VOLUME 30 · NUMBER 32 · NOVEMBER 10 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Estrogen Plus Progestin and Colorectal Cancer Incidence and Mortality

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Submitted March 8, 2012; accepted July 17, 2012; published online ahead of print at www.jco.org on September 24, 2012.

Supported by Contracts No. N01WH22110, 24152, 32100-2, 32105-6, 32108-9, 32111-13, 32115, 32118-32119, 32122, 42107-26, 42129-32, and 44221 from the National Heart, Lung, and Blood Institute, National Institutes of Health (NIH), US Department of Health and Human Services to the Women's Health Initiative program and by Grant No. NIH:NCI P30CA022453 from Cancer Center Support.

Presented as a poster presentation at the 103rd Annual Meeting of the American Association for Cancer Research, Chicago, IL, March 31-April 4, 2012.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical trial information: NCT00000611.

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0732-183X/12/3032-3983/$20.00

DOI: 10.1200/JCO.2012.42.7732

ABSTRACT

Purpose
During the intervention phase in the Women's Health Initiative (WHI) clinical trial, use of estrogen plus progestin reduced the colorectal cancer diagnosis rate, but the cancers were found at a substantially higher stage. To assess the clinical relevance of the findings, analyses of the influence of combined hormone therapy on colorectal cancer incidence and colorectal cancer mortality were conducted after extended follow-up.

Patients and Methods
The WHI study was a randomized, double-blind, placebo-controlled clinical trial involving 16,608 postmenopausal women with an intact uterus who were randomly assigned to daily 0.625 mg conjugated equine estrogen plus 2.5 mg medroxyprogesterone acetate (n = 8,506) or matching placebo (n = 8,102). Colorectal cancer diagnosis rates and colorectal cancer mortality were assessed.

Results
After a mean of 5.6 years (standard deviation [SD], 1.03 years) of intervention and 11.6 years (SD, 3.1 years) of total follow-up, fewer colorectal cancers were diagnosed in the combined hormone therapy group compared with the placebo group (diagnoses/year, 0.12% *v* 0.16%; hazard ratio [HR], 0.72; 95% CI, 0.56 to 0.94; $P = .014$). Bowel screening examinations were comparable between groups throughout. Cancers in the combined hormone therapy group more commonly had positive lymph nodes (50.5% *v* 28.6%; $P < .001$) and were at higher stage (regional or distant, 68.8% *v* 51.4%; $P = .003$). Although not statistically significant, there was a higher number of colorectal cancer deaths in the combined hormone therapy group (37 *v* 27 deaths; 0.04% *v* 0.03%; HR, 1.29; 95% CI, 0.78 to 2.11; $P = .320$).

Conclusion
The findings, suggestive of diagnostic delay, do not support a clinically meaningful benefit for combined hormone therapy on colorectal cancer.

J Clin Oncol 30:3983-3990. © 2012 by American Society of Clinical Oncology

INTRODUCTION

The Women's Health Initiative (WHI) randomized, placebo-controlled trial evaluating estrogen plus progestin identified more risks than benefits for the use of combined hormone therapy.[1] However, during the intervention phase of the trial, there was a statistically significant 44% lower rate of colorectal cancer diagnoses in the estrogen plus progestin group,[2] a finding in agreement with the preponderance of observational studies.[3] Consequently, review articles,[4,5] position statements,[6-10] and executive summaries[11] of professional societies commonly listed reduction of colorectal cancer risk as a benefit of estrogen plus progestin use.

Despite the general perception of colorectal cancer benefit for combined hormone therapy use, the WHI clinical trial findings raised several questions. The colorectal cancers in the combined hormone therapy group had more lymph node involvement and were diagnosed at a substantially higher stage.[2] In addition, colorectal cancer deaths did not differ in the estrogen plus progestin and placebo groups in an early analysis based on the distribution of 44 deaths.[12] Postintervention follow-up through a mean of 7.9 years found that a lower colorectal cancer diagnosis rate was no longer seen after discontinuation of hormones.[13] Therefore, to assess whether combined hormone therapy is associated with meaningful influence on colorectal cancer, we report updated information on colorectal cancer diagnoses and colorectal mortality through a mean of 11.6 years of follow-up.

