ORIGINAL ARTICLE

Estrogen plus Progestin and Colorectal Cancer in Postmenopausal Women

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ABSTRACT

BACKGROUND

Although the Women's Health Initiative (WHI) trial of estrogen plus progestin in postmenopausal women identified more overall health risks than benefits among women in the hormone group, the use of estrogen plus progestin was associated with a significant decrease in the risk of colorectal cancer. We analyzed features of the colorectal cancers that developed and their relation to the characteristics of the participants.

METHODS

In the WHI trial, 16,608 postmenopausal women who were 50 to 79 years of age and had an intact uterus were randomly assigned to a combination of conjugated equine estrogens (0.625 mg per day) plus medroxyprogesterone acetate (2.5 mg per day) or placebo. The main outcome measures were the incidence, stages, and types of colorectal cancer, as determined by blinded central adjudication.

RESULTS

There were 43 invasive colorectal cancers in the hormone group and 72 in the placebo group (hazard ratio, 0.56; 95 percent confidence interval, 0.38 to 0.81; P=0.003). The invasive colorectal cancers in the hormone group were similar in histologic features and grade to those in the placebo group but with a greater number of positive lymph nodes (mean ±SD, 3.2±4.1 vs. 0.8±1.7; P=0.002) and were more advanced (regional or metastatic disease, 76.2 percent vs. 48.5 percent; P=0.004). In exploratory analyses, women in the hormone group with antecedent vaginal bleeding had colorectal cancers with a greater number of positive nodes than women in the hormone group who did not have vaginal bleeding (3.8±4.3 vs. 0.7±1.5 nodes, P=0.006).

CONCLUSIONS

Relatively short-term use of estrogen plus progestin was associated with a decreased risk of colorectal cancer. However, colorectal cancers in women who took estrogen plus progestin were diagnosed at a more advanced stage than those in women who took placebo.

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Colorectal cancer, the second leading cause of death due to cancer in the United States,[1] has been the focus of several randomized trials of chemoprevention,[2] which have shown that calcium,[3] celecoxib,[4] aspirin,[5] and sulindac[6,7] inhibit the recurrence or development of colorectal polyps. The bile acid ursodiol was reported to reduce the incidence of colonic dysplasia or cancer in a prospective study of 52 patients with ulcerative colitis and primary sclerosing cholangitis.[8] Despite these advances, no evidence of a reduction in the risk of colorectal cancer has yet been provided for any intervention in a healthy population.[2]

In observational studies, postmenopausal hormone therapy has been associated with a reduced incidence of colorectal cancer[9-11] and a lowered risk of death from the disease.[12] These studies have generally involved women who took only estrogen or such women together with women who took estrogen plus progestin. A meta-analysis of 18 studies involving postmenopausal women showed a 20 percent reduction in the incidence of colorectal cancers among women who had ever taken hormones and a 34 percent reduction among women who were taking them at the time of the study, as compared with women who had never taken hormones.[13] However, the findings of this analysis have not been confirmed in a randomized trial, nor have the characteristics of the colorectal cancers in the women who took postmenopausal hormones been detailed.

In 2002, the Women's Health Initiative (WHI) reported data from a randomized trial that compared estrogen plus progestin with placebo in postmenopausal women. Although the trial identified more risks with hormone use than benefits, the combination of estrogen plus progestin was found to be associated with a significant decrease in the incidence of colorectal cancer.[14] In the current report, we provide updated information on the effect of estrogen plus progestin on the risk of colorectal cancer and assess the features of the colorectal cancers that have occurred in the WHI trial. We also compare the features of colorectal cancers that developed in women who received active treatment with those in women who received placebo.

METHODS

STUDY DESIGN

In the WHI trial of estrogen plus progestin, 16,608 postmenopausal women at 40 clinical centers were randomly assigned to a study group between 1993 and 1998.[15] The study was approved by the human subjects committee at each institution. Study participants were largely recruited by mass mailings and announcements in the media.[16] Women were eligible if they were between 50 and 79 years of age at entry into the study, were postmenopausal, and provided written informed consent. Women who had previously undergone a hysterectomy or who had a history of breast cancer or medical conditions likely to result in death within three years were excluded. Women with a history of hormone use were eligible after a three-month washout period before base-line assessment. Women who had a history of colorectal cancer (diagnosed more than 10 years previously) or of resection of a colorectal polyp were eligible if they met all the other eligibility criteria.

A global index combining the rates of outcomes anticipated to be influenced by the use of estrogen and progestin was prospectively developed to facilitate monitoring by the data and safety monitoring board and to serve as a supplemental end point for the assessment of overall risk and benefit. The global index included the rates of coronary heart disease, stroke, endometrial cancer, pulmonary embolus, hip fracture, invasive breast cancer, colorectal cancer, and death.

The WHI trial of estrogen plus progestin was a randomized, double-blind, placebo-controlled trial in which conjugated equine estrogens (0.625 mg per day) plus medroxyprogesterone acetate (2.5 mg per day) administered in a single tablet (Prempro, Wyeth–Ayerst) were compared with an identical-appearing placebo. Randomization by the WHI clinical coordinating center was implemented locally by means of a distributed data base and involved the use of medication bottles with unique bar codes for blinded dispensing in the clinic.

