

# A prospective study of menopausal hormones and risk of colorectal cancer (United States)

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(Received 21 May 1996; accepted in revised form 1 July 1996)

The relation of colorectal cancer and its subsites with use of menopausal hormones was evaluated in the United States among 40,464 postmenopausal women, 41 to 80 years of age, who initially volunteered for a nationwide breast-cancer screening program and were followed for an average of 7.7 years. Ever-use of menopausal hormones was not associated with risk of total colorectal cancers (relative risk [RR] = 0.99, 95 percent confidence interval [CI] = 0.79-1.2) or cancers of the colon (RR = 1.1, CI = 0.81-1.6) or rectum (RR = 1.1, CI = 0.59-1.9). Recent hormone users, however, had a small nonsignificant reduction in risk of colorectal cancer (RR = 0.78, CI = 0.55-1.1), which was most pronounced for distal colon (RR = 0.68, CI = 0.29-1.6) and rectal tumors (RR = 0.64, CI = 0.24-1.7). No effect was observed for former hormone users, and risk generally did not vary by time since last use, type of regimen, or duration of use. However, the reduced risk for recent users was stronger for users of five or more years' duration. These data show some lowering of colorectal cancer risk among recent menopausal hormone users of long duration. *Cancer Causes and Control* 1997, 8, 130-138

**Key words:** Colorectal cancer, hormone replacement therapy, menopausal estrogens, United States, women.

## Introduction

Large international variation and migrant shifts in the incidence of colon cancer indicate the importance of environmental exposures, including dietary and other life-style factors. The possible role of reproductive status stems from the observation by Fraumeni *et al*<sup>1</sup> that nuns experienced an excess of large bowel cancer, as well as cancers of the breast, uterus, and ovary. Based on age-gender trends in colorectal incidence and mortality rates, and other considerations, McMichael and Potter<sup>2</sup> hypothesized that multiparity and use of high-dose oral contraceptives (OC) might be protective for the development of colon cancer. Epidemiologic data, however, on

the relation of reproductive factors to colon cancer have been inconclusive.<sup>3</sup> There also has been little support for an effect of OCs, with two early case-control studies<sup>4,5</sup> suggesting a reduced risk of colon cancer, while subsequent case-control<sup>6,7</sup> and cohort studies<sup>8-10</sup> have indicated no association.

Recently, attention also has been given to the possible influence of menopausal hormones on risk of colon cancer. Some studies<sup>11,12</sup> have shown no association for menopausal hormones, while a few have reported slightly elevated risks.<sup>7,8,13</sup> Several studies, however, have suggested protective effects for colorectal,<sup>5,14</sup> colon,<sup>4,6,9,10,14-18</sup> and

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rectal<sup>5</sup> cancers with RR estimates in the range of 0.6 to 0.8 for ever- or current use of menopausal hormones. A study of colorectal adenomatous polyps also found a nonsignificant reduction with menopausal hormones in this range.<sup>19</sup> In two cohort studies of colon cancer mortality,<sup>20,21</sup> risk was halved among current estrogen users, although the later found an elevation in risk among recent quitters leading the authors to conclude that their results may have been due to a healthy estrogen-user bias.

To investigate further the hypothesis that menopausal hormones reduce the risk of colorectal cancer, we analyzed data from a large prospective cohort of women with extensive information on menopausal hormone use.

## Materials and methods

The Breast Cancer Detection Demonstration Project (BCDDP), sponsored by the American Cancer Society and the US National Cancer Institute (NCI), was a breast cancer screening program conducted between 1973 and 1980. The BCDDP provided up to five annual breast examinations to 283,222 women at 29 screening centers in 27 cities throughout the country. The NCI began a cohort study of a subset of the BCDDP participants in 1979. The cohort study included: (i) all women who received a diagnosis of breast cancer during the screening program ( $n = 4,275$ ); (ii) all women who underwent breast surgery during the screening period, with no evidence of malignant breast disease ( $n = 25,114$ ); (iii) all women who had recommendations by the project for a surgical consultation, but who did not have either a biopsy or aspiration performed ( $n = 9,628$ ); and (iv) a sample of women who had neither surgery nor recommendation for surgical consultation during screening participation ( $n = 25,165$ ).

The cohort study was conducted in two stages. The first stage, 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. The second stage involved the administration of a mailed follow-up questionnaire between 1987 and 1989. Nonrespondents to the mailed questionnaire were interviewed by telephone, if possible.

