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Original Contribution

Menopausal Hormone Therapy Use and Risk of Invasive Colon Cancer

The California Teachers Study

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Results from epidemiologic studies of hormone therapy use and colon cancer risk are inconsistent. This question was investigated in the California Teachers Study (1995–2006) among 56,864 perimenopausal or postmenopausal participants under 80 years of age with no prior colorectal cancer by using Cox proportional hazards regression. Incident invasive colon cancer was diagnosed among 442 participants. Baseline-recent hormone therapy users were at 36% lower risk for colon cancer versus baseline-never users (baseline-recent users: relative risk (RR) = 0.64, 95% confidence interval (CI): 0.51, 0.80). Results did not differ by formulation. Estimated risk was lower among baseline-recent hormone therapy users with increasing duration between 5 and 15 years of use (RR = 0.49, 95% CI: 0.35, 0.68), but the trend did not persist in the longest duration group, more than 15 years of use (RR = 0.69, 95% CI: 0.52, 0.92; $P_{trend} = 0.60$). Long-term recreational physical activity, obesity, regular use of nonsteroidal antiinflammatory medications, and daily alcohol intake did not modify these effects; baseline-recent use was more strongly associated with colon cancer risk among women with a family history of colorectal cancer ($P_{heterogeneity} = 0.04$). Baseline-recent hormone therapy use was inversely associated with invasive colon cancer risk among perimenopausal and postmenopausal women in the California Teachers Study.

colonic neoplasms; hormone replacement therapy; lung neoplasms; parity; prospective studies; reproduction; smoking

Abbreviations: CI, confidence interval; HT, hormone therapy; Q2000, third California Teachers Study questionnaire sent in 2000; RR, relative risk; SD, standard deviation.

Previous studies have shown that menopausal hormone therapy is associated with decreased risk of colon cancer (1). The Women's Health Initiative trials found that continuous combined hormone therapy (2), but not unopposed estrogen therapy (3), was associated with decreased colorectal cancer risk. Those associations have been replicated (4) and disputed (5, 6) by subsequent studies. Few studies have investigated a possible dose-response between increasing duration of hormone therapy use and decreasing colon cancer risk. The Nurses' Health Study reported no duration dose response but did report a strong reduction in risk among recent hormone therapy users, which was attenuated with increasing time since last use (7).

In the current analysis, the association between colon cancer and hormone therapy use overall, by formulation, by duration of use, and by time since last use among women participating in the California Teachers Study was assessed. In addition, we investigated the extent to which several factors previously hypothesized to be associated with colon cancer risk, including physical activity (8, 9), body mass index (10, 11), regular nonsteroidal antiinflammatory drug use (12), calcium intake (13, 14), calcium plus vitamin D intake (15), family history of colorectal cancer (16), personal history of colorectal polyps (17), smoking history (18), and alcohol intake (19), might act as effect modifiers of the hormone therapy and colon cancer risk association or

might appear to interact with hormone therapy in the context of colon cancer risk.

MATERIALS AND METHODS

The California Teachers Study is a prospective cohort of current and former female public school teachers and administrators, who were members of the California State Teachers Retirement System in 1995. Cohort participants completed a questionnaire, mailed in 1995, providing detailed information on factors such as hormone therapy use, personal medical history, reproductive history, physical activity, anthropometrics, medication use, diet, and family history of colorectal cancer. The third California Teachers Study questionnaire, sent in 2000 (Q2000), updated information on menopausal status and hormone therapy use. A detailed description of the California Teachers Study is available (20). Use of human subject data was approved by the institutional review boards at each collaborating institution in accord with assurances approved by the US Department of Health and Human Services.

The California Teachers Study cohort comprises 133,479 women. Exclusions, in sequence, were women who, at baseline, lived outside California ($n = 8,867$), had a prior/unknown history of colorectal cancer ($n = 1,559$), had limited participation in breast cancer research ($n = 18$), were 80 years or older ($n = 5,532$), were premenopausal ($n = 47,966$), had unknown menopausal status ($n = 4,961$), or had unknown hormone therapy or progestin-only use ($n = 7,712$). The resulting cohort for the analysis of baseline data consisted of 56,864 women (2,245 perimenopausal and 54,619 postmenopausal).

Case ascertainment and follow-up

Incident invasive colon cancers were identified through annual linkages with the California Cancer Registry, which receives reports of over 99% of cancer diagnoses occurring in California (21). Invasive colon cancer was defined as an *International Classification of Diseases for Oncology*, Second Edition (ICD-O-2), topography code C180–C189 or C260 (large intestine not otherwise specified). C180–C185 codes were considered proximal and C186–C189 and C260 codes were considered distal. Stage, procured from the California Cancer Registry summary stage variable, was classified as localized, regional, and distant. A total of 442 eligible participants were diagnosed with invasive colon cancer during follow-up, which began on the baseline questionnaire date and continued until the diagnosis of colon cancer or the first occurrence of a censoring event (relocation outside California lasting more than 4 months ($n = 4,702$), diagnosis of in situ colon cancer ($n = 26$), death ($n = 5,600$), or end of follow-up, December 31, 2006 ($n = 46,094$)).

