Menopausal Hormone Therapy and Risk of Colorectal Cancer

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Abstract

We evaluated colorectal cancer risk associated with the duration and recency of specific menopausal hormone therapy formulations (i.e., unopposed estrogen versus estrogen plus progestin) and regimens (i.e., sequential versus continuous estrogen plus progestin use) among 56,733 postmenopausal women participating in the Breast Cancer Detection Demonstration Project follow-up study. Hormone therapy use and other risk factors were ascertained through telephone interviews and mailed questionnaires from 1979 to 1998. The final cancer group included 960 women who were identified from self-report, medical records, state registry data, and the National Death Index. Poisson regression was used to generate multivariable rate ratios (RR) and 95% confidence intervals (95% CI). We observed a decreased risk of colorectal cancer among ever users of unopposed estrogen therapy (RR, 0.83; 95% CI, 0.70-0.99). Among estrogen users, the largest reduced risk was observed for current users (RR, 0.75; 95% CI, 0.54-1.05) and users of ≥ten years duration (RR, 0.74; 95% CI, 0.56-0.96). We found a reduced risk among users of estrogen plus progestin therapy (RR, 0.78; 95% CI, 0.60-1.02), with sequential regimen users (progestin <15 days per cycle) having the largest risk reduction (RR, 0.64; 95% CI, 0.43-0.95). Past users of ≥5 years ago (RR, 0.55; 95% CI, 0.32-0.98) had the largest risk reduction. In this study, estrogen plus progestin use, especially sequential regimen use, was associated with the largest overall reduction of colorectal cancer risk. (Cancer Epidemiol Biomarkers Prev 2009;18(1):196–203)

Introduction

Since 1980, the hypothesis that reproductive factors and the use of exogenous sex hormones might be protective for the development of colon cancer (1) has generally been supported by results from observational studies. Most studies have found a decreased risk of colon or colorectal cancer in relation to ever versus never use of menopausal hormones (2-19). A few studies found no association or a nonsignificant increased risk (20-25), whereas one study found a significantly increased risk of colon cancer with use of non–oral contraceptive hormones (26). Together, three meta-analyses suggested an 11% to 20% decreased risk of colorectal cancer from ever compared with never use of menopausal hormones, with stronger associations for current use and long duration use (27-29). Since these meta-analyses were undertaken, additional observational studies have found generally similar findings (30-36).

The importance of specific hormone formulations (i.e., unopposed estrogen versus estrogen plus progestin) in relation to colorectal cancer risk was shown by the two arms of the Women's Health Initiative (WHI) Hormone Trials. In the WHI estrogen plus progestin trial, estrogen plus progestin use for an average of 5.6 years decreased the risk of colorectal cancer among postmenopausal women with an intact uterus (37). In the estrogen-alone arm, there was no significant difference in the rates of colorectal cancer for conjugated equine estrogen versus placebo (38). Although the WHI was a randomized clinical trial, the study was limited by the relatively older age of the subjects and the limited duration of the intervention period. The divergent results between the two arms suggest a need to identify separate risk estimates according to menopausal hormone formulation (30). Yet, only five observational studies have investigated multiple menopausal hormone therapy formulations or regimens (i.e., sequential versus continuous estrogen plus progestin use) with risk of colorectal cancer (15, 17, 22, 30, 32).

In 1997, Troisi et al. reported a suggestive, although not statistically significant, inverse association between use of any menopausal hormone therapy and colorectal cancer risk in the Breast Cancer Detection Demonstration Project (BCDDP) follow-up study, based on follow-up through 1989 (23). Since publication of that paper, we have had an additional nine years of follow-up time and additional case ascertainment and statistical power. During that additional timeframe, estrogen plus progestin therapy use became common, allowing for specific formulations and regimens to be investigated in this analysis. Therefore, we evaluated colorectal cancer risk associated with duration and recency of specific menopausal hormone therapy formulations and regimens.