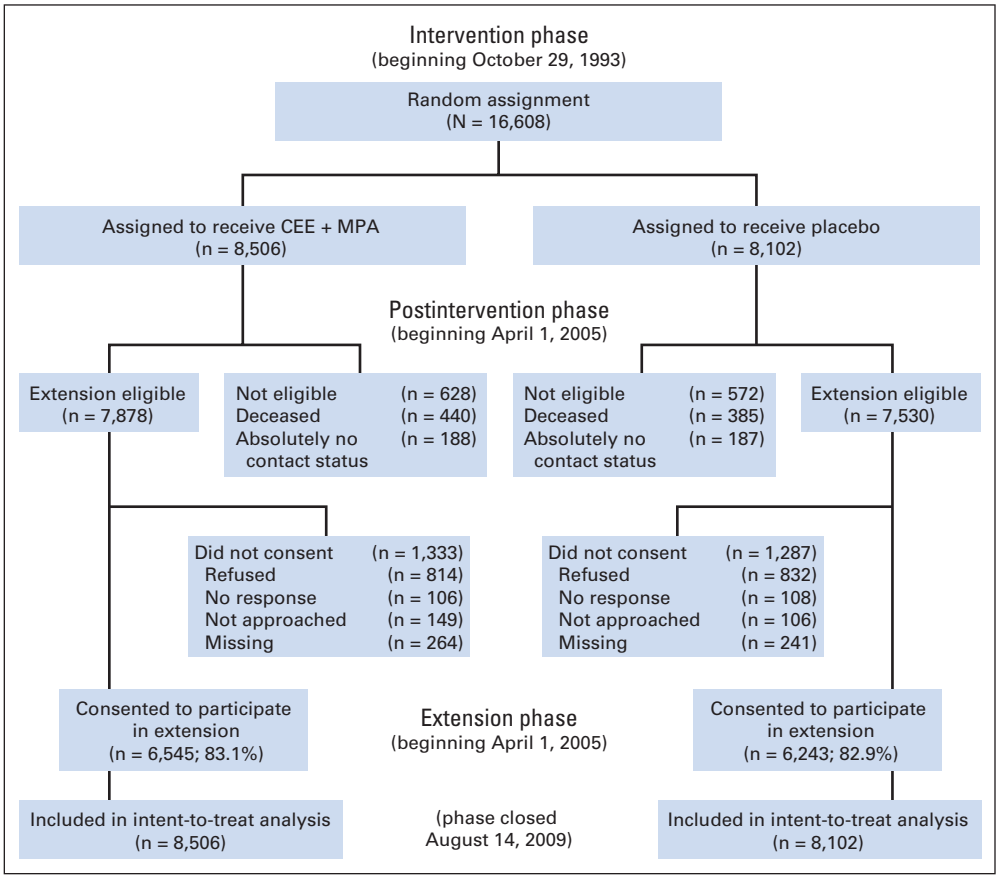

Fig 1. CONSORT diagram. CEE, conjugated equine estrogen; MPA, medroxyprogesterone acetate.

PATIENTS AND METHODS

The WHI trial of estrogen plus progestin randomly assigned 16,608 postmenopausal women to daily conjugated equine estrogens (0.625 mg/d) plus medroxyprogesterone acetate (2.5 mg/d; Prempro, Wyeth-Ayerst, Rouses Point, NY) or placebo at 40 US clinical centers between 1993 and 1998.[1,14] Initially, participants were also randomly assigned to estrogen alone. When published results from the Heart and Estrogen/Progestin Replacement Study (HERS)[15] indicated adherence was not feasible in women with a uterus, the protocol was changed to a 1:1 randomization excluding estrogen alone. The 331 women randomly assigned to estrogen alone were unblinded and reassigned to the estrogen plus progestin group.

The study was approved by institutional review boards at each institution, and all participants signed written informed consent. Study design and implementation have been described previously.[1,14] Eligible women were between 50 and 79 years of age, postmenopausal, with life expectancy of $\geq$ 3 years. Women with prior hysterectomy, any prior breast cancer, or prior colorectal cancer within 10 years were ineligible. Hormone users were eligible after a 3-month washout. Random assignment was performed by the WHI Clinical Coordinating Center by using a computerized permuted block algorithm stratified by clinical center and age group and was implemented at local clinical centers by using a bar code dispensing procedure to ensure participant and staff blinding.

Colorectal cancer diagnoses were elicited semiannually by mail or by telephone questionnaires. Participant self-reports or next-of-kin (proxy) reports of colorectal cancer were verified by centrally trained physician adjudicators at the local clinical centers after medical record review.[16] Final adjudication and coding were performed at the Clinical Coordinating Center by using the Surveillance, Epidemiology, and End Results (SEER) system.[17] Cause of death was based on medical record review by physician adjudicators at the local clinical centers, with final adjudication at the Coordinating Center. Reviewers were blind to randomization allocation.

