Title

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Journal

Epidemiology, 10(4)

ISSN

1044-3983

Authors

Jacobs, Eric J
White, Emily
Weiss, Noel S
et al.

Publication Date

1999-07-01

DOI

10.1097/00001648-199907000-00018

Peer reviewed

Hormone Replacement Therapy and Colon Cancer among Members of a Health Maintenance Organization

Eric J. Jacobs,[1,2] *Emily White*,[1,2] *Noel S. Weiss*,[1,2] *Susan R. Heckbert*,[2] *Andrea LaCroix*,[1,2,3] *and William E. Barlow*[3]

We investigated the association between hormone replacement therapy (HRT), primarily conjugated estrogens with or without medroxyprogesterone acetate, and colon cancer risk in a nested case-control study among women ages 55–79 years enrolled in Group Health Cooperative, a health maintenance organization in Washington state. Cases were diagnosed between 1984 and 1993. We selected controls randomly from enrollment files. HRT use was ascertained from a computerized database containing virtually all prescriptions dispensed since 1977. Among subjects with at least 5 years of pharmacy database information before reference date (1 year before diagnosis date), there were 341 cases of incident colon cancer and 1,679 controls. Estrogen use during the 5 years before reference date was not associated with risk of colon cancer [odds ratio (OR) = 0.85 and 95% confidence interval (CI) = 0.57–1.27 for 1–749 estrogen tablets; OR = 0.97 and 95% CI = 0.68–1.40 for ≥750 estrogen tablets]. An analysis including only women with at least 10 years of pharmacy database coverage found no association with use during the 10 years before reference date [OR = 1.07 (95% CI = 0.61–1.86) for 1–749 estrogen tablets; OR = 1.11 (95% CI = 0.69–1.80) for 750 or more estrogen tablets]. These results do not support the hypothesis that recent HRT use substantially reduces risk of colon cancer. (Epidemiology 1999;10:445–451)

Keywords: colon cancer, colorectal neoplasms, estrogen replacement therapy, hormone replacement therapy, menopause.

The question of whether hormone replacement therapy (HRT), either estrogen alone or in combination with a progestogen, affects risk of colon cancer is of some importance given the high prevalence of HRT use and continuing uncertainty over its potential health benefits and risks. In the United States, colon cancer is behind only lung and breast cancer as the leading cause of cancer death among women.[1]

The results of earlier epidemiologic analyses of ever use of HRT and incident colon cancer have not been consistent. Five of seven population-based case-control studies[2–6] and the two largest of the six cohort studies[7,8] have found decreased risk of colon cancer among ever-users of HRT, but two older case-control studies[9,10] and four cohort studies[11–14] found relative risks very close to 1.0. Results are more consistent for current HRT use. Five studies that presented results for current use reported relative risks of 0.7 or less,[4–8] and two other studies found little association.[11,14] After accounting for recency of use, no study has found increasing duration of HRT use to be associated with reduced risk of incident colon cancer. The general pattern of reduced risk only among recent users has led to the suggestion that HRT may be a late-acting agent in the process of colorectal carcinogenesis[15] and that duration of use among recent users may therefore be of lesser importance.

Most analyses of HRT and colon cancer have been based on self-reported years of HRT use. The two exceptions, pharmacy linkage studies in Canada[13] and Sweden,[12] found no association with ever use of HRT but did not address the issues of dose, type, or recency of HRT use. The purpose of this analysis was to examine the hypothesis that recent HRT users are at reduced risk of colon cancer, capitalizing on the ability of a health maintenance organization pharmacy database to provide information on recent HRT use that is likely to be more accurate and detailed than self-reported HRT exposure with respect to the type, dose, and quantity of HRT.

Subjects and Methods

Subject Selection

Cases were female members of Group Health Cooperative of Puget Sound (GHC), a nonprofit staff-model health maintenance organization established in 1947 in western Washington state. All cases were ages 55–79 years, diagnosed with invasive adenocarcinoma or carcinoma not otherwise specified of the colon (*International Classification of Diseases* site codes 153.0–153.9) dur-

From the [1]Public Health Sciences Division, Fred Hutchinson Cancer Research Center; [2]Department of Epidemiology, University of Washington; and [3]Center for Health Studies, Group Health Cooperative of Puget Sound, Seattle, WA.