Women in this trial could also participate in the WHI trial of calcium plus vitamin D, the WHI trial of dietary modification, or both; 60 percent of the participants entered the former, and 20 percent entered the latter. Equal proportions of women in the estrogen-plus-progestin and placebo groups participated in the trial of calcium plus vitamin D.

FOLLOW-UP

Follow-up procedures have been described previously.[15,17] Information on clinical outcomes was initially obtained by means of self-administered questionnaires or structured telephone interviews at six-month intervals. Local, trained physician ad-

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Table 1. Characteristics of the Participants at Base Line, According to Treatment Group.*

Characteristic	Estrogen plus Progestin† (N=8506)	Placebo (N=8102)	P Value‡
Age at screening — total no.	8506	8102	0.39
Mean — yr	63.2±7.1	63.3±7.1	
50–59 yr — no. (%)	2839 (33.4)	2683 (33.1)	
60–69 yr — no. (%)	3853 (45.3)	3657 (45.1)	
70–79 yr — no. (%)	1814 (21.3)	1762 (21.7)	
Race or ethnic group — total no.	8506	8102	0.33
White — no. (%)	7140 (83.9)	6805 (84.0)	
Black — no. (%)	549 (6.5)	575 (7.1)	
Hispanic — no. (%)	472 (5.5)	416 (5.1)	
American Indian — no. (%)	26 (0.3)	30 (0.4)	
Asian or Pacific Islander — no. (%)	194 (2.3)	169 (2.1)	
Unknown — no. (%)	125 (1.5)	107 (1.3)	
Education — total no.	8460	8044	0.19
Primary school (≤8 yr) — no. (%)	202 (2.4)	177 (2.2)	
Some high school — no. (%)	373 (4.4)	362 (4.5)	
High-school diploma or equivalent — no. (%)	1614 (19.1)	1608 (20.0)	
Some education after high school — no. (%)	3356 (39.7)	3059 (38.0)	
College or postgraduate degree — no. (%)	2915 (34.5)	2838 (35.3)	
Colon disease			
First-degree relatives with colorectal cancer — total no.	7602	7227	0.004
0 — no. (%)	6661 (87.6)	6202 (85.8)	
1 — no. (%)	834 (11.0)	897 (12.4)	
≥2 — no. (%)	107 (1.4)	128 (1.8)	
History of polyp removal — total no.	7532	7447	0.95
Yes — no. (%)	538 (7.1)	530 (7.1)	
Ulcerative colitis or Crohn's disease — total no.	8387	7977	0.14
Yes — no. (%)	82 (1.0)	61 (0.8)	
History of colorectal cancer — total no.	8435	8036	0.32
Yes — no. (%)	24 (0.3)	30 (0.4)	
Diabetes — total no.	8501	8097	
Current or past — no. (%)	488 (5.7)	471 (5.8)	0.84
Treatment (pills or shots) — no. (%)	374 (4.4)	360 (4.4)	0.88
Body-mass index — total no.	8470	8050	0.66
Mean	28.5±5.8	28.5±5.9	
<25 — no. (%)	2579 (30.4)	2479 (30.8)	
25–29 — no. (%)	2992 (35.3)	2834 (35.2)	
≥30 — no. (%)	2899 (34.2)	2737 (34.0)	
Waist circumference — total no.	8482	8075	0.82
Mean	88.0±13.7	88.0±13.8	
≤88 cm — no. (%)	4705 (55.5)	4471 (55.4)	
>88 cm — no. (%)	3777 (44.5)	3604 (44.6)	
Hemoglobin — total no.	8503	8102	0.99
Mean — g/dl	13.6±1.3	13.6±1.8	

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Table 1. (Continued.)