Colorectal screening was not protocol defined. At 6-month intervals, self-administered questionnaires or structured telephone interviews were used to collect information on the frequency of rectal examinations, fecal occult blood tests, sigmoidoscopy and colonoscopy (asked as one question), and barium enema examinations. Because the clinical centers did not provide comprehensive health care, work-ups related to colorectal cancer diagnosis were made largely by participants' local physicians.

After net harm for estrogen plus progestin use was seen, participants were instructed to stop study medication on July 7, 2002. Follow-up continued according to the protocol through March 31, 2005, the original trial completion date. An extension phase began on April 1, 2005, which required reconsent for additional follow-up. Of 15,408 surviving participants, 12,788 or 83% reconsented. A CONSORT diagram detailing the flow of study participants was published previously[18] and is provided in Figure 1.

Our analyses included patients with invasive colorectal cancer and excluded two patients with squamous cell carcinomas and two with infiltrating ductal carcinomas. Prior reports included 115 cases of colorectal cancer reported after mean follow-up of 5.6 years (standard deviation [SD], 1.3 years)[2] with an additional 74 cases reported after mean follow-up of 7.9 years (SD, 1.4 years).[13] Previously, 44 deaths after colorectal cancer were reported.[12] Now, with a mean follow-up of 11.6 years (SD, 3.1 years) through September 30, 2010, there are 263 colorectal cancers and 90 deaths following colorectal cancer diagnosis. In addition, we report, for the first time (to the best of our knowledge), on deaths after colorectal cancer measured from the date of diagnosis.

The sample size was based primarily on hypothesized coronary heart disease benefit. Colorectal cancer was a designated secondary end point. Results for invasive colorectal cancer incidence, deaths directly attributed to colorectal cancer (deaths from colorectal cancer) and deaths from all causes following colorectal cancer diagnosis (deaths after colorectal cancer) were

Table 1. Invasive Colorectal Cancer Outcomes by Tumor Location and by Study Group

Outcome	Combined Hormone Therapy Group*		Placebo Group		HR†	95% CI	*P*
	No.	% Per Year	No.	% Per Year			
Cancer incidence							
Colorectal cancer (all)	118	0.12	145	0.16	0.72	0.56 to 0.94	.014
Colon cancer‡	103	0.10	129	0.14	0.77	0.59 to 1.01	.059
Rectal cancer	20	0.02	17	0.02	1.16	0.60 to 2.25	.65
Deaths from colorectal cancer§							
Colorectal cancer (all)	37	0.04	27	0.03	1.29	0.78 to 2.11	.32
Colon cancer	30	0.03	25	0.03	1.14	0.67 to 1.94	.67
Rectal cancer	7	0.007	2	0.002	3.11	0.65 to 15.0	.16
Deaths after colorectal cancer¶							
Colorectal cancer (all)	46	0.04	44	0.04	0.96	0.63 to 1.45	.83
Colon cancer	40	0.04	41	0.04	0.89	0.57 to 1.38	.61
Rectal cancer	10	0.01	3	0.003	3.14	0.86 to 11.4	.08

Abbreviation: HR, hazard ratio.
*Follow-up starts at random assignment and denominator includes all participants.
†All analyses stratified by age and random assignment in the dietary modification trial.
‡Six participants have both colon and rectal cancer diagnoses.
§Includes deaths attributed to the cancer.
¶Includes all deaths after the cancer diagnosis irrespective of attributed cause.

assessed with time-to-event methods based on the intent-to-treat principle. The total number of events and the annualized percentages for these outcomes were reported. Analyses included all 16,608 randomly assigned participants.

Hazard ratio (HR) estimation for colorectal cancer diagnoses was based on Cox proportional hazards regression defined relative to the date of random assignment. Stratification was based on 10-year baseline age groups, colorectal cancer history, WHI Dietary Modification trial randomization (intervention, control, or nonparticipant), and calcium and vitamin D trial randomization (active, placebo, or nonparticipant). Nominal 95% CIs are presented for HRs, and all significance levels are two-sided. Thirteen interactions with baseline characteristics were tested. Less than one would be expected to be positive by chance alone. Kaplan-Meier plots were used to display rates of colorectal cancer over time. Cumulative incidence curves were computed and were nearly identical to the Kaplan-Meier estimates; hence, they are not presented. For colorectal cancer diagnosis rate analyses, women who did not reconsent to active follow-up after March 31, 2005, were censored at that time. The original consent permitted continued follow-up for vital status. Vital status information from the National Death Index (NDI) was included for all participants with all mortality information censored on September 30, 2010.