Exposure assessment

Women reporting ongoing menstrual periods who had never used hormones for menopausal symptoms were considered premenopausal. Women were classified as perimenopausal if periods had stopped within the last 6 months and they were not currently pregnant, and as postmenopausal if they met any of the following criteria: 1) periods stopped more than 6 months ago, 2) bilateral oophorectomy, 3) age 56 years or older at baseline and not already classified as premenopausal or perimenopausal, 4) started using hormone therapy for menopausal symptoms before periods stopped, and/or 5) hysterectomy before age 56 years but aged 56 years or more at baseline. The age criterion was based on previous work indicating that approximately 90% of women of age 56 years or older were biologically postmenopausal (22).

The principal hormone therapy item on the baseline questionnaire asked, ''Have you ever taken estrogen for symptoms of menopause (the change of life) or for other reasons?'' Response categories were ''no,'' ''yes, and I am currently taking estrogens,'' and ''yes, but I am no longer taking estrogens.'' Subsequent questions included type of hormone used, ages of first and last use, and total years of use for each type of hormone. Variables were created to characterize the pattern of hormone therapy use over time with respect to formulation, duration of use, and years since last use. Hormone therapy was categorized in several ways, first as never or ever hormone therapy user. The ever hormone therapy users included participants who had only ever used a single formulation (ever hormone therapy user, estrogen therapy only or ever hormone therapy user, estrogen-plus-progestin therapy only) and who had used more than one formulation over their lifetimes (ever hormone therapy user, mixed formulations). Analyses assessed the effects by various categorizations of hormone therapy, and sensitivity analyses tested for differences in the effects when analyses were limited to women who had used only one formulation, either estrogen alone or combined estrogen-plus-progestin therapy. Women who reported no hormone therapy use, past hormone therapy use, and current hormone therapy use on the baseline questionnaire will be referred to as ''baseline-never hormone therapy (HT) users,'' ''baseline-former HT users,'' and ''baseline-recent HT users,'' respectively. In addition, for assessment of the possible effect of changes in hormone therapy use status between baseline and Q2000, a time-dependent hormone therapy use variable was created by using information from both questionnaires. Baseline values were used until Q2000, at which point the Q2000 value was used. If no Q2000 value was available, the baseline value was retained. A more simple, combined baseline/Q2000 hormone therapy use variable was also created: baseline-never/Q2000-never, baseline-never/Q2000-former, baseline-never/Q2000-recent, baseline-former/Q2000-former, baseline-former/Q2000-recent, baseline-recent/Q2000-former, or baseline-recent/Q2000-recent.

Statistical analysis

Multivariable Cox proportional hazards regression methods were used to assess the associations of hormone therapy use by various categorizations with invasive colon cancer risk, using ages at the start and the end of follow-up (in days) to define time on study. Models were adjusted for race/ethnicity, body mass index (kg/m^2), and physical

activity, and they were stratified by age at baseline (in single years of age). Hazard rate ratios, presented as relative risks with 95% confidence intervals, were estimated. For ordinal variables, we tested for linear trend in the $\log_e$(relative risk) across exposure categories. To assess the proportional hazards assumption using baseline hormone therapy status (baseline-never HT user vs. baseline-ever HT user), we first visually examined whether Kaplan-Meier survival curves had parallel lines (23). We also plotted scaled Schoenfeld residuals by time to test for a zero slope and tested the null hypothesis of no correlation between the residuals and time on study (24). No evidence for a violation of the proportional hazards assumption was apparent.

We examined the association between invasive colon cancer and hormone therapy use by stage of disease at diagnosis (localized ($n = 159$), regional ($n = 181$), or distant ($n = 90$)) and by location of disease (proximal ($n = 321$) vs. distal ($n = 121$) colon cancer). Sensitivity analyses to test for exclusion of perimenopausal women and to test for differences in effects among women whose hormone therapy use was limited to one formulation did not differ markedly from those presented. We further assessed possible effect modification by physical activity, body mass index, regular nonsteroidal antiinflammatory drug use, calcium intake, calcium plus vitamin D intake combined, first-degree family history of colorectal cancer, personal history of colorectal polyps, smoking history, and alcohol intake, according to the homogeneity of trends in hormone therapy use across categories of each modifier. Additional analyses testing for statistical interaction between hormone therapy use and these factors in which baseline-never HT users in the lowest level of each factor were the reference group did not differ measurably from the results presented herein.