Materials and Methods

Study Population. Details of the BCDDP screening initiative (1973-1980) and follow-up study (1979-1998) have been previously published (39). Briefly, the screening initiative enrolled 283,222 women across the country and provided up to five annual breast examinations. The follow-up study included a subset of women based on their breast cancer screening status: all 4,275 women from the screening program who were diagnosed with breast cancer, all 25,114 women who were diagnosed with benign breast disease, and all 9,628 who were recommended for biopsy or breast surgery but did not have a surgical procedure. An additional 25,165 women sampled from women who had neither surgery nor recommendation for surgical consultation during screening were matched with the above-listed subjects on age, time of entry into the screening program, ethnicity, screening center, and length of participation in the BCDDP, for a total of 64,182 women selected for entry into the follow-up cohort. Appropriate Institutional Review Board approval and written informed consent were obtained.

Analytic Data Set. Of the 64,182 women selected for follow-up, 61,431 women (96%) responded to the baseline interview (administered from 1979 to 1981). Women who had died (*n* = 10) or were diagnosed with breast (*n* = 3,666) or colorectal (*n* = 207) cancer before the start of follow-up were excluded from this analysis. Analyses were restricted to women who were menopausal at baseline or who became menopausal during the course of the study. Menopausal women were defined, as in all BCDDP analyses, as those who had not experienced a menstrual period in the previous three months. Premenopausal women (*n* = 150), women who reported natural menopause before age 35 y (*n* = 178), and women with a missing date of menopause (*n* = 487) were excluded. A total of 56,733 women were available for inclusion in the analysis, representing 798,498 person-years of observation.

Cohort Follow-up. The follow-up study was carried out in four phases. Phase 1, from 1979 to 1986, involved the administration of a baseline telephone interview and up to six, but usually four, annual telephone interviews by personnel at the BCDDP screening centers. For phase 2 (1987-1989), phase 3 (1993-1995), and phase 4 (1995-1998) a single, self-administered mailed questionnaire was used. Respondents who were not known to be deceased received each subsequent mailed questionnaire. Nonrespondents to the mailed questionnaires were interviewed by telephone, if possible. All 56,733 women included in the analysis completed a phase 1 interview.

Exposure Assessment and Covariates. Each interview and questionnaire collected information on current menopausal status and gynecologic surgeries. In phase 2 we collected dietary data and in phase 4 we ascertained family history of colorectal cancer. Measured height and weight and demographic data, including level of education, ethnicity, and income, were obtained during the screening program (1973-1980).

In response to changing patterns of hormone therapy use during the study period, the four data collection phases used slightly different methods of ascertaining menopausal hormone exposure. Information collected from phase 1 of the study included age at first use and duration of use of female hormones other than oral contraceptives. The annual telephone interviews updated the information collected in the previous interview. Data on progestin use were available only for women starting in phase 2. Phase 2 through 4 questionnaires obtained information on unopposed estrogen and estrogen plus progestin in the same month, duration of use of estrogen and progestin, age at first use of progestin, and number of days in the month progestin was used. In phase 3, women who did not know their regimen were asked whether progestin usage was for at least 15 days per cycle. The phase 4 questionnaire used only categories (<10, 10-14, 15-19, or 20-25 d/mo or every day for progestin pill users, or Prempro versus Premphase for combination pill users) to differentiate regimens. Phase 3 and 4 questionnaires collected pill names and doses. Only the phase 4 questionnaire (1995-1998) specifically asked about estrogen and progestin taken in the same pill, which was introduced in 1995.

Women were first divided into never and ever users of postmenopausal hormones. Among ever users, formulation and regimen were combined to create exposure categories. These categories included never use of menopausal hormones, estrogen use alone, or estrogen use in combination with progestin. Women using both estrogen and progestin were further classified into regimens: sequential, continuous, or unknown. Estrogen plus progestin exposure included both pills taken together and combination estrogen plus progestin pills. Sequential users were defined as women using progestin for <15 d/mo, whereas continuous users included women using progestin ≥15 d/mo or taken as a single pill in combination with estrogen (only available from phase 4 follow-up). Periods of hormone use for each woman, based on dates of interview, age at first use, and duration of use, were calculated from phase-specific information as described above. Each period of use was converted into a series of entry and exit ages of estrogen and estrogen plus progestin use, and person-time was summed. As such, women could contribute person-time to multiple hormone exposure categories.

