

Recent Use of Hormone Replacement Therapy and the Prevalence of Colorectal Adenomas

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Abstract

The etiological role of hormone replacement therapy (HRT) (including estrogen only, combined estrogen-progesterone, and progesterone only) in colorectal neoplasia remains unclear. Several large studies have reported a reduced risk of colorectal cancer among HRT users; however, other studies have given inconsistent results. We examined the association between HRT and colorectal adenomatous polyps, precursors of colorectal cancer, among female participants in a case-control study. Subjects were members of a prepaid health plan in Los Angeles who underwent sigmoidoscopy in 1991-1993. Participants received an in-person interview and completed a food frequency questionnaire. A total of 187 histologically confirmed cases and 188 controls, ages 50-75 years, were included in the analysis. Compared with women who did not use HRT during the year before sigmoidoscopy, recent users had an adjusted odds ratio of 0.57 (95% confidence interval, 0.35-0.94). Duration of use was inversely related to the prevalence of colorectal adenomas, with a multivariate-adjusted odds ratio of 0.49 (95% confidence interval, 0.25-0.97) for use of 5 years or more. These results support a protective effect of HRT on colorectal adenomatous polyps.

Introduction

In 1980, McMichael and Potter postulated that exogenous female hormones could reduce the risk of colorectal cancer (1). Exogenous estrogen and progestin modify hepatic cholesterol metabolism (2) and decrease bile acid synthesis and secretion (1, 3, 4) in animals and humans. Bile acids, particularly sec-

ondary bile acids, have been shown to promote colon carcinogenesis (5). Exogenous estrogen also might act via a direct effect on colonic mucosa. Estrogen receptors have been found in human colon carcinoma, in adenomatous polyps, and in the adjacent normal mucosa (6, 7). In addition, an inhibitory effect of estrogen on the growth of colon cancer has been observed *in vivo* and *in vitro* (8, 9).

Epidemiological data on menopausal hormone use in relation to risk of colorectal cancer are inconsistent (10-24). Several recent studies (10-13, 15, 16), however, consistently found an inverse association, which may be due to changes in hormone use. Two studies of colorectal adenomatous polyps have been reported (25, 26), and both suggested that replacement hormones were protective.

Adenomatous polyps are considered to be precursors of colorectal cancer (27-30). Therefore, a better understanding of the etiology of adenomas may provide information about the pathogenesis and prevention of colorectal cancer. In addition, studying polyps allows measurement of exposure closer to the initiation of the neoplastic process, improving recall of past hormone use.

We examined the association between menopausal hormone use and the prevalence of colorectal adenomatous polyps in a case-control study among female members of a large prepaid health plan in southern California.

Subjects and Methods

The methods of the present study have been described in detail elsewhere (31). Subjects were eligible for the study if they underwent sigmoidoscopy at either of two Southern California Kaiser Permanente Medical Centers (Bellflower and Sunset) from January 1, 1991 through August 25, 1993. Eligible subjects were ages 50-75; were free of invasive cancer, inflammatory bowel disease, and familial polyposis; were fluent in English; had no previous bowel surgery; were residents of the metropolitan Los Angeles area; and had no physical or mental disability precluding an interview. In addition, subjects who had symptoms suggestive of any organic intestinal disease were excluded. Cases were subjects diagnosed for the first time with one or more histologically confirmed adenomatous polyp. Controls had no polyps of any type at sigmoidoscopy, had no history of polyps, and were individually matched to cases by gender, age (within 5-year categories), date of sigmoidoscopy (within 3-month categories), and Kaiser Center.

During the accrual period, we identified 628 cases and 689 controls who were potentially eligible. Of these, 70 cases and 94 controls refused interview, and we were unable to contact 29 cases and 32 controls. Thus, we obtained interview data for 529 cases and 563 controls. The response rate (number interviewed: number eligible) was 84% among cases and 82% among controls.