To examine the potential effect of censoring follow-up times for women who did not reconsent to follow-up after March 31, 2005, several secondary analyses were performed, including comparison of reconsent rates by random assignment and adjusting the HR analyses for reconsent status. Adherence was routinely measured by weighing or counting returned pills at the annual visits. Sensitivity analyses for colorectal cancer diagnosis and mortality rates by medication adherence were conducted by using inverse probability weighting analyses. Nonadherence (using $<$ 80% of study pills or initiating nonprotocol hormone therapy) probabilities were estimated by logistic regression models that included baseline variables of age, ethnicity, education, body mass index, smoking, self-reported general health, night sweats, hot flashes, breast tenderness, and treatment assignment; at year 1, breast tenderness, night sweats, and hot flashes, and the inverse of these estimated probabilities were used as the weights in the Cox models for HR estimation.

To facilitate comparison with observational studies, we systematically reviewed the literature (PubMed) from 1970 to December 2011 and identified 10 cohort studies that examined estrogen plus progestin association with colorectal cancer risk. Relative risks across all studies were combined by using a random effects model. The relative risks used were from the multivariable adjusted estimates provided in the original studies.

The study sponsor provided input into the design and conduct of the trial and participated in the review of this report but not in its preparation. The corresponding authors had full access to all data and final responsibility for submitting the report for publication.

RESULTS

Baseline characteristics for the 16,608 initially randomly assigned participants have been published,[1] and characteristics of participants in the two randomly assigned groups were comparable in the initial population and in the reconsenting population of 12,788 women with somewhat more women in the placebo group having a family history of colorectal cancer (Appendix Table A1, online only).

Outcome information was available on 16,560 (99.7%) of the 16,608 originally randomly assigned participants. Survival status was available for 12,430 (97.2%) of 12,788 participants who consented for the extension follow-up and through September 2010 for 3,121 (81.74%) of the remaining 3,820 participants. The mean follow-up was 11.6 years (SD, 3.1 years) with maximum follow-up of 16.5 years.

There were 118 women in the combined hormone therapy group with a diagnosis of invasive colorectal cancer compared with 145 in the placebo group (diagnoses/year, 0.12% *v* 0.16%; HR, 0.72; 95% CI, 0.56 to 0.94; $P = .014$; Table 1 and Fig 2). There were fewer colon cancers in the estrogen plus progestin group (103 *v* 129 cases; 0.10% *v* 0.14%; HR, 0.77; 95% CI, 0.59 to 1.01; $P = .059$). Only 37 rectal cancer cases were diagnosed with no difference between randomization groups (20 *v* 17 cases; 0.02% *v* 0.02%; HR, 1.16; 95% CI, 0.60 to 2.25; $P = .65$). The influence of estrogen plus progestin on the rate of colorectal cancer diagnosis was limited to the intervention period (HR, 0.75; 95% CI, 0.57 to 1.00) because no reduction was seen postintervention (HR, 0.96; 95% CI, 0.67 to 1.39; $P = .83$).

Colorectal cancer incidence results were similar for analyses excluding 54 women with a remote colorectal cancer history (HR, 0.77; 95% CI, 0.60 to 0.98; $P = .033$) and for analyses adjusting for a family history of colorectal cancer (HR, 0.72; 95% CI, 0.56 to 0.94; $P = .014$).

Forty-one percent of participants in each group reported having had colonoscopy or sigmoidoscopy before study entry. The frequency

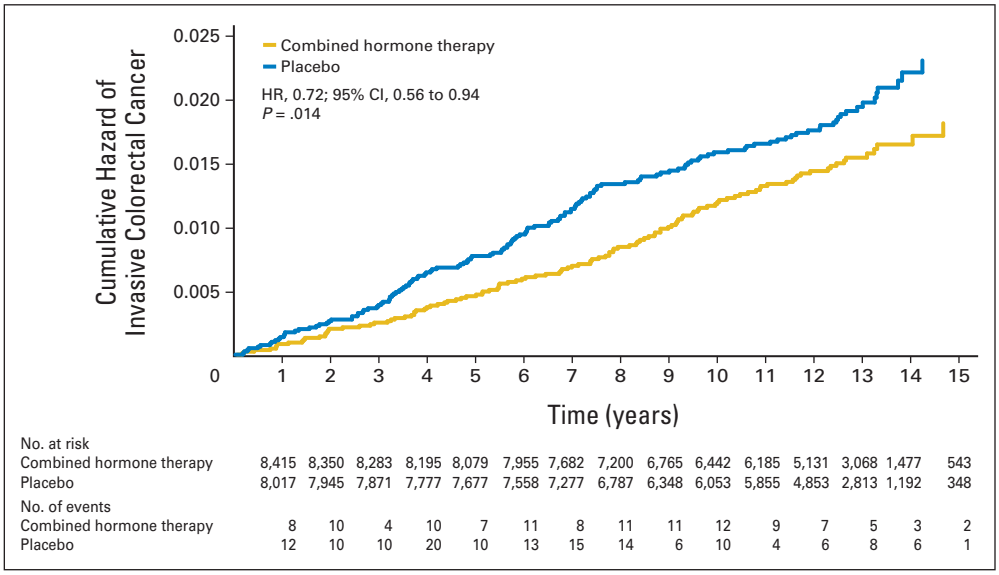

Fig 2. Colorectal cancer incidence by random allocation group. HR, hazard ratio.