For women who did not complete all four phases of follow-up, person-time associated with hormone exposure status after the last completed questionnaire was assumed to be the same as was last reported for nonusers and for past users of menopausal hormones. Among past users, however, duration of use and recency of use were classified as unknown. For current users at the last completed questionnaire, subsequent person-time associated with exposure status was classified as unknown, as was duration of use and recency of use. Switches from known to unknown use occurred at the midpoint between the last completed questionnaire and the estimated date of questionnaire completion for the subsequent phase.

Case Identification. Women with colorectal cancer were identified based on self-report, linkage to state cancer registries, and the National Death Index. When possible, medical records were obtained and reviewed using a standardized abstraction form. The final colorectal cancer group included 960 women, comprising 461 cases identified from medical records, 201 from state

registry data, 195 from death certificates, and 103 from self-report only. Diagnosis date was defined hierarchically from medical records, state cancer registry data, self-report, and date of death from death certificates. A total of 44,139 women (77.8%) of the 56,733 women who participated in and completed phase 1 of the BCDDP follow-up study were linked against state cancer registries.

Statistical Analysis. Follow-up began at the baseline interview (for postmenopausal women) or the date of menopause (for women who became postmenopausal during follow-up). Person-years accrued until the earliest of the following dates: colorectal cancer diagnosis, death, or phase 4 questionnaire completion. Based on the National Death Index and cancer registry linkages, women without a phase 4 questionnaire were assumed alive and disease-free. These women contributed person-time until the date of last contact in phase 4 or the date that we estimated they would have completed the phase 4 questionnaire, which was assigned based on the average time interval between completed questionnaires.

To include exposure most likely to have been causal, time-dependent hormone therapy variables were computed up to 1 y before attained age (i.e., current age). Risk estimates were based on comparisons of age and calendar time–adjusted frequency of disease among women contributing person-time to different exposure categories. Given that menopausal hormone therapy is a time-dependent exposure, and given that exposure categories for individual women could potentially change multiple times during the follow-up period, many women contributed person-time to multiple exposure categories. When exposure status or duration became unknown, subsequent person-years went to the "unknown" category. Because progestin use was not collected until the phase 2 questionnaire, exposed person-time and cancers from estrogen therapy users who only completed the phase 1 interviews were included in the "estrogens, unknown progestins" category.

Due to the complexity of the time-dependant variables, we used Poisson regression to calculate rate ratios (RR) and 95% confidence intervals (95% CI) using standard likelihood ratio methods (Epicure 1.4 software, HiroSoft International Corp.). Poisson regression has been the main analytic approach for other BCDDP analyses (23, 39-42). For the Poisson regression, we summarized person-time in a multidimensional table defined by categories of attained age (six categories, <55, 55-59, 60-64, 65-69, 70-74, and ≥75 y) and calendar time (four categories, 1979-1983, 1984-1988, 1989-1993, 1994-1998) as well as hormone therapy variables, nonsteroidal anti-inflammatory drug use, cigarette smoking, family history of colorectal cancer, percent of calories from fat, and red meat intake. Hormone therapy variables, attained age, and calendar time were all time-dependent. Potential confounding variables were included in the models only if they changed the estimates associated with hormone use by ≥10%. The age-adjusted models included adjustment for age and calendar time, whereas the multivariate models included additional adjustment for nonsteroidal anti-inflammatory drug use, cigarette smoking, family history of colorectal cancer, and red meat intake; estrogen plus progestin models also

included adjustment for percent of calories from fat. All covariates were modeled as categorical variables as shown in Table 1. Women who had never used menopausal hormones throughout the observation period were the reference group for all rate ratios.

Results

The mean duration of follow-up was 15.02 years (range, 1 month-19.8 years). The mean age at the start of follow-up was 55.7 years. Women of white race/ethnicity, younger age at menopause (i.e., <48 years), low body mass index (i.e., <18.5 kg/m^2), and never users of oral contraceptives were more likely to have used any form of menopausal hormones (Table 1). Women with education past high school were more likely to have used estrogen plus progestin hormone therapy.

Among women reporting use of menopausal hormone therapy, use of any formulation was associated with a modest decrease in risk of colorectal cancer compared with women with no previous use (RR, 0.91; 95% CI, 0.80-1.04; Table 2). When the analysis was restricted to women for whom formulation and regimen were known, risk estimates for ever use of unopposed estrogen or estrogen plus progestin were somewhat stronger and, depending on the comparison, confidence intervals excluded the null value. Among estrogen plus progestin users, the greatest reduction in colorectal cancer risk was among women who reported sequential estrogen plus progestin use (RR, 0.64; 95% CI, 0.43-0.95). Continuous estrogen plus progestin users had a nonsignificant multivariate-adjusted RR of 0.75 (95% CI, 0.46-1.21).