Address correspondence to: Eric Jacobs, Department of Epidemiology and Surveillance Research, American Cancer Society, 1599 Clifton Road NE, Atlanta, GA 30329-4251.

Eric Jacobs was supported by Cancer Prevention Training Grant T32 CA09661 from the National Cancer Institute.

Submitted August 10, 1998; final version accepted February 3, 1999.

ing the 10-year period between January 1, 1984, and December 31, 1993. We identified cases (N = 441) through the Seattle-Puget Sound Surveillance Epidemiology and End Results registry, which covers the geographic area served by GHC. For each case, we randomly selected five controls, matched simultaneously on year of birth (5-year categories) and length of GHC enrollment (3-year categories) from the pool of women enrolled in GHC on the case diagnosis date. We defined the reference date as a date 1 year before diagnosis for cases. We assigned controls the same reference date as their matched case. Because cases and controls were matched for age at diagnosis date on the basis of 5-year categories of year of birth, we selected some controls who had ages outside the 55–79-year age range of the cases. After we excluded these women (N = 25), 2,180 controls were available for analysis.

Ascertainment of Hormone Replacement Therapy and Covariates

The primary source of information on use of HRT was the GHC computerized pharmacy database, which has been operational since March 1977. The pharmacy database contains a record for each individual prescription dispensed from GHC pharmacies. Each prescription record includes a patient identifier, tablet quantity, dosage, and formulation.

A secondary source of information on HRT use and other potentially relevant factors was the GHC breast cancer screening (BCS) questionnaire. This questionnaire included questions on potential breast cancer risk factors including lifetime HRT use (reported in categories of 1–4, 5–9, 10–14, and ≥15 years), as well as height, weight, parity, age at first birth, use of oral contraceptives, hysterectomy status, age at menopause, and smoking status. The BCS questionnaire was first mailed out to all female GHC members age 40 years and above in 1984–1986. Subsequently, new enrollees age 40 years or above were sent the questionnaire at enrollment.

Specific Analyses

We conducted two separate analyses of HRT use, each including overlapping subsets of the full set of 2,621 subjects (441 cases, 2,180 controls). The primary analysis examined recent use, determined solely from the pharmacy database. A secondary analysis examined lifetime use, including use before the establishment of the pharmacy database or before enrollment in GHC. Lifetime use was estimated by combining information from the pharmacy database with information on HRT use obtained from the BCS questionnaire.

Recent Hormone Replacement Therapy Use Analysis

In the recent use analysis, we examined the risk of colon cancer associated with use of HRT during both a 5-year period and a 10-year period immediately before reference date. We considered HRT prescriptions received during these periods to be recent use. For the 5-year-period analysis, we included only subjects with complete pharmacy database records during at least the 5 years immediately before reference date. After this restriction, 341 of the 441 cases and 1,679 of the 2,180 controls were available for analysis. Similarly, the 10-year-period analyses included only the 150 cases and 694 controls with 10 complete years of pharmacy database coverage immediately before reference date.

We classified women who filled only one prescription for estrogen tablets as never-users of estrogen. Similarly, we classified women who had filled only one prescription for a progestogen as never-users of progestogens. We excluded a small number of women (N = 4 in the 5-year analysis) who had used unopposed progestogens from all recent-use analyses.

We obtained the cumulative dose of conjugated estrogens (CE) by calculating the dose in each prescription (quantity of tablets multiplied by dose per tablet) and summing up the total doses from each prescription dispensed. Similarly, we obtained the cumulative dose of progestogen by summing up doses from medroxyprogesterone acetate (MDPA) tablets. We excluded from the analysis of cumulative estrogen dose all women (N = 44 in the 5-year analysis) who had received a prescription for oral estrogens other than CE (that is, ethinyl estradiol or esterified estrogens). Similarly, we excluded from the analysis of cumulative progestogen dose all women (N = 5 in the 5-year analysis) who had used progestogens other than MDPA.