Additional analyses to determine whether inclusion of updated exposure information influenced the results included women eligible for analysis at baseline, who were postmenopausal at baseline and postmenopausal at Q2000, and who provided complete hormone therapy information at Q2000. Cox regression models were used to test the potential effect of hormone therapy, incorporating hormone therapy information from both the baseline questionnaire and Q2000. Adjusted relative risks of invasive colon cancer were computed for the time-dependent hormone therapy variable described above. Additional models examined exclusion of participants with missing Q2000 values or use of the simpler variable. Covariate classifications used in the analyses are presented in Table 1. All statistical analyses were performed by using SAS, version 9.1, software (SAS Institute, Inc., Cary, North Carolina). *P* values were not adjusted for multiple comparisons.

RESULTS

Nearly 76% of the 56,864 perimenopausal and postmenopausal women included in the analyses of baseline data reported ever using hormone therapy; 15% were baseline-former users and 61% were baseline-recent users (Table 1). Of the 34,433 baseline-recent HT users, 44% were using unopposed estrogen and 56% were using combined estrogen plus progestin; 44% of the 442 women diagnosed with invasive colon cancer were baseline-recent HT users. Baseline-recent HT users were younger than baseline-former or baseline-never HT users, with mean ages of 58.9 (standard deviation (SD) = 8.5), 65.0 (SD = 8.8), and 62.7 (SD = 9.2) years, respectively (Table 1).

Any use of hormone therapy, compared with baseline-never use, was associated with a 28% decreased risk of incident invasive colon cancer (relative risk $(RR)_{\text{ever HT use}} = 0.72$, 95% confidence interval (CI): 0.58, 0.88) (Table 2). This relative risk did not differ when any hormone therapy use was categorized further as estrogen therapy use only, estrogen-plus-progestin therapy use, or mixed hormone therapy use (Table 2). The reduction in colon cancer risk was restricted to baseline-recent HT users ($RR_{\text{baseline-recent HT use}} = 0.64$, 95% CI: 0.51, 0.80). Reductions in risk for baseline-recent users of unopposed estrogen and for baseline-recent users of estrogen-plus-progestin therapy were similar ($RR_{\text{unopposed estrogen}} = 0.59$, 95% CI: 0.45, 0.77 and $RR_{\text{estrogen + progestin}} = 0.71$, 95% CI: 0.54, 0.93). Reductions in risk for baseline-recent users of hormone therapy were similar for distal versus proximal colon cancers ($RR_{\text{distal}} = 0.57$, 95% CI: 0.37, 0.87 and $RR_{\text{proximal}} = 0.67$, 95% CI: 0.52, 0.87) (data not shown). The risk decreased among baseline-recent HT users with increasing duration of use through 5–15 years of use ($RR_{<5\text{ years' use}} = 0.76$, 95% CI: 0.54, 1.08 and $RR_{5\text{–}15\text{ years' use}} = 0.49$, 95% CI: 0.35, 0.68), but the trend did not persist in the longest duration group ($RR_{>15\text{ years' use}} = 0.69$, 95% CI: 0.52, 0.92; $P_{\text{trend}} = 0.06$). The variable years since last hormone therapy use was associated with colon cancer risk among baseline-former HT users.

Table 3 demonstrates that the association between hormone therapy and invasive colon cancer risk appeared to be stronger for tumors diagnosed at the regional and distant stages. For regional-stage tumors, the association was stronger for participants who had ever used a progestin ($RR_{\text{ever HT user, estrogen therapy only}} = 0.84$, 95% CI: 0.59, 1.20; $RR_{\text{ever HT user, estrogen + progestin therapy only}} = 0.49$, 95% CI: 0.24, 0.99; and $RR_{\text{ever HT user, mixed formulations}} = 0.65$, 95% CI: 0.43, 0.98). For distant-stage tumors, the magnitude of the association did not differ clearly ($RR_{\text{ever HT user, estrogen therapy only}} = 0.50$, 95% CI: 0.30, 0.84; $RR_{\text{ever HT user, estrogen + progestin therapy only}} = 0.80$, 95% CI: 0.38, 1.67; and $RR_{\text{ever HT user, mixed formulations}} = 0.42$, 95% CI: 0.23, 0.76). The effect was statistically significant among baseline-recent HT users only, for regional-stage tumors ($RR_{\text{baseline-recent HT user}} = 0.68$, 95% CI: 0.48, 0.96), and distant-stage tumors ($RR_{\text{baseline-recent HT user}} = 0.33$, 95% CI: 0.20, 0.56) (Table 3).

