable	CEE alone	Placebo	Hazard Ratio ¹ 95% CI	P-value for Interaction ²
<1 drink/wk	22 (0.17%)	12 (0.09%)	1.86 (0.92,3.76)	0.88
≥ 1 drink/wk	16 (0.15%)	19 (0.17%)	0.96 (0.49,1.89)	
Dietary selenium (mcg/day)				
<74.4	21 (0.16%)	18 (0.14%)	1.22 (0.65,2.29)	0.69
74.5–106.3	18 (0.16%)	13 (0.11%)	1.44 (0.71,2.95)	
>106.3	19 (0.16%)	17 (0.14%)	1.07 (0.55,2.06)	
Treated Diabetes				0.96
Never	52 (0.15%)	46 (0.13%)	1.15 (0.77,1.71)	
Current or past	6 (0.22%)	7 (0.25%)	1.12 (0.36,3.48)	
Use of NSAID drugs				0.78
No	40 (0.16%)	37 (0.14%)	1.11 (0.71,1.74)	
Yes	18 (0.15%)	16 (0.13%)	1.18 (0.60,2.33)	
Prior use of menopausal hormones				0.90
No	32 (0.16%)	30 (0.15%)	1.07 (0.65,1.76)	
Yes	26 (0.14%)	23 (0.11%)	1.17 (0.67,2.05)	
Prior use of oral contraceptives				0.35
No	38 (0.17%)	34 (0.14%)	1.15 (0.72,1.82)	
Yes	20 (0.14%)	19 (0.13%)	1.08 (0.57,2.02)	
Bilateral oophorectomy at baseline				
No	25 (0.12%)	28 (0.13%)	0.89 (0.52,1.52)	
Yes	28 (0.21%)	24 (0.16%)	1.25 (0.72,2.16)	

¹ Cox regression models are stratified according to age groups, DM participation, prior colorectal cancer. CaD participation is adjusted as a time-dependent covariate.

² Test of linear trend is used for age, BMI, height, and waist circumference.

³ p-value for interaction derived from exact test under conditional logistic regression model.