Lifetime Hormone Replacement Therapy Use Analysis

To avoid bias, we limited the lifetime HRT analysis to subjects who had completed a BCS questionnaire before the diagnosis date for the case in each case-control set. A total of 353 subjects never completed a questionnaire, and 752 returned their questionnaires after diagnosis date, primarily those with diagnosis dates from 1984–1986, before the largest mass mailings of the questionnaire, which occurred in 1986. There were 276 cases and 1,240 controls remaining who had completed the questionnaire before diagnosis, but we excluded additional subjects from the lifetime HRT analysis because they had missing data on HRT use from the BCS questionnaire (8 cases and 46 controls) or because there were gaps in GHC enrollment after completion of the BCS questionnaire (3 cases and 8 controls). We also excluded an additional 3 cases and 27 controls who could not be classified with certainty as never, former, or current HRT users at reference date, either because they had not been enrolled at GHC during the entire 1-year period preceding reference date or because they received only one estrogen prescription during this one-year period. A total of 262 cases and 1,159 controls remained in the lifetime analysis.

We classified HRT users in the lifetime analysis as either current or former users on the basis of the number of estrogen prescriptions filled during the 1-year period before reference date. Women who filled two or more estrogen prescriptions during this 1-year period were

classified as current users, whereas ever-HRT users who filled no estrogen prescriptions during this time were classified as former users. Most estrogen prescriptions at GHC during the study period were for quantities that would provide for 3 months of use, assuming perfect compliance. Women who had filled only one estrogen prescription during the 1-year period were excluded.

We estimated duration of lifetime use by combining HRT use reported on the BCS questionnaire with HRT use recorded in the pharmacy database. Specifically, use was determined as the sum of two variables: (1) use before questionnaire completion and (2) use after questionnaire completion.

We calculated use before questionnaire completion as the larger of the following two parameters: (1) the minimum of the range checked off on the questionnaire (that is, 5 years, if the woman had reported 5–9 years of use on her questionnaire), and (2) the number of years of use before completion of the questionnaire as calculated from the pharmacy database. We calculated years of use from the pharmacy data by assigning a duration of use to each estrogen prescription based on tablet quantity and dosing instructions (when available) and then summing up the durations from each individual prescription. When dosing instructions were not available, tablet quantity alone was used to determine the duration of that prescription, based on usual prescribing practices at GHC. The great majority of estrogen prescriptions were prescribed in quantities that were multiples of 25, for use 25 times a month, or in multiples of 30, for daily use.

Use after questionnaire completion was determined on the basis of the pharmacy database alone. As described above, we calculated years of use by estimating the duration for each prescription and adding up the duration for all prescriptions dispensed.

Statistical Analysis

We used unconditional logistic regression to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) for colon cancer associated with categories of HRT use. We chose cutpoints for categories of HRT use in all recent use analyses based on the approximate median value among control subjects in the 5-year period before reference date. The cutpoint for estrogen (750 tablets) is also easily interpretable, because it represents 2½ years of use (half of the 5-year period), assuming 100% compliance and 25 tablets/month, the most common regimen prescribed at GHC. We adjusted for age at diagnosis in all analyses using 5-year categories. We also examined the matching variables of diagnosis year and length of GHC enrollment as potential confounders. In addition, we categorized all potential confounders obtained from the BCS questionnaire (smoking, height, weight, body mass index, oral contraceptive use, parity, age at first birth, age at menopause, and hysterectomy status) and examined them as potential confounders in the subset of women who had completed questionnaires before diagnosis, or the equivalent date for controls (62% of subjects with at least 5 years of pharmacy records). Because colon cancer can result in weight loss before diagnosis, we examined weight and body mass index only among women who had completed their questionnaire at least 2 years before their diagnosis date (or the diagnosis date of their matched case). Adjustment for any of these factors did not alter the ORs for either recent or lifetime hormone use by more than 5%. Therefore, the recent use analyses included all subjects regardless of whether they had completed the BCS questionnaire. We repeated the primary analyses taking the matched sets into account using conditional logistic regression, with very similar results. We explored subsite differences by comparing the OR estimated for proximal colon cancer (cecum through splenic flexure) and distal colon cancer (descending and sigmoid colon).