First-degree family history of colorectal cancer may modify the association between hormone therapy and colon cancer risk ($P_{\text{heterogeneity}} = 0.04$) (Table 4). Further, colon cancer risk was lower among baseline-recent HT users with a positive family history of colorectal cancer (RR = 0.45, 95% CI: 0.26, 0.78) than among baseline-recent HT users with no family history (RR = 0.71, 95% CI: 0.56, 0.90) (data not shown). No other statistically significant effect modification or interaction was apparent in these data.

Table 1. Distribution of Baseline Characteristics by Baseline Status of Hormone Therapy Use Among 56,864 Perimenopausal and Postmenopausal Participants in the California Teachers Study, 1995–2006

Characteristics	Total No.	Status of HT Use at Baseline (Estrogen, Estrogen + Progestin, or User of Mixed Formulations)		
		Baseline-Never HT User	Baseline-Former HT User	Baseline-Recent HT User
No. of participants	56,864	13,778	8,653	34,433
No. of invasive colon cancer cases	442	151	98	193
Mean age at baseline, years (SD)		62.7 (9.2)	65.0 (8.8)	58.9 (8.5)
Menopausal status, %[a]				
Perimenopausal	2,235	44.7	9.9	45.3
Postmenopausal, natural menopause	29,397	34.7	18.3	47.0
Postmenopausal, bilateral oophorectomy	8,851	4.2	12.1	83.6
Postmenopausal, other reason	16,381	13.5	12.0	74.5
Race/ethnicity, %[a]				
White	50,746	23.2	15.2	61.6
African American	1,609	38.8	19.0	42.1
Other[b]	4,509	30.1	14.1	55.7
Long-term recreational physical activity, %[a,c]				
Low (<0.5 hour/week of any activity)	8,920	27.0	15.7	57.3
Intermediate	28,614	21.8	14.0	64.3
High (≥3 hours/week of any activity)	18,963	24.4	14.4	61.3
Body mass index, kg/m^2[a]				
<25	30,578	21.0	13.2	65.7
25–29	15,300	23.6	15.4	61.0
≥30	8,378	29.6	15.9	54.6
Regular NSAID use[a,d]				
Low	49,058	23.9	14.3	61.9
High	5,944	18.8	14.8	66.4
Calcium intake, mg[a,e]				
≤696.8	25,944	24.1	15.5	61.4
>696.8	25,945	22.2	13.8	64.0
Calcium, mg, + vitamin D, IU, intake[a,f]				
Low	44,377	23.5	14.2	62.3
High	7,512	20.8	14.0	65.3

Table continues

Analyses of association between hormone therapy use and colon cancer risk, incorporating hormone therapy information from Q2000, produced essentially the same results as those presented. For example, using information provided at baseline and Q2000 and treating the baseline-never/Q2000-never HT use group (n = 6,878) as the referent, we found that being a recent user at both time points (n = 18,023) was associated with a 40% reduction in colon cancer risk (RR = 0.60, 95% CI: 0.44, 0.83) (data not shown). Similarly, the time-dependent hormone therapy exposure variable supported the above-stated results in that recent hormone therapy users were at decreased risk for colon cancer (RR = 0.60, 95% CI: 0.44, 0.81) (data not shown).

DISCUSSION

Our results support the hypothesis that hormone therapy use is associated with decreased risk of invasive colon cancer. Baseline-recent HT use in the form of unopposed estrogen or combined estrogen-plus-progestin therapy was associated with a 36% decrease in colon cancer risk. This risk reduction was similar for unopposed estrogen users and for estrogen-plus-progestin users. Baseline-former use of hormone therapy was not associated with colon cancer risk.

Results of previous observational epidemiologic studies investigating the association between hormone therapy use and colon cancer risk have been inconsistent. A 1999 meta-analysis characterized the broad heterogeneity in findings among 18 cohort and case-control studies addressing the

Table 1. Continued

Characteristics	Total No.	Status of HT Use at Baseline (Estrogen, Estrogen + Progestin, or User of Mixed Formulations)		
		Baseline-Never HT User	Baseline-Former HT User	Baseline-Recent HT User
Family history of colorectal cancer[a,g]				
No	49,073	23.3	14.2	62.5
Yes	6,174	24.4	16.1	59.5
Personal history of colorectal polyps[a,h]				
No	51,425	23.6	14.2	62.3
Yes	3,822	21.0	18.1	61.0
Smoking history[a,i]				
Never smoker	33,035	24.4	14.0	61.6
Former smoker	19,878	20.9	14.8	64.3
Current smoker	3,631	30.0	15.4	55.0
Alcohol intake, g/day[a,j]				
0	17,520	27.9	15.4	56.7
<20	31,240	21.2	13.6	65.2
≥20	5,516	22.0	14.5	63.5

Abbreviations: HT, hormone therapy; NSAID, nonsteroidal antiinflammatory drug; SD, standard deviation.