Characteristic	Estrogen plus Progestin† (N=8506)	Placebo (N=8102)	P Value‡
Physical activity — total no.	7670	7596	0.80
None — no. (%)	1427 (18.6)	1356 (17.9)	
>0–3.75 MET/wk — no. (%)	1501 (19.6)	1519 (20.0)	
>3.75–8.75 MET/wk — no. (%)	1355 (17.7)	1352 (17.8)	
>8.75–17.5 MET/wk — no. (%)	1648 (21.5)	1634 (21.5)	
>17.5 MET/wk — no. (%)	1739 (22.7)	1735 (22.8)	
Use of nonsteroidal antiinflammatory drugs — total no.	8506	8102	0.20
Yes — no. (%)	2447 (28.8)	2404 (29.7)	
Ibuprofen — no. (%)	918 (10.8)	900 (11.1)	0.51
Prescribed agent — no. (%)	401 (4.7)	390 (4.8)	0.76
Aspirin (≥100 mg/day) — no. (%)	1390 (16.3)	1375 (17.0)	0.28
Use of acetaminophen — total no.	8506	8102	0.37
Yes — no. (%)	847 (10.0)	841 (10.4)	
Daily dietary intake			
Energy — total no.	8213	7836	0.29
Mean — kcal	1554.7±599.1	1544.8±588.2	
Energy from fat — total no.	8213	7836	0.29
Mean — % of intake	34.4±8.4	34.3±8.4	
Fiber — total no.	8213	7836	0.92
Mean — g	15.0±6.5	15.0±6.6	
Selenium — total no.	8213	7836	0.67
Mean — μg	87.7±37.4	87.5±37.3	
Red meat — total no.	8155	7776	0.25
Mean — servings	0.56±0.50	0.55±0.50	
Fruits and vegetables — total no.	8213	7836	0.56
Mean — servings	3.4±2.0	3.4±2.0	
Daily use of vitamins and supplements — total no.	8506	8102	
Multivitamin — no. (%)	3035 (35.7)	2855 (35.2)	0.55
Calcium — no. (%)	4149 (48.8)	4018 (49.6)	0.30
Vitamin D — no. (%)	3678 (43.2)	3489 (43.1)	0.81
Selenium — no. (%)	2674 (31.4)	2621 (32.4)	0.21
Current alcohol use — total no.	8403	8035	0.15
None — no. (%)	2399 (28.4)	2318 (28.8)	
<1 drink/wk — no. (%)	2844 (34.2)	2630 (32.7)	
≥1 drink/wk — no. (%)	3160 (37.4)	3087 (38.4)	
Smoking status — total no.	8420	7994	0.84
Never — no. (%)	4178 (49.6)	3999 (50.0)	
Past — no. (%)	3362 (39.9)	3157 (39.5)	
Current — no. (%)	880 (10.5)	838 (10.5)	
Current or prior use of oral contraceptives — total no.	8506	8102	0.24
Yes — no. (%)	3693 (43.4)	3444 (42.5)	

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Table 1. (Continued.)

Characteristic	Estrogen plus Progestin† (N=8506)	Placebo (N=8102)	P Value‡
Prior use of hormones during menopause — total no.	8506	8101	0.30
None — no. (%)	6277 (73.8)	6020 (74.3)	
<5 yr — no. (%)	1539 (18.1)	1470 (18.1)	
5–9 yr — no. (%)	427 (5.0)	356 (4.4)	
≥10 yr — no. (%)	263 (3.1)	255 (3.1)	
Prior colonoscopy, sigmoidoscopy, or flexible sigmoidoscopy — total no.	7626	7568	0.67
No — no. (%)	4528 (59.4)	4440 (58.7)	
Yes — no. (%)	3098 (40.6)	3128 (41.3)	
<5 yr ago — no. (%)	1830 (24.0)	1847 (24.4)	
≥5 yr ago — no. (%)	1255 (16.5)	1269 (16.8)	

* For each variable, the number of women for whom data were available is given as the total number. Plus–minus values are means ±SD. Because of rounding, not all percentages total 100. MET denotes metabolic equivalents.
† This group included 331 women who had previously been randomly assigned to estrogen only and who were reassigned to estrogen plus progestin after a protocol change, as previously described.[8]
‡ P values were calculated by a two-sample t-test for continuous variables or a chi-square or Fisher's exact test for categorical variables.

judicators reviewed medical records and pathology reports from cases of identified colorectal cancer. Instances of colorectal cancer were then confirmed by blinded adjudication at the clinical coordinating center and coded with the use of the Surveillance, Epidemiology, and End Results system.[18]

The frequency of bowel examinations was not defined by the protocol. Self-administered questionnaires or structured telephone interviews were used every six months to monitor the frequencies of rectal examination, fecal occult-blood testing, sigmoidoscopy and colonoscopy (asked as one question), and barium enema examination. Information concerning the duration and severity of vaginal bleeding was also collected every six months. Symptoms of bloating or gas, constipation, diarrhea, and abdominal pain or discomfort were ascertained at base line and after one year. With the exception of the above-mentioned practices, the participating clinical centers did not provide comprehensive health care. Decisions regarding the workup related to the diagnosis of colorectal cancer were made almost exclusively by the women's own local physicians.

A blood specimen was obtained from all the women after an overnight, eight-hour fast at base line and at the first annual visit. Serum specimens were frozen at −70°C and shipped to the WHI central storage facility. A randomly selected sample (8.6 percent) of the blood specimens obtained at both times was analyzed for serum levels of glucose and insulin. The random-sampling procedure was stratified according to age, clinical center, hysterectomy status, and race or ethnic group (to oversample minority women). Serum insulin was measured in a blinded fashion by means of a stepwise, sandwich enzyme-linked immunosorbent assay[19] by Medical Research Laboratories.

TERMINATION OF THE STUDY

After a mean follow-up of 5.2 years, the WHI data and safety monitoring board recommended stopping the trial because the relative risk of breast cancer exceeded the predefined stopping boundary and because the overall risk of adverse outcomes (as measured by the global index) exceeded the benefits of treatment. At that time (when outcomes had been identified through April 2002), 112 colorectal cancers had been reported after local adjudication.[15] The current report is based on a mean follow-up of 5.6 years and 122 centrally adjudicated colorectal cancers, which were diagnosed before July 8, 2002, the date participants were instructed to discontinue their study medication.