Results

Table 1 shows diagnosis age for cases (and the corresponding age for controls) who had at least 5 years of pharmacy database coverage immediately before reference date and were therefore included in the primary analysis of recent HRT use. Cases and controls were similar with respect to age, since they were matched on year of birth. Among subjects in the 5-year analysis for whom data were available (because they had completed a BCS questionnaire before diagnosis date), increased weight and body mass index were associated with somewhat increased risk of colon cancer, whereas smoking and reproductive history factors were not.

Table 2 presents age-adjusted ORs for colon cancer associated with HRT use during the 5-year period before reference date. Further adjustment of the ORs associated with HRT use for the variables shown in Table 1 did not change the results by more than 5%. Risk of colon cancer was not associated with HRT use. The OR was 0.97 (95% CI = 0.68–1.40) for women receiving ≥750 estrogen tablets (median = 1,275 estrogen tablets) during the 5-year period. Assuming 100% compliance and 25 tablets per month (the most common regimen prescribed at GHC), 750 tablets would provide for 2½ years of use.

The great majority of women in the highest estrogen tablet count category in table 2 (≥750 estrogen tablets received during the 5-year period) appear to have been HRT users at reference date. Among women receiving ≥750 estrogen tablets, 93% of cases and 95% of controls had received two or more estrogen prescriptions during the 1-year period before reference date. Among all women in the 5-year analysis, the OR for use at reference date (as defined by receiving two or more estrogen prescriptions during the year before reference date) as compared with no use during the 5-year period was 0.90 (95% CI = 0.64–1.25).

Women receiving ≥750 estrogen tablets during the 5-year period also appeared likely to have been estrogen users throughout all 5 years, as defined by receiving two or more estrogen prescriptions during each of the five 1-year periods included in the 5-year period (63% of cases and 67% of controls). Among all women in the

TABLE 1. Frequency of Potential Risk Factors Among Colon Cancer Cases and Controls with 5 or More Years of Pharmacy Records*

	Cases		Controls	
	N	%	N	%
Age at diagnosis (years)				
55–59	31	9.1	132	7.9
60–64	43	12.6	236	14.1
65–69	77	22.6	396	23.6
70–74	103	30.2	486	29.0
75–79	87	25.5	429	25.6
Smoking status				
Never smoked	108	49.1	501	50.5
Former smoker	79	35.9	326	32.9
Current smoker	33	15.0	165	16.6
Weight† (kg)				
<50	9	6.0	50	7.1
50–59	28	18.5	178	25.1
60–69	55	36.4	234	33.1
70–79	33	21.9	157	22.2
80–89	13	8.6	54	7.6
≥90	13	8.6	35	4.9
Body mass index† (kg/m^2)				
<20	11	7.3	64	9.1
20–<23	38	25.2	164	23.3
23–<26	41	30.5	218	31.0
26–<29	25	16.6	120	17.1
29–<32	17	11.3	76	10.8
≥32	19	12.6	62	8.8
Parity				
Nulliparous	30	13.2	122	11.9
Parous	198	86.8	907	88.1
Age at natural menopause‡ (years)				
≤44	9	6.8	69	11.2
45–50	53	40.2	255	41.5
51–54	50	37.9	202	32.9
≥55	20	15.2	88	14.3
Age at hysterectomy (years)				
Never	133	67.9	629	70.2
≤44	31	15.8	130	14.5
45–50	21	10.7	84	9.4
51–54	8	4.1	42	4.7
≥55	3	1.5	11	1.2

* Age is among all cases (N = 341) and controls (N = 1,679) with 5 or more years of pharmacy records. All other variables are among cases (N = 228) and controls (N = 1,029) with 5 or more years of pharmacy records who also completed a questionnaire before diagnosis.
† Among women completing the breast cancer screening questionnaire at least 2 years before diagnosis.
‡ Among women age 55 or older when completing the questionnaire. Excludes women reporting surgical menopause.

5-year analysis, the OR for use throughout all 5 years (as defined above) compared with no use during the 5-year period was 0.98 (95% CI = 0.64–1.50).