[a] All percentages, except those for race/ethnicity and menopausal status, are age standardized by 5-year age categories to the age distribution of the analytical cohort; the numbers of missing and unknown participants are not shown in the table.

[b] "Other" includes Hispanic, Asian, Native American, mixed, or none reported.

[c] Long-term recreational physical activity combines strenuous and moderate activity and is defined as low, intermediate, or high average weekly hours of long-term recreational physical activity.

[d] Regular NSAID use combines information on aspirin and ibuprofen use. High NSAID use was defined as use ≥4 times per week for more than 4 years; low/no regular NSAID use included all others.

[e] Calcium intake (mg) from diet and supplements was cut at the median value for participants in this analysis, 696.8 mg/day.

[f] Calcium intake plus vitamin D intake (from diet and supplements) was dichotomized as the highest quartile for both calcium and vitamin D versus all others.

[g] A positive family history of colorectal cancer was defined as colon or rectal cancer in at least 1 first-degree relative (mother, father, sister, or brother).

[h] Self-reported personal history of colon or rectal polyps (not cancer) was categorized as no, yes, or unknown.

[i] Smoking history was categorized as never, former, or current smoker.

[j] Alcohol intake was categorized as 0 g/day, <20 g/day, or ≥20 g/day.

association between hormone therapy use and colon and rectal cancer separately, reporting a summary age-adjusted relative risk for the association between ever hormone therapy use and colon cancer risk of 0.80 (95% CI: 0.74, 0.86) (1). The majority of hormone therapy prescribed during the course of these studies was unopposed estrogen. Only 3 studies provided results for combined estrogen-plus-progestin therapy: 2 found statistically nonsignificant risk reductions (25, 26) and 1 found no effect (27). That baseline-recent HT use, but not baseline-former HT use, is associated with lower colon cancer risk has been reported previously (7).

In the Women's Health Initiative trials (28), continuous combined estrogen-plus-progestin therapy was associated with decreased colorectal cancer risk (2), whereas unopposed estrogen therapy was not (3). It is possible that the inclusion of rectal cancer in the outcome may have attenuated the estrogen result, but a 1999 meta-analysis reported a summary age-adjusted relative risk for the hormone therapy–rectal cancer association of 0.81 (95% CI: 0.72, 0.92).

Three studies have been published on hormone therapy and colon cancer risk since the Women's Health Initiative publication. Newcomb et al. (4) reported an inverse association between colorectal cancer risk and current estrogen-plus-progestin formulations in a large case-control study but no association with use of unopposed estrogen therapy or former estrogen-plus-progestin therapy. In contrast, Campbell et al. (5) reported lower risk of colorectal cancer among ever users of hormone therapy in a case-control study, with no statistically significant difference in the main effect by formulation. However, Campbell et al. did report a differential effect of current versus past use comparable to our results, but only among unopposed estrogen users. Finally, a report from the Breast Cancer Detection Demonstration Project follow-up study has provided results similar to ours with respect to formulation and recency of use (baseline-recent vs. baseline-former) (6).

The apparent attenuation of the duration dose response among baseline-recent HT users after 15 years of use has

Table 2. Adjusted[a] Relative Risks and 95% Confidence Intervals for the Association Between Baseline Status of Menopausal Hormone Therapy Use and Incident Invasive Colon Cancer Among Perimenopausal and Postmenopausal Participants in the California Teachers Study, 1995–2006

Status of HT Use at Baseline (Estrogen, Estrogen + Progestin, or User of Mixed Formulations)	Total No.	Person-Years	No. of Cases	Relative Risk[a]	95% Confidence Interval
Ever HT use, at baseline					
Never HT user	13,778	136,333	151	1.00	Referent
Ever HT user (former and recent HT users)	43,086	434,940	291	0.72	0.58, 0.88
Ever HT use, at baseline[b]					
Never HT user	13,778	136,333	151	1.00	Referent
Ever HT user, estrogen therapy only	16,427	162,541	142	0.71	0.56, 0.90
Ever HT user, estrogen + progestin therapy only	5,324	53,509	32	0.71	0.48, 1.06
Ever HT user, mixed formulations	21,335	218,891	117	0.72	0.56, 0.93
Former or recent HT use, at baseline[b]					
Never HT user	13,778	136,333	151	1.00	Referent
Former HT user	8,653	84,417	98	0.88	0.68, 1.15
Recent HT user	34,433	350,524	193	0.64	0.51, 0.80
Type of HT used at baseline[b]					
Never HT user	13,778	136,333	151	1.00	Referent
Former HT user	8,653	84,417	98	0.88	0.68, 1.14
Recent estrogen therapy user	15,090	151,523	93	0.59	0.45, 0.77
Recent estrogen + progestin therapy user	19,343	199,000	100	0.71	0.54, 0.93
Duration of HT use, at baseline[b]					
Never HT user	13,778	136,333	151	1.00	Referent
Ever HT user, <5 years' duration	19,265	196,235	120	0.85	0.66, 1.10
Ever HT user, 5–15 years' duration	13,541	137,519	69	0.57	0.42, 0.76
Ever HT user, >15 years' duration	8,097	79,596	87	0.73	0.55, 0.96
P_{trend}[c]					0.19
Duration of HT use, at baseline by former/recent use[b]					
Never HT user	13,778	136,333	151	1.00	Referent
Former HT user					
<5 years' duration	5,788	56,747	64	0.94	0.69, 1.26
5–15 years' duration	1,770	17,277	20	0.87	0.55, 1.39
>15 years' duration	730	6,854	10	0.91	0.48, 1.73
P_{trend}[c]					0.97