STATISTICAL ANALYSIS

Primary results were assessed with time-to-event methods based on the intention-to-treat principle.

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Table 2. Annualized Rate of Colorectal Cancer, According to Treatment Group.*

Variable	Estrogen plus Progestin (N=8506)	Placebo (N=8102)	Hazard Ratio (95% CI)	P Value
	no. of women (annualized %)			
Colorectal cancer	48 (0.10)	74 (0.16)	0.61 (0.42–0.87)	0.007
Invasive colorectal cancer	43 (0.09)	72 (0.16)	0.56 (0.38–0.81)	0.003
Colon cancer	35 (0.07)	61 (0.14)	0.54 (0.36–0.82)	0.004
Rectal cancer	8 (0.02)	11 (0.02)	0.66 (0.26–1.64)	0.37

* The mean follow-up time was 67.8 months in the estrogen-plus-progestin group and 66.8 months in the placebo group. Annualized percentages were calculated according to treatment group as the percentage of women with an event, divided by total follow-up time in years. Hazard ratios and P values were calculated with the use of Cox proportional-hazards models, stratified according to age, presence or absence of a history of colorectal cancer, and randomization group in the trials of dietary modification and calcium and vitamin D. CI denotes confidence interval.

Comparisons of rates of cancer are presented as hazard ratios, nominal 95 percent confidence intervals, and Wald z-statistic P values from Cox proportional-hazards models, stratified according to age and randomization in the WHI trial of dietary modification, the WHI trial of calcium and vitamin D, or both trials. Since participants in the calcium and vitamin D trial were randomly assigned to a study group in that trial one to two years after their entry into the hormone trial, adjustment for participation in the calcium and vitamin D trial was based on the randomization date in that trial as a time-dependent covariate. No adjustments were made for multiple analyses over time, since the incidence of colorectal cancer had little direct influence on the decision to stop the trial. However, we included a Bonferroni-adjusted 95 percent confidence interval, adjusted for seven end points, as indicated in the monitoring plan.

Kaplan–Meier plots were used to analyze the rates of colorectal cancer over time. Potential effects of base-line characteristics of the participants, including recognized risk factors for colorectal cancer, were assessed in expanded proportional-hazard models that included the designated risk factor and randomization assignment (as the main effects) and the interaction between them. P values for possible interactions were computed with likelihood-ratio tests, and models with and without the interaction term were compared. Women with missing values for the risk factor in a given analysis were excluded from the analysis. Fourteen subgroup comparisons were performed; the results of 11 (all but those in the subgroups based on prior use of oral contraceptives, estrogen alone, or estrogen plus progestin) are provided. Because 14 comparisons were conducted, fewer than 1 of the comparisons would be expected to yield a significant result at the level of $P<0.05$ by chance alone. P values for mean differences in the results of blood analyses according to treatment group were computed with the use of two-sample t-tests. A global index, described above, was used to summarize net benefits versus net risks in the entire cohort and selected subgroups.

RESULTS

The average follow-up period was 5.6 years; the maximum was 8.6 years. Outcome information obtained through January 31, 2003, was available for 15,931 of the 16,608 participants (95.9 percent), and survival status was known for 16,067 (96.7 percent). As previously described,[15] 42 percent of the women in the estrogen-plus-progestin group and 38 percent of those in the placebo group stopped taking their study medication for some period. Drop-ins (women who reported off-protocol use of postmenopausal hormones) constituted 6.2 percent of the hormone group and 10.7 percent of the placebo group.

Age, level of education, body-mass index, presence or absence of a history of polyp removal, presence or absence of diabetes, use or nonuse of nonsteroidal antiinflammatory medication, hemoglobin level, use or nonuse of calcium and vitamin D supplements, dietary variables, and level of physical activity were similar in the two groups (Table 1). More women in the placebo group than in the hormone group had first-degree relatives with colorectal cancer (14.2 percent vs. 12.4 percent, P=0.004).

According to intention-to-treat analyses, women in the hormone group had fewer colorectal cancers

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of all histologic types than women in the placebo group (48 vs. 74; hazard ratio, 0.61; 95 percent confidence interval, 0.42 to 0.87; P=0.007) (Table 2). Of the 122 colorectal cancers, 3 in the hormone group and 1 in the placebo group were stage 0 (carcinoma in situ). The 122 cancers also included 1 squamous-cell carcinoma (in the placebo group) and 2 carcinoids (in the hormone group). The analyses were limited to the remaining 115 invasive colorectal cancers (Table 2). There were 43 cases of invasive colorectal cancer in the hormone group and 72 in the placebo group (hazard ratio, 0.56; 95 percent confidence interval, 0.38 to 0.81; P=0.003). The Bonferroni 95 percent confidence interval for this comparison (adjusted for seven outcomes) was 0.33 to 0.94. Kaplan–Meier plots of the cumulative hazard for colorectal cancer according to treatment group are shown in Figure 1.