Among interviewed subjects, the indications for sigmoidoscopy were: (a) routine for 45% of cases and 44% of controls;

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(b) referred for specific minor symptoms for 16% of cases and 13% of controls; and (c) not given for 39% of cases and 43% of controls. The average penetration of the flexible sigmoidoscope was 55 cm for cases (SD = 11 cm) and 59 cm for controls (SD = 5 cm). Fifteen cases had carcinoma *in situ* in addition to adenomatous polyps.

Participants provided data on smoking, therapeutic drug use, physical activity, height, weight, family history of cancer, and other factors during a 45-min in-person interview. The interview was administered on average 5 months after sigmoidoscopy. Questions about exposure referred to the time before sigmoidoscopy. The interviewer remained unaware of participants' case or control status for 70% of cases and 87% of controls. Data on HRT² was identified from the list of medications reported by subjects in response to questions regarding use of medication other than analgesics during the year before their sigmoidoscopy. Brand name, dose, and duration of use were ascertained. A woman was defined as a recent user of HRT if she reported use of menopausal hormones (including estrogen only, combined estrogen-progesterone, and progesterone only) during the year before sigmoidoscopy. Otherwise, she was classified as a nonrecent user. A 126-item semiquantitative food frequency questionnaire (32) that inquired about diet in the year before sigmoidoscopy was also completed by participants.

The present analysis was limited to female subjects. To make use of data for the unmatched subjects (15 cases and 16 controls), unconditional logistic regression (ignoring the matched pairs) was used to estimate ORs and CIs. Covariates included in the multivariate model were age (5-year intervals), date of sigmoidoscopy (10-month intervals), Kaiser center, ethnicity (white, black, Hispanic, and Asian), body mass index (≤ 25.5 , >25.5 – 29.5 , and >29.5 kg/m²), vigorous leisure time activity (MET-h/week), and smoking status (never, current, and past) (Refs. 31 and 33–36).

Selected characteristics of the 187 cases and 188 controls are shown in Table 1. The subjects were mostly white. The mean age of the cases was 60.8 years, and that of the controls was 60.4 years. Recent use of HRT was reported by 20% of cases and 31% of controls. About 60% of women who reported HRT use used estrogen only; 39% used combined estrogen-progestin therapy. The brand of estrogen most frequently reported was Premarin (97% of estrogen users), with 0.625 mg being the preferred dose (81% of Premarin reported); progestin users reported use of either Provera or medroxyprogesterone, with 2.5 mg being the preferred dose (46%); 10 mg was reported by 40%. The limited number of subjects reporting use of other dosage levels of estrogen or any given level of progesterone precluded us from examining dose-specific associations. Other details on the use of HRT (*i.e.*, age started and therapeutic regimen) were not collected.

Results

Compared with women who did not use HRT during the year before sigmoidoscopy, women who reported HRT use had a lower prevalence of colorectal adenomatous polyps (Table 2). The MV-A OR for recent use was 0.57 (95% CI, 0.35–0.94). The estimate was similar to the one obtained by adjusting for the matching variables only (OR = 0.54; 95% CI, 0.34–0.88). Further adjustment for intake of total calories, red meat, fruit

Table 1 Characteristics of the study population

	Cases (n = 187)	Controls (n = 188)
Age (mean, yr)	60.8	60.4
Ethnicity ^a %		
White	52.1	49.7
Black	19.7	19.8
Hispanic	17.6	19.3
Asian	10.6	11.2
Smoking (%)		
Never	50.3	58.5
Current	20.3	7.5
Former	29.4	34.0
Body mass index (%; kg/m ²)		
≤ 25.5	47.3	35.3
>25.5 – 29.5	24.0	34.8
>29.5	28.7	29.9
Vigorous leisure activity ^b (mean; MET-h/week)	4.2	5.5
Dietary intake		
Fruit and vegetable intake ^c (mean; servings/day)	6.0	6.7
Alcohol (mean; g/day)	3.7	2.6
Red meat (mean; g/day)	65.5	53.5

^a Three cases and three controls with missing or "other" race were assumed white.