For unopposed estrogen users compared with never users, the risk of colorectal cancer decreased with longer years of use (Table 3), with the greatest reduction in risk among women who reported ≥10 years duration (RR, 0.74; 95% CI, 0.56-0.96). In an examination of recency of use, current use of unopposed estrogen was associated with a stronger inverse association than past use relative to women who had never used hormones. The multivariate-adjusted RR was 0.75 for current use versus never use, although the confidence interval just included 1.0 (95% CI, 0.54-1.05). Among past users of unopposed estrogen, the risk of colorectal cancer was similar to that of women who had never used hormones, regardless of time since last use.

Among estrogen plus progestin therapy users, reduced risk of colorectal cancer was most pronounced only for users of moderate duration (Table 4). Estrogen plus progestin users of 2 to 5 years, relative to never users, had a multivariate-adjusted RR of 0.52 (95% CI, 0.32-0.87). In contrast to findings for unopposed estrogen, past but not current estrogen plus progestin use was associated with decreased risk of colorectal cancer, relative to never users. The strongest inverse associations were observed among women with past use of estrogen plus progestin therapy of ≥5 years ago (RR, 0.55; 95% CI, 0.32-0.98). The risk estimates were similar for duration and recency of sequential and continuous regimen users of estrogen plus progestin were based on a small number of colorectal cancer cases (data not shown).

For all analyses, adjustment for recruitment category (i.e., benign breast disease, recommendation for biopsy

Table 1. Distribution of person-years according to selected factors and hormone therapy formulation

	None (%)	Unopposed estrogens (%)	Estrogen plus progestin (%)	Estrogen, progestin unknown (%)
Total person-years	307,752	229,841	100,740	119,512
Attained age, y				
<55	0.25	0.10	0.07	0.26
55-59	5.72	3.82	9.59	5.57
60-64	17.17	12.90	25.32	14.86
65-69	25.32	21.05	28.18	21.23
70-74	21.67	25.17	20.22	22.68
≥75	29.87	36.97	16.62	35.41
Race/Ethnicity				
White	84.34	88.96	90.08	86.19
Non-white	15.66	11.04	9.92	13.81
Education				
≤High school	58.66	57.16	42.86	57.95
>High school	40.53	42.19	56.20	41.12
Unknown	0.81	0.65	0.94	0.93
Household income, US Dollars				
<10,000	24.05	19.52	10.53	21.92
10,000-29,999	60.63	64.29	67.64	60.96
≥30,000	10.47	12.28	18.79	12.31
Unknown	4.85	3.91	3.04	4.81
Family history of colorectal cancer				
No	55.51	63.59	73.46	48.93
Yes	8.89	10.92	12.15	8.90
Unknown	35.60	25.50	14.39	42.17
Age at menopause, y				
<48	38.33	58.17	37.39	61.34
48-51	35.00	25.73	33.53	23.50
≥52	26.67	16.10	29.08	15.16
Parity				
0	14.57	14.45	12.67	13.70
1	12.08	13.01	10.53	13.04
2	28.25	29.55	29.75	29.46
≥3	45.06	42.97	47.04	43.72
Unknown	0.04	0.03	0.01	0.08
Red meat intake (g/d)				
<18	19.62	22.97	22.42	16.71
18-33	16.44	19.99	21.60	14.96
34-51	16.14	18.55	19.80	13.48
52-80	15.72	17.88	18.83	13.96
≥81	32.09	20.61	17.36	40.90
Percent calories from fat				
<28	19.47	22.96	22.40	16.99
28-33	19.43	23.05	24.65	16.30
34-37	14.94	18.01	18.19	13.38
38-41	13.49	15.26	15.48	11.72
≥42	32.68	20.72	19.29	41.61
Oral contraceptive use				
Never	77.04	75.78	58.69	70.15
Ever	22.86	24.02	41.21	29.66
Unknown	0.10	0.20	0.10	0.19
Nonsteroidal anti-inflammatory drug use				
No	29.13	41.23	43.13	35.44
Yes	43.21	42.89	47.86	31.33
Unknown	27.66	15.88	9.01	33.22
Body mass index, kg/m^2				
<18.5	58.00	63.67	72.17	63.47
18.5-24.9	4.46	3.93	4.95	4.27
25-29.9	26.05	24.19	17.86	23.58
30-34.9	8.15	6.18	3.96	6.60
≥35	3.34	2.03	1.06	2.08
Smoking status				
Never	33.92	39.93	45.80	30.85
Ever	48.23	55.65	51.47	40.85
Unknown	17.84	4.41	2.73	28.30