When unopposed estrogen and use of progestogens in combination with estrogen (combination HRT) were examined separately, results were nearly null and similar for both HRT regimens (Table 2). The OR was 1.04 (95% CI = 0.59–1.82) for women who received ≥180 progestogen tablets (median = 380 progestogen tablets) during the 5-year period. Assuming 100% compliance and 10 progestogen tablets per month (the most common regimen prescribed at GHC), 180 tablets would provide for 1½ years of use.

CE accounted for more than 96% of estrogen prescriptions in the 5-year analysis. The most common dose of CE was 0.625 mg per tablet (65% of case prescriptions, 56% of control prescriptions), although there were substantial numbers of prescriptions for both 0.3-mg and 1.25-mg CE tablets.

Cumulative dose of CE was not associated with colon cancer risk (Table 2). Similarly, no association with colon cancer risk was found when users of estrogens other than CE and users of lower-dose CE tablets (<0.625 mg CE) were excluded [OR = 1.29 (95% CI = 0.81–2.04) for ≥750 estrogen tablets].

MDPA accounted for at least 99% of the progestogen prescriptions for both cases and controls in the 5-year analysis, and the great majority of MDPA prescriptions were for 10-mg tablets. Results for cumulative dose of MDPA were very similar to those for progestogen tablet count (data not shown).

Table 3 presents age-adjusted ORs for colon cancer associated with HRT use during the 10-year period before reference date. Neither estrogen tablet count nor cumulative dose of CE were associated with increased risk of colon cancer. Results were similar and close to null when unopposed and combination HRT were examined separately (data not shown). The distribution of types and doses of estrogens and progestogens in the 10-year analysis was similar to that in the 5-year analysis described above.

Table 4 presents ORs for lifetime use of HRT derived from combining questionnaire and pharmacy data. There was no association between HRT use and risk of colon cancer, even for women who were current HRT users at reference date and had used HRT for 10 or more years (OR = 0.86; 95% CI = 0.54–1.37), although statistical power was limited.

The association between HRT and colon cancer did not appear to differ substantially by age, tumor stage, or colon subsite, although the CIs were wide for these subanalyses. In the 5-year analysis, the age-adjusted OR for ≥750 estrogen tablets *vs* none was 1.14 (95% CI = 0.71–1.83) for women ages 55–69 years, as compared with 0.79 (95% CI = 0.45–1.41) for women ages 70–79 years. The OR for ≥750 tablets was 1.24 (95% CI = 0.71–2.17) for local disease as compared with 0.88 (95% CI = 0.57–1.38) for regional or distant disease. When examined by subsite, the OR for ≥750 estrogen tablets *vs* none was 1.14 (95% CI = 0.73–1.78) for proximal colon cancer and 0.80 (95% CI = 0.45–1.40) for distal colon cancer.

Discussion

This study, specifically designed to examine recent use, found no suggestion of decreased risk of colon cancer for recent HRT users. These results contrast with the reduction in risk found in most other studies that have examined recent or current use.[4–8]

TABLE 2. Odds Ratios and 95% Confidence Intervals for Colon Cancer Associated with Recent Hormone Replacement Therapy (HRT) during a 5-Year Period*

	Cases	Controls	Age-Adjusted OR	95% CI
Unopposed estrogen or combination HRT†				
Estrogen tablet count				
0‡	268	1,294	1.0	
<750	32	180	0.85	0.57–1.27
≥750	41	205	0.97	0.68–1.40
Cumulative dose of conjugated estrogen (mg)§				
0‡	268	1,294	1.0	
<375	28	169	0.80	0.53–1.23
≥375	39	178	1.08	0.74–1.56
Unopposed estrogen‖				
Estrogen tablet count				
0‡	268	1,294	1.0	
<750	21	117	0.86	0.53–1.40
≥750	28	129	1.07	0.69–1.65
Cumulative dose of conjugated estrogens (mg)§				
0‡	268	1,294	1.0	
<375	18	112	0.78	0.46–1.30
≥375	30	112	1.32	0.68–2.03
Combination HRT¶				
Progestogen tablet count				
0‡	268	1,294	1.0	
<180	8	65	0.59	0.28–1.24
≥180	16	74	1.04	0.59–1.82

* Based exclusively on pharmacy data during a 5-year period up to reference date (1 year before diagnosis date). Includes only cases and controls with 5 complete years of pharmacy data before reference date. All analyses exclude users of progestogen only.
† Includes estrogen users regardless of progestogen use.
‡ Referent category.
§ Excludes users of estrogens other than conjugated estrogens.
‖ Excludes progestogen users.
¶ Excludes users of unopposed estrogen.