^b Sum of the hours/week spent in vigorous leisure-time activities, with the hours spent at each activity weighted by the ratio of energy expenditure in that activity to energy expenditure at rest.

^c Seven cases and four controls had no dietary data.

and vegetables, and alcohol and use of nonsteroid anti-inflammatory agents had essentially no effect on the results (data not shown). Increasing duration of HRT use was inversely associated with the prevalence of polyps (MV-A β for duration of HRT in years as a continuous variable = -0.065 ; SE of β = 0.026). The MV-A OR for use of HRT for over 10 years *versus* nonrecent use was 0.26 (95% CI, 0.09–0.74). Results remained unchanged after excluding subjects with carcinoma *in situ*.

The protective effect seemed to be stronger among those who used estrogen only. Compared with women who did not use HRT during the year before sigmoidoscopy, those who recently used only estrogen had a MV-A OR of 0.42 (95% C.I., 0.22–0.79), whereas those who used combined estrogen-progestin therapy had a MV-A OR of 0.87 (95% C.I., 0.42–1.78). The *P* for comparison of the effect of combined therapy to the effect of estrogen only was 0.11. The stronger effect among users of estrogen only was manifest even after accounting for duration of use in the analysis.

Subsite analysis revealed no substantial differences in association between the left colon and rectum. The MV-A OR for recent use of HRT was 0.54 for the left colon (95% CI, 0.30–0.96) and 0.67 (95% CI, 0.33–1.39) for the rectum.

Sixteen percent of cases and 15% of controls were referred for specific minor symptoms. We excluded subjects with minor symptoms from the analysis, and the result was similar to the estimated effect of recent HRT use shown in Table 2 (MV-A OR = 0.54; 95% CI, 0.31–0.94).

To focus on a more homogeneous group, we performed an analysis after excluding women who were likely to be premenopausal. Because the menopausal status was not ascertained in this study, we defined the following subjects as postmenopausal: (a) those who were 55 or more years old, if they were nonsmokers; or (b) those who were 54 or more years old, if they were smokers (*n* = 340) (Ref. 15). The effect of recent use was slightly stronger than that observed in the complete study group (MV-A OR = 0.48; 95% CI, 0.28–0.82).

² The abbreviations used are: HRT, hormone replacement therapy; MET, metabolic equivalents; OR, odds ratio; CI, confidence interval; MV-A, multivariate-adjusted.

Table 2 Adjusted OR^a of adenomatous colorectal polyps in relation to recent use of HRT

	No. of cases	No. of controls	OR ₁ ^b	95% CI	OR ₂ ^c	95% CI
Nonrecent users ^d	150	130	1		1	
Recent users	37	58	0.54	0.34–0.88	0.57	0.35–0.94
Years of use						
≤5 yr	21	28	0.65	0.34–1.24	0.64	0.34–1.25
>5 yr	16	30	0.49	0.25–0.97	0.48	0.23–0.97
P ^e			0.01		0.02	

^a Unconditional logistic regression.

^b OR adjusted for matching variables: age (5-year age intervals); sigmoidoscopy date (10-month intervals); and Kaiser Center.

^c OR adjusted for matching variables: age (five 5-year age groups); sigmoidoscopy date (three 10-month interval categories); Kaiser Center; plus physical activity (continuous), body mass index (≤25.5, >25.5–29.5, and >29.5 kg/m²), smoking (never, current, and past), and ethnicity (white, black, Hispanic, and Asian).

^d Recent users: use of HRT (including estrogens and/or progestin) during the year before the sigmoidoscopy. Nonrecent users are those who did not take hormones (estrogen and/or progestin) during the year before the sigmoidoscopy.

^e P for trend was estimated by entering duration of use as a continuous variable into the model.