or surgery, or normal) did not alter the risk estimates, and stratification by self-reported history of colorectal cancer screening (i.e., colonoscopy, sigmoidoscopy, or fecal occult blood test) did not suggest differential risk patterns. There were no statistically significant inter- actions by body mass index, age, and nonsteroidal anti- inflammatory drug use. Analyses were also conducted by colorectal cancer subsite, including cancers of the colon (493 cancers), proximal colon (275 cancers), distal colon (357 cancers), and rectum (139 cancers). The results

Table 2. Relative risk of colorectal cancer associated with use of menopausal hormone therapy

	No. cases	No. person-years	Age-adjusted RR (95% CI)	Multivariate-adjusted* RR (95% CI)
Never use	393	307,752	1.0 (reference)	1.0 (reference)
Any use	513	455,306	0.84 (0.73-0.96)	0.91 (0.80-1.04)
Unopposed estrogen only	239	229,841	0.76 (0.65-0.90)	0.83 (0.70-0.99)
Estrogen plus progestin	85	100,740	0.71 (0.55-0.90)	0.78 (0.60-1.02)
E+P sequential	31	49,539	0.56 (0.39-0.82)	0.64 (0.43-0.95)
E+P continuous	21	27,747	0.63 (0.40-0.99)	0.75 (0.46-1.21)
E+P unknown days progestin	33	23,454	1.00 (0.70-1.44)	1.16 (0.80-1.67)
Progestin only	2	4,744	0.40 (0.10-1.60)	0.42 (0.10-1.71)
Progestin, unknown estrogen	0	469	NA	NA
Estrogen, unknown progestin	187	119,512	1.07 (0.90-1.28)	1.02 (0.85-1.22)
Unknown use	54	35,440	1.10 (0.83-1.47)	1.18 (0.88-1.58)

Abbreviations: E+P, estrogen plus progestin; NA, data not applicable.
*Adjusted for age, calendar time, NSAID use, cigarette smoking, family history of colorectal cancer, and red meat intake. Estrogen plus progestin categories also adjusted for percent calories from fat.

did not indicate any subsite-specific associations that differed substantially from those of all colorectal cancers combined (data not shown).

Discussion

In this prospective study of 56,733 postmenopausal women, ever use of menopausal hormone therapy was associated with a reduced risk of colorectal cancer. We observed a statistically significant 17% decreased risk of colorectal cancer among ever users of unopposed estrogen compared with never users. Among these unopposed estrogen users, we observed the largest risk reduction among current users and among users of ≥10 years duration. In contrast, we found a nonsignificant 22% reduction in colorectal cancer risk among users of estrogen plus progestin, with sequential regimen users having a larger reduction in risk at 36% compared with continuous users at 25%. Among estrogen plus progestin users, women who had stopped hormone therapy for >5 years and women who had used estrogen plus progestin for medium duration of 2 to 5 years had the largest reduction in colorectal cancer risk. An overall dose-response pattern was not evident for duration of use among estrogen plus progestin users. For estrogen with unknown progestin users, a null result was found and it is unclear how this may affect our above findings.

Despite the recent decrease in use of all menopausal hormones, these results suggest an important protective effect of all hormone formulations, especially estrogen plus progestin, for the many women who continue to need and use menopausal hormone therapy.