TABLE 3. Odds Ratios and 95% Confidence Intervals for Colon Cancer Associated with Recent Hormone Replacement Therapy (HRT) during a 10-Year Period*

	Cases	Controls	Age-Adjusted OR	95% CI
Estrogen tablet count				
0†	96	490	1.0	
<750	18	86	1.07	0.61–1.86
≥750	26	118	1.11	0.69–1.80
Cumulative dose of conjugated estrogens (mg)‡				
0†	96	490	1.0	
<375	17	86	1.03	0.59–1.83
≥375	23	95	1.24	0.75–2.07

* Based exclusively on pharmacy data during a 10-year period up to reference date (1 year before diagnosis). Includes only cases and controls with 10 complete years of pharmacy data before reference date.
† Referent category.
‡ Excludes users of estrogens other than conjugated estrogens.

The Nurses' Health cohort,[8] the Iowa Women's cohort,[7] and three population-based case-control studies[4–6] all found relative risks between 0.5 and 0.7 for incident colon cancer among women who were current users of HRT. Two smaller cohort studies found relative risks close to 1.0 for colon cancer associated with current use.[13,14] A large American Cancer Society mortality study found a relative risk of 0.6 (95% CI = 0.4–0.8) for colon cancer among current HRT users at the beginning of a 9-year follow-up.[16] In addition, two case-control studies of the prevalence of colorectal adenomatous polyps found similarly decreased risk among HRT users, most[17] or all[15] of whom were recent users. Recently, the Nurses' Health Study found decreased risk for large, but not small, colorectal adenomatous polyps among current HRT users.[8]

Because our results differ from those of other studies it may be important to consider definitions of current use. Current use has been defined as use at the time of the baseline questionnaire several years before the end of follow-up for some cohort studies,[7,16] use at the date of the last updated annual or biennial questionnaire for other cohort studies,[9,16] and use at a reference date 1 year[5] or 2 years[4,6] before date of diagnosis for the case-control studies. In our 5-year recent use analysis, the great majority of women in the highest category of HRT use (≥750 estrogen tablets during the 5-year period) had filled at least two estrogen prescriptions in the year before reference date, indicating they were likely to have been users at reference date. In general, our measure of recent use appears to correspond reasonably closely to current use as defined in other studies.

It is unclear why our results for recent use differ from those of most previous studies, which found substantially reduced risk. Our measure of recent exposure is probably more accurate than that of most other studies. Therefore, if recent HRT use provides substantial protection against colon cancer, we would have expected to find reductions in risk as great as or greater than those found in other studies. Chance is always a possible explanation.

We also examined lifetime duration of HRT use and found little association, even for long duration use (≥10 years). No study of colon cancer incidence has found a trend with duration of use that is independent of recency of use. The very large American Cancer Society study of colon cancer mortality did find a trend of decreasing risk with increasing duration of HRT among both current and former users, but the magnitude of this trend was relatively small.[16]

The primary strength of our analysis is that recent HRT use as measured from the pharmacy database records should be highly accurate, detailed, and complete. GHC members are unlikely to have received HRT elsewhere, because the cost of HRT is substantially reduced if they receive it through the GHC pharmacy. In a 1995 survey of randomly selected GHC women ages 50–80 years, 97% of the 462 self-reported current HRT users reported filling all of their HRT prescriptions at

TABLE 4. Odds Ratios and 95% Confidence Intervals for Colon Cancer Associated with Lifetime Use of Hormone Replacement Therapy (HRT), by Recency and Duration of Use*