of bowel examinations during the study was similar in both randomly assigned groups over time (Appendix Fig A1, online only). During the study course, 67% of participants had at least one colonoscopy or sigmoidoscopy and 67% had at least one fecal occult blood test.

Vaginal bleeding was more common in the combined hormone therapy group (58% *v* 7%; $P < .001$). In the 96 women with vaginal bleeding before colorectal cancer was diagnosed, the mean number of positive lymph nodes (2.5 ± 4.3) was greater than in the 167 women with no such bleeding (1.2 ± 2.5 positive nodes; $P = .014$). The patients with colorectal cancer had similar histology, location, and grade in the two randomly assigned groups. However, patients with colorectal cancer in the hormone group were more likely to have positive lymph nodes (50.5% *v* 28.6%; $P < .001$) and were more likely to have been diagnosed with distant disease (19.3% *v* 6.5%; $P = .003$; Table 2).

Forty-six women who were diagnosed with colorectal cancer in the estrogen plus progestin group died during follow-up compared with 44 in the placebo group (0.04% *v* 0.04%; HR, 0.96; 95% CI, 0.63 to 1.45; $P = .83$; Table 1). Of these, 37 deaths were directly attributed to colorectal cancer in the estrogen plus progestin group compared with 27 in the placebo group (0.04% *v* 0.03%; HR, 1.29; 95% CI, 0.78 to 2.11; $P = .32$; Table 1). Colorectal cancer mortality from random assignment date by study group is depicted in Figure 3. Thus, although there were 27 fewer colorectal cancers diagnosed in the combined hormone therapy group, there were 10 more deaths attributed to the disease. For this reason, an exploratory analysis examined the survival of women from the time of their colorectal cancer diagnosis by random assignment group. Survival after colorectal cancer diagnosis appeared to be greater in the placebo group compared with the combined hormone therapy group, although these differences were not statistically significant (HR, 1.42; 95% CI, 0.92 to 2.18; $P = .11$; Fig 4). The estimated 5-year survival rates were 0.65 (SE, 0.050) for combined hormone therapy and 0.78 (SE, 0.038) for the placebo group.

Of 13 subgroups examined, only smoking status had a nominally significant interaction with the risk of colorectal cancer diagnosis (Appendix Fig A2, online only). Current smokers in the combined hormone therapy group had an increased rate of colorectal cancer diagnosis (HR, 2.65; 95% CI, 0.96 to 7.37) compared with never smokers (HR, 0.83; 95% CI, 0.58 to 1.17; interaction $P = .01$), although the finding is based on only 20 cases among current smokers.

Reconsent status was similar for the combined hormone therapy (76.9%) and placebo groups (77.0%). Adjusting for reconsent status did not change the colorectal cancer incidence (HR, 0.72; 95% CI, 0.56 to 0.94; $P = .014$) or colorectal mortality results (HR, 1.31; 95% CI, 0.80 to 2.15; $P = .29$). Colorectal cancer incidence results were similar when the estimated probability of nonadherence to study medication was used as a weighting factor in the models (HR, 0.73; 95% CI, 0.51 to 1.04; $P = .08$).

In the meta-analyses of 10 cohort studies, estrogen plus progestin use was associated with a modest but statistically significant 14% lower colorectal cancer incidence (HR, 0.86; 95% CI, 0.76 to 0.97; $P < .001$; Table 3).

DISCUSSION

In the WHI randomized, placebo-controlled trial, estrogen plus progestin use was associated with a lower colorectal cancer diagnosis rate. However, the advanced stage of the cancers and the absence of lower colorectal cancer mortality in the hormone group raise concern regarding the clinical relevance of the findings. Because colorectal cancer is the third most common cancer in women in the United States,[27,28] it is important to determine the influence of the still commonly used estrogen plus progestin therapy[19] on the clinical course of this disease.