Since the number of first-degree relatives with a history of colorectal cancer differed significantly between the two groups, we calculated the hazard ratio for colorectal cancer in the hormone group, as compared with the placebo group, after adjustment for this factor and found it to be 0.49 (95 percent confidence interval, 0.32 to 0.73; P=0.001). Exclusion of the 54 women with a history of colorectal cancer gave similar results (hazard ratio in the hormone group, 0.58; 95 percent confidence interval, 0.40 to 0.85; P=0.005).

There were 35 cases of cancer of the colon in the hormone group and 61 cases in the placebo group (hazard ratio, 0.54; 95 percent confidence interval, 0.36 to 0.82; P=0.004). There were 8 cases of rectal cancer in the hormone group and 11 in the placebo group (hazard ratio, 0.66; 95 percent confidence interval, 0.26 to 1.64; P=0.37).

The invasive colorectal cancers in the two groups were similar in location, tumor grade, and histologic features (Table 3). There were more colorectal cancers with lymph-node involvement in the hormone group than in the placebo group (59.0 percent vs. 29.4 percent, P=0.003). In addition, the number of positive nodes was greater in the hormone group than in the placebo group (3.2±4.1 vs. 0.8±1.7, P=0.002), and the stage at diagnosis was more advanced in the hormone group (rate of regional or metastatic disease, 76.2 percent, vs. 48.5 percent in the placebo group; P=0.004).

The reduction in the risk of colorectal cancer in the hormone group was due mainly to a decrease in the risk of local, rather than regional or metastatic, disease (hazard ratio for local disease, 0.26; 95 percent confidence interval, 0.13 to 0.53; P<0.001; hazard ratio for regional or metastatic disease, 0.87; 95 percent confidence interval, 0.54 to 1.41; P=0.57). However, even within the category of regional or metastatic disease, the cancers in the hormone group were associated with a greater number of positive nodes than the corresponding types of cancer in the placebo group (3.6±4.2 vs. 1.6±2.1 nodes, P=0.012). There were nine deaths due to colorectal cancer in the hormone group and eight in the placebo group.

The frequency of bowel examinations in the two groups did not differ significantly at any time (Fig. 2). Each year, about 8 to 12 percent of the study participants underwent sigmoidoscopy or colonoscopy, and nearly twice that number underwent a rectal examination, guaiac-based fecal occult-blood testing, or both. During the course of the study,

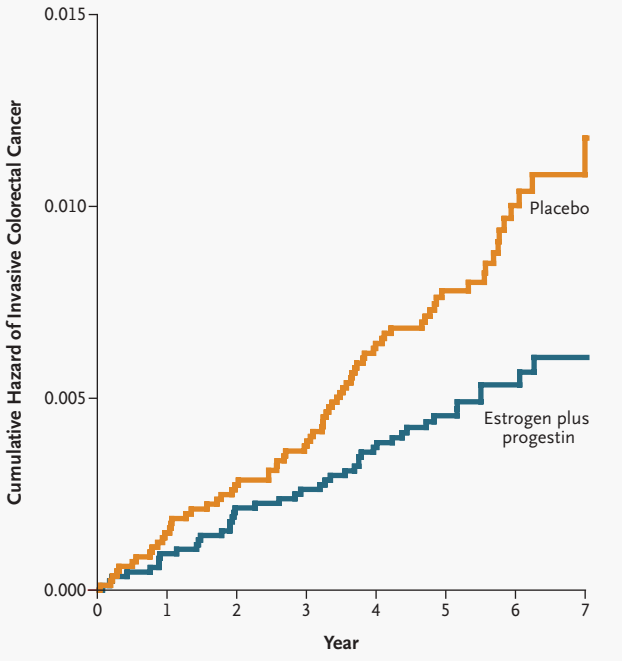

Figure 1. Kaplan–Meier Plots of the Cumulative Hazard of Invasive Colorectal Cancer, According to Treatment Group.

The hazard ratio for colorectal cancer in the group that received estrogen plus progestin, as compared with the group that received placebo, was 0.56 (95 percent confidence interval, 0.38 to 0.81). The data shown do not include two carcinoid tumors among women in the estrogen-plus-progestin group and one squamous-cell carcinoma among women in the placebo group.

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Table 3. Characteristics of the Cases of Invasive Colorectal Cancer, According to Treatment Group.*