Several biological mechanisms, via secondary bile acids, insulin-like growth factors, and estrogen and progesterone receptors, have been postulated for the protective effect of menopausal hormone therapy on risk of colorectal cancer. A comprehensive overview of the biological aspects of hormones on colorectal cancer was recently published by Newcomb and colleagues (43). In brief, the original biological mechanism was proposed in 1980 when McMichael and Potter suggested that increased concentrations of bile acids within the colon may enhance colon carcinogenesis and that exogenous estrogens and progestins may reduce bile acid production (1). More recently, epidemiologic research, although inconsistent, suggests a relation between serum insulin-like growth factor-1 (IGF-1) and IGF binding protein-3 (IGFBP-3) levels and colorectal cancer risk. Studies suggest that use of menopausal hormone therapy decreases both IGF-1 and IGFBP-3 levels (44, 45). In addition, estrogen receptors, including estrogen receptor α and estrogen receptor β, and progesterone receptors have been identified in colon epithelial cells (46-48). Research indicates that decreasing levels of estrogen receptor β coincide with the loss of differentiation of malignant

Table 3. Relative risks and 95% confidence intervals associated with duration and recency of unopposed estrogen use

		No. cases	Age-adjusted RR (95% CI)	Multivariate-adjusted* RR (95% CI)
Never use		393	1.0 (reference)	1.0 (reference)
Duration (y)	<5	131	0.83 (0.68-1.02)	0.90 (0.73-1.11)
	5-9	40	0.74 (0.53-1.02)	0.83 (0.59-1.15)
	≥10	68	0.69 (0.53-0.89)	0.74 (0.56-0.96)
Recency[†] (years ago)	Current	40	0.59 (0.42-0.82)	0.75 (0.54-1.05)
	<5	42	0.96 (0.69-1.32)	0.94 (0.68-1.31)
	5-9	34	0.81 (0.57-1.16)	0.87 (0.61-1.25)
	≥10	98	0.81 (0.65-1.02)	0.88 (0.69-1.11)

*Adjusted for age, calendar time, nonsteroidal anti-inflammatory drug use, cigarette smoking, family history of colorectal cancer, and red meat intake.
†Unknown recency of use accounted for 25 cancers and 24,264 person-years.

Table 4. Relative risks and 95% confidence intervals associated with duration and recency of estrogen plus progestin use

		No. cases	Age-adjusted	Multivariate-adjusted*
			RR (95% CI)	RR (95% CI)
Never use		393	1.0 (reference)	1.0 (reference)
Duration (y)	<2	48	0.79 (0.58-1.07)	0.83 (0.60-1.15)
	2-5	18	0.46 (0.29-0.74)	0.52 (0.32-0.87)
	>5	19	0.92 (0.58-1.47)	1.12 (0.67-1.82)
Recency [†] (years ago)	Current	32	0.78 (0.54-1.13)	0.99 (0.67-1.47)
	<5	14	0.58 (0.34-0.99)	0.60 (0.34-1.05)
	≥5	14	0.56 (0.32-0.95)	0.55 (0.32-0.98)

*Adjusted for age, calendar time, nonsteroidal anti-inflammatory drug use, cigarette smoking, family history of colorectal cancer, percent calories from fat, and red meat intake.
†Unknown recency of use accounted for 25 cancers and 21,984 person-years.

colon cells, supporting a protective mechanism of estrogen receptor β (49, 50). Age-associated CpG island methylation of the estrogen receptor gene is also evident in colorectal tumors, further suggesting a protective effect of estrogen receptors (51).

Menopausal hormone therapy was introduced nearly 70 years ago, with widespread use of unopposed estrogens. The 1970s showed a marked decreased in prescriptions due to an observed increase in endometrial cancer among hormone users, an outcome that could be mitigated by the addition of progestin (52). As such, estrogen plus progestin use became common for women with an intact uterus, but it was not until 1995 that estrogen and progestin were introduced in the same pill. Therefore, only a limited number of observational studies exist with the ability to investigate colorectal cancer risk with specific menopausal hormone formulations.