Table continues

not been reported previously. Most prior studies have categorized duration of hormone therapy use as <5 years or ≥5 years (4, 5, 7, 27, 29). The report from the Breast Cancer Detection Demonstration Project follow-up study showed a dose response with increasing duration up to ≥10 years of use (6). In the California Teachers Study, with restriction to women who had used only one hormone therapy formulation, this attenuation in risk for the longest duration (>15 years) was stronger among recent users of combined estrogen-plus-progestin therapy than among recent users of unopposed estrogen (data not shown). Further analytical strategies aimed at testing the consistency of the attenuation of the duration dose-response effect among the long-term baseline-recent HT users, such as exclusion of participants who were perimenopausal, those with early menopause (<43 years), or those who ended follow-up on December 31, 2001, which tests for misclassification of the longest duration baseline-recent HT due to undetected cessation of use, did not alter the results in the California Teachers Study. No statistically significant association was evident with years since last hormone therapy use among baseline-former HT users. These results agree with some (30, 31), but not all (26), previous studies.

Table 2. Continued

Status of HT Use at Baseline (Estrogen, Estrogen + Progestin, or User of Mixed Formulations)	Total No.	Person-Years	No. of Cases	Relative Risk[a]	95% Confidence Interval
Recent HT user					
<5 years' duration	13,487	139,488	56	0.76	0.54, 1.08
5–15 years' duration	11,771	120,242	49	0.49	0.35, 0.68
>15 years' duration	7,367	72,743	77	0.69	0.52, 0.92
P_{trend}[c]					0.60
Duration of HT use, at baseline by formulation[b]					
Never HT user	13,778	136,333	151	1.00	Referent
Ever HT user, estrogen therapy only					
<5 years' duration	6,231	61,785	59	0.89	0.65, 1.21
5–15 years' duration	4,489	45,284	28	0.60	0.40, 0.91
>15 years' duration	5,203	50,663	53	0.68	0.49, 0.94
P_{trend}[c]					0.08
Ever HT user, estrogen + progestin therapy only					
<5 years' duration	2,387	23,959	18	0.91	0.55, 1.53
5–15 years' duration	1,873	18,926	7	0.52	0.24, 1.12
>15 years' duration	701	6,972	6	0.79	0.35, 1.79
P_{trend}[c]					0.64
Ever HT user, mixed formulations					
<5 years' duration	10,647	110,491	43	0.76	0.52, 1.12
5–15 years' duration	7,179	73,309	34	0.53	0.36, 0.79
>15 years' duration	2,193	21,962	28	0.81	0.53, 1.25
P_{trend}[c]					0.58
Years since last HT use for former HT users, at baseline[b]					
Never HT user	13,778	136,333	151	1.00	Referent
Former HT user, ≤5 years since last use	3,873	38,596	28	0.82	0.54, 1.24
Former HT user, >5 years since last use	4,747	45,499	70	0.92	0.68, 1.23

Abbreviation: HT, hormone therapy.

[a] Adjusted for race (as shown), body mass index (continuous measure), and physical activity (low, intermediate, high) and stratified by age at cohort entry (continuous measure in years).

[b] The number of missing is not shown in the table.

[c] The trend effect was estimated by using the continuous variable of HT duration (in years) among users.

Few previous epidemiologic studies have addressed the possible association between hormone therapy use and colon cancer risk with respect to stage of disease at diagnosis. Nurses' Health Study investigators reported similar associations with hormone therapy for higher and lower stage colon cancers (7). Results from the Women's Health Initiative estrogen-plus-progestin trial indicated a statistically significant decreased risk for less advanced cancers and no statistically significant effect for regional or metastatic disease; in addition, colon cancers diagnosed in the estrogen-plus-progestin arm tended be of more advanced stage compared with those in the placebo arm (32). Recent Women's Health Initiative analyses have not shown lower colorectal mortality in the estrogen-plus-progestin arm than in the placebo arm (33). In contrast, the current California Teachers Study results suggest that the association between hormone therapy and invasive colon cancer is stronger in nonlocal disease; however, it is possible that this difference may be explained by a high level of screening among hormone therapy users in the California Teachers Study, which might increase the number of detected local cases. The California Teachers Study does not have data on colon screening specifically, precluding evaluation of an association between high socioeconomic status and overdiagnosis of colon cancer.