Variable	Estrogen plus Progestin	Placebo	P Value†
Women with invasive colorectal cancer — no. (%)	43 (0.1)	72 (0.2)	
Tumor size			0.34
Mean — cm	4.9±2.5	4.3±2.5	
≤3.9 — no. of women (%)	10 (31.3)	26 (48.1)	0.18
4.0–5.9 — no. of women (%)	11 (34.4)	18 (33.3)	
≥6.0 — no. of women (%)	11 (34.4)	10 (18.5)	
Data missing — no. of women (%)	11 (25.6)	18 (25.0)	0.94
Lymph-node examination — no. of women	42	70	
No. of lymph nodes examined — mean	11.0±11.8	11.6±8.0	0.74
No. of positive lymph nodes			0.002
Mean	3.2±4.1	0.8±1.7	
None — no. of women (%)	13 (36.1)	47 (70.1)	0.001
≥1 — no. of women (%)	1 (2.8)	0	
1–3 — no. of women (%)	11 (30.6)	15 (22.4)	
≥4 — no. of women (%)	11 (30.6)	5 (7.5)	
Data missing — no. of women (%)	7 (16.3)	5 (6.9)	0.13
Lymph-node involvement — no. of women (%)			0.003
No	16 (41.0)	48 (70.6)	
Yes	23 (59.0)	20 (29.4)	
Data missing	4 (9.3)	4 (5.6)	0.47
Stage of disease — no. of women (%)			0.009
Localized	10 (23.8)	36 (51.4)	
Regional	24 (57.1)	29 (41.4)	
Metastatic	8 (19.1)	5 (7.1)	
Data missing	1 (2.3)	2 (2.8)	1.00
Morphologic grade — no. of women (%)			0.56
Well differentiated	1 (2.6)	6 (9.1)	
Moderately differentiated	28 (73.7)	47 (71.2)	
Poorly differentiated	9 (23.7)	12 (18.2)	
Anaplastic	0	1 (1.5)	
Data missing	5 (11.6)	6 (8.3)	0.74
Location of cancer — no. of women (%)			0.82
Colon	35 (81.4)	61 (84.7)	
Cecum	8 (18.6)	16 (22.2)	
Ascending colon	6 (14.0)	14 (19.4)	
Hepatic flexure of colon	1 (2.3)	3 (4.2)	
Transverse colon	3 (7.0)	4 (5.6)	
Splenic flexure	2 (4.7)	3 (4.2)	
Descending colon	2 (4.7)	5 (6.9)	
Sigmoid colon	11 (25.6)	11 (15.3)	
Rectosigmoid junction	1 (2.3)	5 (6.9)	
Unknown	1 (2.3)	0	
Rectum	8 (18.6)	11 (15.3)	

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Table 3. (Continued.)

Characteristic	Estrogen plus Progestin	Placebo	P Value†
Histologic features — no. of women (%)			0.80
Adenocarcinoma, not otherwise specified	25 (58.1)	49 (68.1)	
Adenocarcinoma in adenomatous polyp	3 (7.0)	5 (6.9)	
Adenocarcinoma in tubulovillous adenoma	1 (2.3)	2 (2.8)	
Adenocarcinoma in villous adenoma	7 (16.3)	7 (9.7)	
Other	7 (16.3)	9 (12.5)	

* Plus–minus values are means ±SD. The data shown do not include two carcinoid tumors among women in the estrogen-plus-progestin group and one squamous-cell carcinoma among women in the placebo group.
† P values were calculated by a two-sample t-test for continuous variables or a chi-square or Fisher's exact test for categorical variables. The P value for a given characteristic represents the association between groups on the basis only of known values of the characteristic. The P value for "data missing" represents the association between groups of the percentage of missing data for a given characteristic.

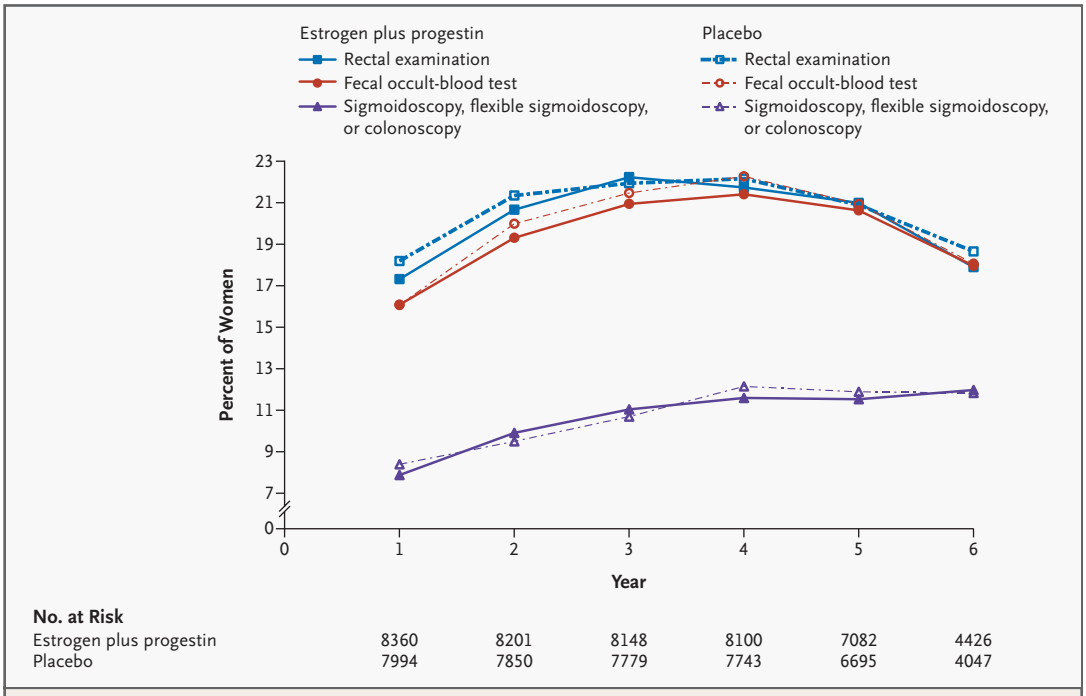

Figure 2. Frequency of Bowel Examinations, According to Treatment Group.

about 40 percent of the participants underwent at least one sigmoidoscopy or colonoscopy and about 28 percent did not undergo a bowel examination of any kind.