Although there were fewer colorectal cancers in the combined hormone therapy group, the cancers were diagnosed at a more advanced stage. Because screening bowel examinations and grade of cancers were similar across randomization groups, diagnostic delay represents a potential contributor to the difference in diagnosis rate. In any event, because colorectal cancer presents with localized disease in only approximately 40% of cases and has a 5-year risk of death of approximately 30% for all newly diagnosed cases,[4] it is improbable

Table 2. Characteristics of Invasive Colorectal Cancer Cases, According to Treatment Group*

Characteristic	Combined Hormone Therapy Group				Placebo Group				P†
	No. of Patients	%	Mean	SD	No. of Patients	%	Mean	SD	
Invasive colorectal cancer	118	1.4			145	1.8			
Tumor size, cm	(n = 85)		4.3	2.3	(n = 108)		4.2	2.3	.751
≤ 3.9	38	44.7			54	50.0			.465
4.0-5.9	25	29.4			34	31.5			
≥ 6.0	22	25.9			20	18.5			
No. of positive lymph nodes	(n = 90)		2.3	4.1	(n = 130)		1.1	2.5	.011
None	42	46.7			91	70.0			.007
1	16	17.8			13	10.0			
2-3	15	16.7			13	10.0			
≥ 4	17	18.9			13	10.0			
Lymph node involvement	(n = 101)				(n = 133)				
No	50	49.5			95	71.4			< .001
Yes	51	50.5			38	28.6			
Stage of disease‡	(n = 109				(n = 138)				
Localized	34	31.2			67	48.6			.003
Regional	54	49.5			62	44.9			
Distant	21	19.3			9	6.5			
Morphologic grade	(n = 100)				(n = 130)				
Well differentiated	6	6.0			14	10.8			.173
Moderately differentiated	68	68.0			91	70.0			
Poorly differentiated	26	26.0			22	16.9			
Anaplastic	0	0.0			3	2.3			
Location of cancer§	(n = 109)				(n = 117)				
Proximal	56	51.4			56	47.9			.519
Distal	31	28.4			31	26.5			
Rectum	22	20.2			30	25.6			
Histologic features	(n = 111)				(n = 141)				
Adenocarcinoma, not otherwise specified	66	59.5			92	65.2			.134
Adenocarcinoma in adenomatous polyp	7	6.3			15	10.6			
Adenocarcinoma in villous adenoma	6	5.4			2	1.4			
Adenocarcinoma in tubulovillous adenoma	13	11.7			16	11.3			
Mucin secreting	4	3.6			5	3.5			
Signet ring cell	0	0.0			2	1.4			
Medullary	1	0.9			0	0.0			
Other	14	12.6			9	6.4			

Abbreviation: SD, standard deviation.
*For each variable, "n" is the number of women for whom data were available.
†*P* values were calculated by a two-sample *t* test for continuous variables or a χ^2 or Fisher's exact test for categorical variables.
‡Difference between number with node involvement and number with stage relates to those with distant stage not routinely having resection of the primary cancer to provide node assessment.
§The cancer site was classified as proximal (cecum, ascending colon, hepatic flexure, and transverse colon), distal (splenic flexure, descending colon, and sigmoid colon), or rectal (rectosigmoid junction and rectum).

that an intervention that reduced colorectal cancer incidence by 44% during active use would not have some favorable influence on colorectal mortality after 11.9 years of follow-up. In contrast, measured from random assignment, there is no suggestion of lower colorectal cancer mortality for women in the combined hormone therapy group.

Most colorectal cancers are not identified by bowel screening examinations, but patients commonly present with nonspecific findings, including abdominal pain and change in bowel habits that lead to diagnostic work-up.[29,30] Because receiving an alternative diagnosis is associated with delay in the diagnosis of colorectal cancer,[31] the association seen in the trial between antecedent vaginal bleeding and increased lymph node status suggests that attention to vaginal bleeding may have delayed assessment of the colorectal problem.

It is unknown whether implementing a prospective bowel screening program would identify the same number of colorectal cancers in women using estrogen plus progestin but find them at an earlier stage, which suggests clinical benefit or, alternatively, would find substantially more colorectal cancers earlier in combined hormone therapy users, which suggests diagnostic delay.

Early observational case-control studies, which uncommonly separated influence of estrogen alone from estrogen plus progestin use, associated menopausal hormone therapy use with lower colorectal cancer diagnosis rates.[32] Several cohort studies have specifically evaluated the association between use of estrogen plus progestin and colorectal cancer.[3,12,19-27] In both a meta-analysis of eight such studies[27] and this meta-analysis incorporating 10 studies, a modest but statistically significant lower colorectal cancer incidence is associated with combined hormone therapy use. Such results agree with the current randomized clinical trial results regarding diagnosis rates but do not address the question of clinical relevance of the findings, since