Although the sample size was small, recent use of HRT in relation to the prevalence of colorectal adenomas was also examined according to body mass index, smoking status, physical activity, ethnicity, and alcohol consumption. Subjects were divided into several categories, and the effect estimates were compared across groups. The results were similar across levels of those factors except for ethnicity (likelihood ratio $\chi^2 = 8.85$, 3 degrees of freedom; $P = 0.03$). Recent use of HRT seemed to be preventive in whites (MV-A OR = 0.54; 95% CI, 0.27–1.07), blacks (MV-A OR = 0.18; 95% CI, 0.05–0.66), and possibly for Asians (MV-A OR = 0.42; 95% CI, 0.08–2.23). The results for Hispanics, however, suggested an increased risk (MV-A OR = 2.13; 95% CI, 0.68–6.70), but this estimate was based on only 11 exposed cases.

Discussion

We found an inverse relation between recent postmenopausal hormone use and colorectal adenomatous polyps. Moreover, the decrease in risk was proportional to the duration of HRT use. Two other studies have examined the association of HRT with colorectal adenomatous polyps (25, 26). In a colonoscopy-based study, Potter *et al.* (26) found an inverse relationship between HRT and colorectal adenomatous polyps, with an OR of 0.39 (95% CI, 0.32–0.85) for HRT use of 5 years or more. An inverse association was also suggested by the other colonoscopy-based study (25). Perhaps due to the smaller sample size, however, the latter findings were also consistent with no effect. Although previous studies of replacement therapy and colorectal cancer have yielded inconsistent results, our results agree with several recent studies (10–13, 15, 16). The consistently inverse association found by recent studies might be partly due to the recency and duration effects, because recent studies are likely to include more recent and long-term users.

Jacobs *et al.* (12) postulated that the relatively recent addition of progestin to HRT might have increased its protective effect against colorectal cancer. In a recent large study of the HRT and colon cancer association by type of HRT (15), however, the result was similar for combined estrogen-progestin therapy and estrogen only. Our results also suggested that combined therapy has no additional beneficial effect above that of estrogen alone.

Because subjects were asked to provide detailed information on their medications only for the year before sigmoidoscopy, we were not able to distinguish women who stopped taking HRT 1 year or more before the sigmoidoscopy from those who had never received HRT. The reference group there-

fore consisted of past users as well as never users. Several studies that have shown an inverse relationship between use of HRT and the risk of colorectal cancer reported that the former use of HRT either had no effect (12, 15) or its effect was weaker compared with current use of HRT (10). If past use does have an effect on polyp risk, the effect observed in this study could be stronger if the reference group had been confined to never users only. Previous validation studies have demonstrated that subjects can fairly accurately recall postmenopausal hormone use (37, 38), and that recall tends to be better for the more recent past (38). Although the questions on HRT were posed differently in our study than in the validation studies, focusing on recent exposure might have somewhat decreased measurement error.

The present study was restricted to left-sided adenomas. Polyps might have been present among subjects in the colon beyond the reach of a sigmoidoscope. About 20% of subjects with no family history who have no polyps detected by a sigmoidoscope may have one or more polyps in the proximal colon (39, 40). If the effect of HRT did not differ according to colon site, our results would be underestimates of the true effect when applied to the entire colon. Moreover, the protective effect of HRT might be greater for the proximal colon (1, 12, 41). Therefore, the results of this study of left-sided polyps are best not generalized to the entire colon. A protective role of HRT on cancer of the rectum was generally not supported by previous studies, although Furner *et al.* (14) found a relative risk of rectal cancer of 0.2 (95% CI, 0.03–0.77) among users of HRT. In the present study, separate analyses of left-sided colon and rectum yield similar results.

In contrast to the previous studies of HRT and polyps (25, 26), our study consisted of cases and controls who were largely asymptomatic; therefore, differential recall of HRT use was probably minimized. The hypotheses tested in the present study are not well known by the public, and the interviewers were blinded to disease status for most of interviews. Moreover, because all women in the source population underwent the same endoscopic procedure, possible differential misclassification of outcome status was also minimized. Selection bias was also likely to be minimal because of the relatively high participation rates.

Our study lends further support to a protective effect of HRT on the risk of colorectal neoplasia and suggests that HRT might exert a protective effect against colorectal cancer in the early stage of carcinogenesis.

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