Our findings of a general protective effect of hormones, regardless of formulation, on the risk of colorectal cancer are consistent with results of the three previous case-control studies in which separate risk estimates by type of hormone formulation and duration and/or recency were provided. These studies each found a statistically significant 15% to 46% reduction in the risk of colon or colorectal cancer among unopposed estrogen users and a 25% to 46% reduction in the risk of colon or colorectal cancer among estrogen plus progestin users (15, 30, 32). The greatest reduction in colorectal cancer risk varied according to formulation between two studies, whereas the third study found a 46% reduction in colon cancer risk among both estrogen and estrogen plus progestin users. One of the two studies that investigated duration found the most pronounced risk reduction among ≥5 years estrogen use (odds ratio, 0.74; 95% CI, 0.59-0.92), similar to our results, and the other found that users of unopposed estrogen of <5 years duration (odds ratio, 0.58; 95% CI, 0.41-0.82) had the greatest risk reduction (30, 32). These two studies also reported the greatest reduction in risk of colorectal cancer among estrogen plus progestin users of shorter duration, defined as <5 years, at 28% to 40%. The only study in which recency of hormone use by formulation was assessed found the greatest reduction in risk among current users of estrogen at 45% and among former users of estrogen plus progestin at 44% (30). None of these studies examined the regimen of estrogen plus progestin use against which to compare our results.

Randomized clinical trial data from the WHI indicated a decreased risk of colorectal cancer among estrogen plus progestin users, and no difference in the rates of colorectal cancer among estrogen alone users (37, 38). The WHI trial of estrogen plus progestin enrolled 16,608 postmenopausal women and had a mean follow-up time of 5.6 years. This trial found a 39% decreased risk of colorectal cancer among women taking continuous combined estrogen plus progestin (0.625 mg/day conjugated equine estrogen plus 2.5 mg/day medroxyprogesterone acetate) versus placebo (hazard ratio, 0.61; 95% CI, 0.42-0.87; ref. 37). The WHI trial of unopposed estrogen enrolled 10,739 postmenopausal women with a hysterectomy and had a mean follow-up time of 6.8 years (40). This trial concluded there was no significant difference in the rates of colorectal cancer among women taking estrogen (0.625 mg/day conjugated equine estrogen) versus placebo (hazard ratio, 1.08; 95% CI, 0.63-1.86; ref. 38). Two observational studies also found a nonsignificant increased risk of colorectal cancer associated with unopposed estrogen menopausal hormone therapy use (22, 24). Although our findings are similar to those of the WHI for estrogen plus progestin users, direct comparison of clinical trial data with that of observational data in this context is limited.

It is tempting to focus primarily on the WHI results because they originate in a randomized trial, but it is important to note that the WHI was designed as a prevention study in older women, meaning it has unique design features that distinguish it from observational studies such as the BCDDP. For example, in the WHI estrogen plus progestin trial, two thirds of the women were age ≥60 years at randomization and roughly 75% had never used hormone therapy before being randomly assigned to placebo or estrogen plus progestin (37). In contrast, in the BCDDP, nearly two thirds of participants had already used hormone therapy by age 60 years and most of that use would have been in response to menopausal symptoms. Timing and indication for exposure was distinctly different in the BCDDP which, in turn, means the two studies were designed to investigate different aspects of potential risks of hormone therapy use. Despite these differences in study population characteristics, we saw somewhat similar results for estrogen plus progestin in the BCDDP as WHI investigators observed in their study, but the null finding for unopposed estrogen in WHI was contrary to our finding of a reduced risk of recent long term use of unopposed

estrogen. Perhaps a major difference between WHI and BCDDP that could help explain this discrepancy is the relatively short duration of hormone therapy in WHI, making it impossible to observe the effects of long-term use in the way we could in BCDDP.

Several limitations are present in our study. The risk estimates generated for estrogen plus progestin users, and most notably among sequential and continuous regimen users, are based on relatively small numbers of women who developed colorectal cancer. As a result, our relative risk estimates may be unreliable or imprecise for assessing the effects of estrogen plus progestin regimens. Hormone therapy exposure was a self-reported measure in our study and, therefore, may be subject to error. Whereas hormone therapy use was not validated in our study, others have reported good reliability for self report of hormone therapy exposures (53). We adjusted for several potential confounders, but the possibility remains for residual confounding by imperfectly measured covariates and for confounding by variables not considered or measured.

In summary, our study found that ever use of any menopausal hormone therapy was associated with a reduced risk of colorectal cancer. In this study, estrogen plus progestin use, especially sequential regimen use, was associated with the overall largest reduction of colorectal cancer risk. These findings expand upon estrogen plus progestin regimens that are inversely associated with colorectal cancer risk.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

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