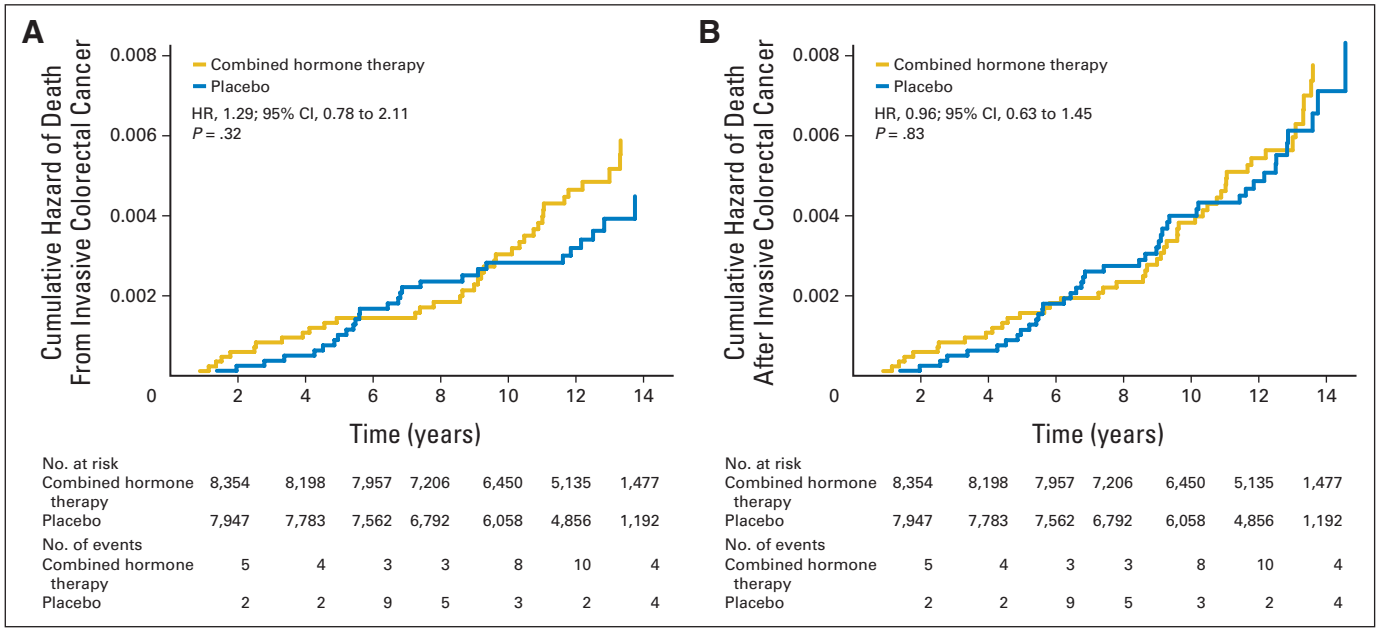

Fig 3. (A) Risk of death from invasive colorectal cancer and (B) risk of death after invasive colorectal cancer from date of random allocation by randomly assigned group. HR, hazard ratio.

influence on colorectal mortality was not reported in the observational studies.

Four prior studies examined postmenopausal hormone therapy and survival measured from colorectal cancer diagnosis date and provided mixed results. In three studies,[33-35] between 36% and 41% fewer cancer-related deaths were seen after colorectal cancer diagnosis in recent hormone users. In contrast, Newcomb et al[36] found that neither estrogen alone nor estrogen plus progestin users had a lower colorectal cancer mortality compared with nonusers. Of the three positive observational studies, two did not adjust for screening[33,34] and one adjusted for stage,[35] potentially adjusting away an adverse effect of stage on combined hormone therapy use. In this randomized trial, median survival after the date of colorectal cancer diagnosis in the combined hormone therapy group was about 2 years shorter than that in the placebo group. In the WHI randomized clinical trial evaluating estrogen alone, survival in the hormone and placebo groups measured from diagnosis date was similar.[37] Currently, there is no compelling explanation for divergent survival results after colorectal cancer seen between most observational studies and the randomized trials.