Of the plethora of California Teachers Study data items collected on the baseline questionnaire, several have been hypothesized to be associated with risk of colon or colorectal cancer. These include decreased physical activity (8, 9), body mass index (10, 11), nonsteroidal antiinflammatory drug use (12), calcium intake (13, 14), calcium plus vitamin D intake (15), family history of colorectal

Table 3. Adjusted[a] Relative Risks and 95% Confidence Intervals for the Association Between Baseline Status of Menopausal Hormone Therapy Use and Incident Invasive Colon Cancer, by Stage of Disease at Diagnosis,[b] Among Perimenopausal and Postmenopausal Participants in the California Teachers Study, 1995–2006

Status of HT Use at Baseline	Localized			Regional			Distant		
	No. of Cases	Relative Risk	95% Confidence Interval	No. of Cases	Relative Risk	95% Confidence Interval	No. of Cases	Relative Risk	95% Confidence Interval
Ever HT use, at baseline									
Never HT user	44	1.00	Referent	60	1.00	Referent	39	1.00	Referent
Ever HT user, estrogen therapy only	48	0.80	0.53, 1.23	66	0.84	0.59, 1.20	25	0.50	0.30, 0.84
Ever HT user, estrogen + progestin therapy only	14	1.06	0.57, 2.00	9	0.49	0.24, 0.99	9	0.80	0.38, 1.67
Ever HT user, mixed formulations	53	1.17	0.76, 1.78	46	0.65	0.43, 0.98	17	0.42	0.23, 0.76
Former or recent HT use, at baseline									
Never HT user	44	1.00	Referent	60	1.00	Referent	39	1.00	Referent
Former HT user	34	0.98	0.61, 1.55	37	0.84	0.55, 1.27	24	0.95	0.57, 1.58
Recent HT user	81	0.96	0.65, 1.40	84	0.68	0.48, 0.96	27	0.33	0.20, 0.56

Abbreviation: HT, hormone therapy.

[a] Adjusted for race (as shown), body mass index (continuous measure), and physical activity (low, intermediate, high) and stratified by age at cohort entry (continuous measure in years).

[b] Participants with missing stage ($n = 12$) are not shown in the table.

cancer (16), personal history of colorectal polyps (17), smoking history (18), and alcohol intake (19). Such factors were hypothesized to modify the association between hormone therapy and colon cancer risk or perhaps to interact with hormone therapy in the context of colon cancer risk. In this investigation, the most clear modification was a greater risk reduction associated with baseline-recent HT use among participants with a positive first-degree family history of colorectal cancer. Although the main effect between positive family history and increased colon cancer risk has been established by previous studies (16), only one case-control study has investigated the possible modification of the hormone therapy–colon cancer risk association by family history of colon cancer (34); no evidence for such an effect was detected (17, 18, 35).

A likely mechanism linking hormone therapy use with decreased colon cancer risk is regulation of apoptosis genes, perhaps through regulation by the estrogen receptor-β. Estrogen receptor-β is the dominant estrogen receptor in the human colon (36), and 17β-estradiol induces apoptosis in colon cancer cells through gene expression regulation mediated by estrogen receptor-β (37, 38).

Our study has several strengths. Its prospective design prevents the differential misclassification of exposure due to errors in recall, because exposures were measured before diagnosis. The large number of incident colon cancers provides substantial statistical power to detect associations of modest size. Linkage with the California Cancer Registry provides virtually complete case ascertainment and access to detailed information about tumor stage and location.

A consideration for the analyses herein is that classification of recent hormone therapy users was defined by hormone therapy status prior to 2002. The widely publicized early stopping of the Women's Health Initiative combined estrogen-plus-progestin trial due to evidence that overall risks exceeded the benefits of the treatment (2) in 2002 increases the likelihood that baseline-recent HT users stopped use shortly after baseline. Results of a sensitivity analysis in which follow-up was ended on December 31, 2001, did not differ measurably from those presented herein.

Other limitations include the lack of information in the California Teachers Study on dose for each formulation, which precluded examination of this detail, and possible residual confounding, which cannot be completely ruled out, even in light of the information on possible confounders obtained by the California Teachers Study.

The California Teachers Study cohort has a high baseline prevalence of hormone therapy use (20), consistent with the participants' above-average access to health insurance and health care and with levels of hormone therapy use in comparable cohorts (39). As described above, sensitivity analyses were performed to test the stability of our results to several such issues and found results consistent with an overall reduction in risk for baseline-recent HT users.