Lifetime HRT Use	Cases (N = 262)	Controls (N = 1159)	Age-Adjusted OR	95% CI
Never user†	135	585	1.0	
Former user‡				
<10 years	60	271	0.95	0.68–1.33
≥10 years	20	85	1.00	0.59–1.69
Current user§				
<10 years	21	88	1.02	0.60–1.73
≥10 years	26	130	0.86	0.54–1.37

* Based on BCS questionnaire and pharmacy data; excludes women with only one estrogen prescription during the 1-year period preceding reference date.
† Referent category.
‡ Former use defined as filling no estrogen prescriptions during the one-year period before reference date.
§ Current use defined as filling two or more estrogen prescriptions during the one-year period before reference date.

GHC [Katherine Newton (GHC), 1997, personal communication]. Although not every HRT prescription dispensed may have been actually taken, it seems highly likely that women repeatedly filling prescriptions for HRT were in fact using them (women receiving only one prescription of HRT were considered nonusers). The pharmacy database records of HRT use also allowed examination of tablet count and cumulative dose, rather than years of use, the measure typically estimated from interview- or questionnaire-based studies. Self-reported years of use is limited by memory and does not reflect variation in HRT exposure owing to varying compliance with taking prescribed medications. Finally, although ours is a case-control study, all exposure data were collected prospectively, that is, before diagnosis. As a result, there is unlikely to be differential measurement error.

Measurement of HRT use in our lifetime analysis is more vulnerable to misclassification, because it was based in large part on self-report. Since the questionnaire was administered before the onset of disease, any bias from this misclassification is likely to be nondifferential, potentially obscuring a small protective effect.

An additional strength of this analysis is that there was no opportunity for subject participation rates to bias our results, because there was no direct subject participation. This differs from most case-control studies of HRT use and colon cancer, which could have underestimated risk (that is, suggested a protective effect when none exists), if for example, women who used HRT were more likely to participate as controls than women who did not.

A considerable proportion of cases and controls were excluded from either the recent use analysis or the lifetime analysis owing to incomplete information on HRT use. In the recent-use analysis, many subjects were excluded because they had not been enrolled at GHC for 5 or more years (precluding accurate ascertainment of HRT use in this time period). In the lifetime analysis, many cases and controls were excluded because they had not completed a BCS questionnaire before diagnosis date of the case (often because their diagnosis date preceded the first large mailings of the BCS questionnaire). These exclusions were based on enrollment or response status before diagnosis. We therefore have no reason to believe that they could have biased our results.

A limitation of this study is that we had no information on potential confounders such as diet, physical activity, endoscopic screening, and alcohol use. A high-fiber and high-vegetable diet, more physical activity, and endoscopic screening (potentially resulting in removal of precancerous polyps) would be expected to be associated with decreased risk of colon cancer. These characteristics may also be associated with HRT use in U.S. populations. Greater physical activity has been weakly associated with HRT use in some U.S. populations.[19,20] In the Nurses' Health Study, 16% of women currently taking hormones reported undergoing screening sigmoidoscopy compared with 11% of women who had never used hormones.[8] Nevertheless, possible confounding by physical activity, diet, or screening endoscopy would most likely result in the observed risk being lower than the true risk associated with HRT.

A greater concern is that alcohol use appears to be somewhat more common among HRT users in U.S. populations,[19,21] and moderate or high alcohol use may be associated with increased risk of colon cancer.[22,23] Lack of adjustment for alcohol use could therefore result in overestimating the risk associated with HRT, obscuring any true protective effect. The prevalence of alcohol use among older women at GHC was relatively low, however, and did not appear to be dramatically higher among HRT users: among postmenopausal controls in another GHC study from the same time period as our study, 13.3% of women who had never used HRT reported five or more drinks a week compared with 18.2% of current HRT users (unpublished results; study described in Ref 24). These results suggest that strong confounding by alcohol use is unlikely.

In conclusion, this moderately large study used accurate and detailed information from a pharmacy database to examine recent HRT use, the usage pattern that has been most consistently associated with reduced colon cancer risk. Our results do not support a substantial protective effect of HRT use on risk of colon cancer.

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