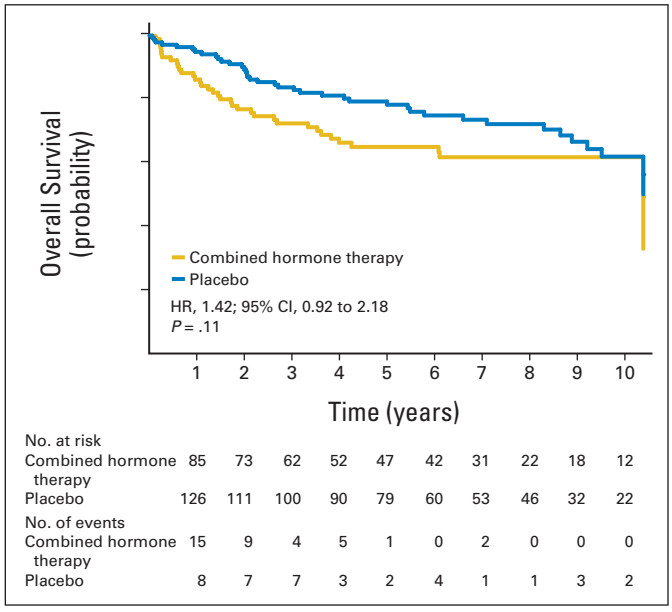

Fig 4. Overall survival after colorectal cancer diagnosis by random allocation group. HR, hazard ratio.

HERS evaluated the same estrogen plus progestin regimen used in the WHI trial in 2,763 postmenopausal women with or at risk for coronary disease. Fewer colorectal cancers were diagnosed during the intervention period in the hormone therapy group, but the difference was not statistically significant.[38]

Smoking status was the one subgroup with a significant interaction in which increased colorectal cancer incidence was seen with estrogen plus progestin use. An association between colorectal neoplasia and cigarette smoking has been described,[39,40] particularly for rectal cancers.[41] Our findings, taken together with the increased lung cancer mortality risk previously described in this trial,[42] suggest that smokers who use estrogen plus progestin may be at increased risk for adverse cancer outcomes.

Study strengths include the randomized double-blind trial design, the large and diverse study population, serial assessment of bowel screening, long duration of follow-up, and central adjudication of cancers. Limitations include the study medication discontinuation rate, the limited number of colorectal cancer deaths, and absence of information on cancer therapy. However, therapy is fairly uniform by stage with surgery only for localized disease and one commonly used adjuvant chemotherapy regimen for node-positive disease.[43]

Despite concerns raised by prior colorectal cancer findings in this trial,[2,12] position statements[6-10] and executive summaries[11] of professional societies continue to list reduction of colorectal cancer risk as a

Table 3. Meta-Analyses: Cohort Studies of Estrogen Plus Progestin Association With Colorectal Cancer Risk

Study	Sample Size	No. of Patients	Outcome	Follow-Up (years)	RR	95% CI
Risch and Howe[19]	32,973	464	CRC	15	1.07	0.58 to 1.98
Persson et al[20]	22,597	233	CRC	13	0.60	0.38 to 0.95
Pukkala et al[21]	94,505	83	CRC	3.2	0.85	0.64 to 1.12
Tannen et al[22]	18,462	N/A	CRC	5.5	0.56	0.36 to 0.88
Green et al[23]	N/A	383	CRC	7.4	0.83	0.73 to 0.94
Johnson et al[24]	56,733	717	CRC	14	0.78	0.60 to 1.02
Hildebrand et al[25]	67,412	776	CRC	13.2	0.93	0.70 to 1.23
Henderson et al[26]	56,864	442	Invasive colon cancer	11	0.71	0.48 to 1.06
Prentice et al[12]	32,084	175	CRC	5.5	1.15	0.74 to 1.79
Tsilidis et al[27]	136,275	1,186	CRC	9	0.94	0.77 to 1.14
Overall	517,915				0.86	0.76 to 0.97

Abbreviations: CRC, colorectal cancer; N/A, not applicable; RR, relative risk.

benefit of estrogen plus progestin use. Our results suggest that this assessment, with its potential for broad influence on clinical practice, should be re-evaluated.

In the WHI randomized trial, a lower rate of colorectal cancer diagnosis with estrogen plus progestin use was seen. However, the cancers were diagnosed at a more advanced stage, and no suggestion of reduced colorectal cancer mortality emerged with extended follow-up. These findings, in a cancer that can run a fatal course if there is a delay in diagnosis,[4,27,28] do not support a clinically meaningful benefit for use of estrogen plus progestin in colorectal cancer. Future studies of estrogen plus progestin use and colorectal cancer should go beyond incidence analyses to address influence on tumor characteristics, stage, and colorectal cancer mortality.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** Rowan T. Chlebowski, AstraZeneca (C), Novartis (C), Amgen (C), Pfizer (C) **Stock Ownership:** None **Honoraria:** Rowan T. Chlebowski, AstraZeneca, Novartis, Amgen, Pfizer; Ross L. Prentice, Wyeth Ayerst **Research Funding:** Rowan T. Chlebowski, Amgen **Expert Testimony:** None **Other Remuneration:** None

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Provision of study materials or patients: Michael S. Simon, Rowan T. Chlebowski, Jean Wactawski-Wende
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Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors

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