The frequency of abdominal symptoms after one year was similar in the two groups. However, vaginal bleeding was more frequent in the hormone group; some bleeding was reported during the first year of study participation by 58 percent of women in that group, as compared with 7 percent in the placebo group (P<0.001). By the fourth year, the frequency of vaginal bleeding in the hormone group had declined to less than 20 percent (data not shown). In the 26 women who had vaginal bleeding before colorectal cancer was diagnosed, the number of positive lymph nodes (3.8±4.3) was

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Table 4. Annualized Rate of Invasive Colorectal Cancer, According to Base-Line Characteristics and Treatment Group.*

Variable	Estrogen plus Progestin	Placebo	Hazard Ratio	P Value for Interaction
	no. of women (annualized %)			
Age at screening				0.57
50–59 yr	7 (0.04)	8 (0.05)	0.79	
60–69 yr	22 (0.10)	38 (0.19)	0.54	
70–79 yr	14 (0.14)	26 (0.28)	0.51	
Race or ethnic group				NA
White	36 (0.09)	60 (0.16)	0.56	
Black	2 (0.06)	9 (0.29)	0.21	
Hispanic	2 (0.08)	0	NA	
American Indian	0	0	NA	
Asian or Pacific Islander	2 (0.19)	2 (0.22)	0.78	
Unknown or not reported	1 (0.15)	1 (0.18)	1.00	
Family history of colorectal cancer				0.91
Yes	30 (0.08)	55 (0.16)	0.50	
No	6 (0.09)	13 (0.20)	0.48	
Prior use of postmenopausal hormones				0.50
No	35 (0.10)	55 (0.16)	0.60	
Yes	8 (0.06)	17 (0.15)	0.41	
Body-mass index†				0.69
<25	11 (0.08)	20 (0.14)	0.53	
25–29	17 (0.10)	26 (0.16)	0.63	
≥30	14 (0.09)	26 (0.17)	0.49	
Waist circumference				0.74
≤88 cm	20 (0.07)	36 (0.14)	0.53	
>88 cm	23 (0.11)	35 (0.18)	0.60	

greater than the number of positive nodes in the 7 women without antecedent vaginal bleeding (0.7±1.5) (P=0.006).

Several characteristics of the participants were examined for possible interaction with the use of estrogen plus progestin and the risk of colorectal cancer (Table 4). No statistically significant interactions were found, although statistical power was limited by the small numbers of women in subgroups.

Information on the serum levels of fasting glucose and insulin at base line and after one year of therapy was available for 686 and 653 women, respectively. The difference between these two time points in glucose levels (mean [±SE] decrease, 2.60±1.02 mg per deciliter; P=0.01) and insulin levels (mean decrease, 0.73±0.35 μIU per milliliter; P=0.04) were both significantly greater in the hormone group than in the placebo group.

Analysis of the global index indicated that the risk associated with the use of estrogen plus progestin in the overall study population outweighed the benefit (hazard ratio for colorectal cancer, 1.12; 95 percent confidence interval, 1.01 to 1.23). The global index provided no evidence of a benefit among women at increased risk for colorectal cancer, those with diabetes (hazard ratio, 1.13; 95 percent confidence interval, 0.83 to 1.55), or those with prior colorectal polyps (hazard ratio, 1.04; 95 percent confidence interval, 0.72 to 1.50).

DISCUSSION

In this randomized trial, the use of estrogen plus progestin was associated with a statistically significant decrease in the incidence of colorectal cancer among postmenopausal women. Our result validates observational studies in which postmeno-

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Table 4. (Continued.)

Variable	Estrogen plus Progestin	Placebo	Hazard Ratio	P Value for Interaction
	no. of women (annualized %)			
Smoking status				0.65
Never	19 (0.08)	37 (0.17)	0.47	
Past	19 (0.10)	30 (0.17)	0.60	
Current	4 (0.08)	4 (0.09)	0.91	
Current alcohol use				0.91
None	13 (0.10)	20 (0.16)	0.58	
<1 drink/wk	14 (0.09)	25 (0.17)	0.52	
≥1 drink/wk	16 (0.09)	26 (0.15)	0.59	
Dietary selenium				0.62
≤74.4 μg/day	13 (0.09)	23 (0.16)	0.52	
74.5–106.3 μg/day	15 (0.10)	18 (0.12)	0.78	
>106.3 μg/day	15 (0.10)	28 (0.19)	0.49	
Diabetes				0.31
Never	36 (0.08)	65 (0.15)	0.52	
Current or past	7 (0.26)	7 (0.28)	0.93	
Use of nonsteroidal antiinflammatory drugs				0.67
No	35 (0.10)	56 (0.18)	0.58	
Yes	8 (0.06)	16 (0.12)	0.47	
History of polyp removal				0.96
No	36 (0.09)	52 (0.14)	0.68	
Yes	4 (0.14)	6 (0.21)	0.63	

* The data shown do not include two carcinoid tumors among women in the estrogen-plus-progestin group and one squamous-cell carcinoma among women in the placebo group. Annualized percentages were calculated according to treatment group as the percentage of women with an event, divided by follow-up time in years. NA denotes not applicable. Hazard ratios and P values were calculated with the use of Cox proportional-hazards models, stratified according to age, presence or absence of a history of colorectal cancer, and randomization group in the trials of dietary modification and calcium and vitamin D.