Baseline-recent HT use was associated with decreased risk of invasive colon cancer. Similar results were found for unopposed estrogen and estrogen-plus-progestin therapy. This association was modified by family history of colorectal cancer. These results highlight a need to understand the organ-specific effects of hormone therapy.

Table 4. Adjusted[a] Relative Risks and 95% Confidence Intervals of Invasive Colon Cancer, by Baseline Status of Menopausal Hormone Therapy Use, for Selected Potential Effect Modifiers, Among Perimenopausal and Postmenopausal Participants in the California Teachers Study, 1995–2006

	No. of Cases	Baseline Status of HT Use[b]						P_{trend}	$P_{homogeneity}$
		Baseline- Never HT User		Baseline- Former HT User		Baseline- Recent HT User			
		Relative Risk[a]	95% Confidence Interval	Relative Risk[a]	95% Confidence Interval	Relative Risk[a]	95% Confidence Interval		
Long-term recreational physical activity[c]									
Low	95	1.00	Referent	1.00	0.60, 1.67	0.47	0.29, 0.77	0.003	0.18
Intermediate/high	346	1.00	Referent	0.86	0.64, 1.16	0.70	0.54, 0.89	0.005	
Body mass index, kg/m^2									
<30	340	1.00	Referent	0.78	0.58, 1.01	0.66	0.52, 0.85	0.001	0.49
≥ 30	84	1.00	Referent	1.29	0.78, 2.14	0.52	0.30, 0.88	0.016	
Regular NSAID use[d]									
Low	396	1.00	Referent	0.87	0.66, 1.15	0.67	0.53, 0.85	<0.001	0.13
High	36	1.00	Referent	0.86	0.37, 1.95	0.37	0.17, 0.80	0.009	
Calcium intake, mg[e]									
≤ 696.8	204	1.00	Referent	0.84	0.57, 1.22	0.59	0.43, 0.82	0.001	0.60
>696.8	191	1.00	Referent	0.82	0.54, 1.23	0.67	0.48, 0.93	0.018	
Calcium, mg, + vitamin D, IU, intake[a,f]									
Low	330	1.00	Referent	0.86	0.63, 1.16	0.64	0.50, 0.83	<0.001	0.70
High	65	1.00	Referent	0.67	0.33, 1.35	0.56	0.32, 0.98	0.046	
Family history of colorectal cancer[g]									
No	375	1.00	Referent	0.89	0.66, 1.18	0.71	0.56, 0.90	0.005	0.04
Yes	55	1.00	Referent	0.96	0.51, 1.79	0.34	0.17, 0.66	0.001	
Personal history of colorectal polyps[h]									
No	392	1.00	Referent	0.93	0.71, 1.22	0.63	0.50, 0.80	<0.001	0.35
Yes	38	1.00	Referent	0.62	0.22, 1.69	0.87	0.40, 1.87	0.848	
Smoking history[i]									
Never smoker	248	1.00	Referent	0.90	0.64, 1.28	0.67	0.49, 0.90	0.007	0.96
Ever smoker	193	1.00	Referent	1.39	0.54, 3.62	0.68	0.27, 1.71	0.385	
Alcohol intake, g/day[j]									
0	141	1.00	Referent	0.92	0.59, 1.46	0.75	0.51, 1.10	0.864	0.34
>0	271	1.00	Referent	0.80	0.57, 1.13	0.60	0.45, 0.79	0.771	

Abbreviations: HT, hormone therapy; NSAID, nonsteroidal antiinflammatory drug.

[a] Adjusted for race (as shown), body mass index (continuous measure), and physical activity (low, intermediate, high) and stratified by age at cohort entry (continuous measure in years).

[b] "HT use" refers to use of any of the following: estrogen therapy only, estrogen + progestin therapy only, and mixed formulations.

[c] Long-term recreational physical activity combines strenuous and moderate activity and is defined as low, intermediate, or high average weekly hours of long-term recreational physical activity.

[d] Regular NSAID use combines information on aspirin and ibuprofen use. High NSAID use was defined as use ≥ 4 times per week for more than 4 years; low/no regular NSAID use included all others.

[e] Calcium intake (mg) from diet and supplements was cut at the median value for participants in this analysis, 696.8 mg/day.

[f] Calcium intake plus vitamin D intake (from diet and supplements) was dichotomized as highest quartile for both calcium and vitamin D versus all others.

[g] A positive family history of colorectal cancer was defined as colon or rectal cancer in at least 1 first-degree relative (mother, father, sister or brother).

[h] Self-reported personal history of colon or rectal polyps (not cancer) was categorized as no, yes, or unknown.

[i] For analyses of effect modification, smoking was categorized as never smoker or ever smoker.

[j] For analyses of effect modification, alcohol intake was categorized as 0 g/day or >0 g/day.

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