† The body-mass index was calculated as the weight in kilograms divided by the square of the height in meters.

pausal hormone therapy was found to be associated with a reduced risk of colorectal cancer.[9,12,13]

More of the colorectal cancers in the hormone group than in the placebo group were characterized by lymph-node involvement, and the stage of cancer was more advanced in the hormone group than in the placebo group, despite similarities between the groups in histologic features and grade. Moreover, more women in the hormone group than in the placebo group had metastatic colorectal cancer. The reasons for these differences are unknown. The finding of a decreased number of colorectal cancers diagnosed at a more advanced stage is difficult to explain on the basis of a single hormonal effect. The similar grades and histologic features of cancers in the two groups do not explain the higher incidence of cancers at an advanced stage in the hormone group. The frequency of screening for colorectal cancer, which was similar in the two groups, also does not explain it. A difference in the risk of localized disease accounted for most of the difference between the two groups in the overall risk of colorectal cancer. This difference began to emerge early in the initial follow-up year, suggesting an effect on established cancers.

Abdominal pain, a change in bowel habits, and rectal bleeding are common symptoms in patients presenting with colorectal cancer.[20,21] The symptoms are not infrequently attributed to other, less serious causes,[22] and women are perhaps more likely than men to delay seeking care.[23] In the current study, vaginal bleeding was more common among

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women in the hormone group than among those in the placebo group, and this factor may have delayed assessment and accounted for the higher incidence of advanced cancer in the hormone group.

There is wide support for a policy of regular bowel screening for women 50 years of age or older.[24,25] Nonetheless, the experience in this trial, in which only a minority of the participants underwent routine bowel screening, reflects that of the general population.[26] The more advanced colorectal cancers seen in the hormone group suggests that women who receive estrogen plus progestin might benefit from routine bowel screening, despite their reduced risk of colorectal cancer.

Observational reports provide mixed information on whether postmenopausal hormone therapy has a favorable effect only on the risk of colon cancer[11] or on the risks of both colon cancer and rectal cancer.[27-29] In our trial, the use of estrogen plus progestin reduced the incidence of colon cancer, but the limited number of rectal cancers precludes a definitive assessment of the effect on the risk of rectal cancer.

Possible mechanisms of the effect of postmenopausal hormone therapy on the risk of colorectal cancer include the influence of estrogen on bile acids,[7,30] changes mediated by estrogen receptors on intestinal epithelium,[31,32] and alteration of insulin and insulin-like growth factor I.[33,34] The evidence supporting a role for hyperinsulinemia and hyperglycemia in the risk of colorectal cancer has recently been reviewed.[35] The reduction in the serum levels of fasting glucose and insulin with the use of estrogen plus progestin, as seen in this and other studies,[36] supports the idea that hyperglycemia and hyperinsulinemia contribute to the development of colorectal cancer.

There are limited data from other randomized trials with regard to a possible effect of postmenopausal hormone therapy on the risk of colorectal cancer. In the Heart and Estrogen/Progestin Replacement Study,[37] which involved women with coronary heart disease, fewer colorectal cancers were found in the hormone group than in the placebo group (11 vs. 16 cases; hazard ratio, 0.69; 95 percent confidence interval, 0.32 to 1.49), but the difference was not statistically significant.

The effects of estrogen plus progestin on breast and colorectal cancer suggest that the use of these hormones can delay the diagnosis of two of the three most common cancers in postmenopausal women. Such findings should be part of the discussion of risks and benefits when combined postmenopausal hormone therapy is being considered.

The rates of discontinuation of the study medication in the two groups is a limitation of this study. However, these rates were similar to those in other trials of postmenopausal hormones and are lower than the rates in clinical practice.[38] Screening for colorectal cancer before entry and the frequency of bowel examinations were not defined in the study protocol. However, the similar rates of bowel examinations in the two groups suggest that this factor did not affect the outcome. Nonetheless, regular colonoscopies or even colonoscopies on exit from the study might have allowed a more precise assessment of the effect.

In summary, this randomized trial showed that the use of estrogen plus progestin was associated with a decreased risk of colorectal cancer. However, the cancers diagnosed in women who were using estrogen and progestin had greater lymph-node involvement and a more advanced stage than the cancers in the placebo group. These findings support wider implementation of bowel screening among postmenopausal women who are using hormone therapy. Current data are insufficient to support the use of estrogen plus progestin to reduce the risk of colorectal cancer in any population. Before therapy with estrogen plus progestin is used in any setting by postmenopausal women, all identified[15] and emerging[17,39] risks associated with these agents should be considered.

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APPENDIX

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