### Study population

Of the 64,182 women selected for follow-up, 61,434 (96 percent) responded to the baseline interview. Women with a diagnosis of breast or colorectal cancer before the start of follow-up were excluded from the analytic cohort. Analyses were restricted to postmenopausal women, defined as those who had not experienced a menstrual period in the previous three months. Women reporting surgical menopause without removal of both ovaries were considered menopausal when they reached 52.75 years of

age (the median age at natural menopause in this cohort) or the age at hysterectomy, whichever was later.

There were 40,464 women available for inclusion in the analysis representing a total of 312,981 person-years (PY) of observation. A total of 33,779 (83 percent) of these women completed the follow-up questionnaire. Follow-up questionnaires were not completed by 3.2 percent of subjects due to death, 1.1 percent due to illness, 2.6 percent due to refusal, 4.3 percent because the study ended before an interview was completed, and 5.3 percent because they could not be located. Most study subjects were White (89 percent), with small percentages of Blacks (five percent) and Asian-Americans (five percent).

### Case identification

Colorectal cancer cases were ascertained on the 1987-89 follow-up questionnaire and by death certificate. Subjects reported on the questionnaire whether they had ever been told by a doctor that they had cancer. Pathology reports were obtained for 83 percent of women reporting a diagnosis of colorectal cancer after the date of the baseline interview. Pathology reports were not obtained for all potential cases largely due to nonresponse by hospitals and physicians. Of the pathology reports retrieved, 97 percent confirmed a diagnosis of adenocarcinoma of the colon or rectum (ICD-9<sup>22</sup> codes 153.0-153.9 for colon, and 154.0-154.1 for rectal cancer). Self-report of site (colon/rectum) by subjects was less accurate. The sensitivity of self-report of rectal cancer was only 33 percent; thus, 67 percent of rectal cancer cases were self-reported as colon cancer. Deaths due to colorectal cancer were identified from routinely collected death certificates; pathology reports were unavailable for these subjects.

Of the 313 cases of colorectal cancer, 229 were identified by the follow-up questionnaire (pathology reports confirmed 193 cases and were not retrieved for 36 cases), and 84 by death certificate. Of the pathologically confirmed cases, 146 had colon cancer, including 74 proximal (cecum to splenic flexure), 57 distal (descending and sigmoid), and 15 unspecified colon; 47 had rectal cancer. The splenic flexure was included with the proximal colon since it is beyond the reach of the flexible sigmoidoscope.

Since the accuracy of self-reporting was high among cases verified by pathology report, and death certificate data generally are accurate in identifying deaths due to colorectal cancer (although less so for colon or rectum separately<sup>23</sup>), we initially performed the analyses combining the confirmed and unconfirmed cases of colon and rectal cancer. Separate analyses were performed on all cases of colorectal cancer (self-reported on the follow-up questionnaire and identified by death certificate), and those cases identified by self-report only, to determine whether results varied by case ascertainment. Given difficulties in accurately discriminating between colon

and rectal cancers from self-reports or death certificates, estimates for the individual sites were based on pathologically confirmed cases.

#### *Exposures and covariates*

At the baseline interview of the follow-up study, subjects were asked about reproductive factors, including parity, type of menopause, and age at menopause. In addition, information was collected on duration of and age at first use of birth control pills and other female hormones (excluding creams), and whether use of hormones was for menopause or for other reasons. Annual telephone interviews and the follow-up questionnaire updated the information collected in the previous interview. On the follow-up questionnaire, information also was collected on use of menopausal estrogens and progestins in the same month, duration of use of estrogens in combination with progestins, age at first use of progestins, and number of days in the month progestins were used. Thus, information on use of progestins was available only for women who completed the follow-up questionnaire. For the majority of the analyses, we did not distinguish between estrogen and progestin use. While extremely rare, some women used progestins only; thus, for the remainder of the paper we refer to hormone rather than estrogen use. Levels of education and income, and measured height and weight were available from forms completed during the screening program. Body mass index (BMI) was defined as weight (kg) divided by height (m) squared.

#### *Statistical analysis*

Follow-up began with the date of completion of the baseline interview for women who were postmenopausal, and with the date of menopause for premenopausal women who became postmenopausal during follow-up. PYs were accrued until the earliest of the following dates: diagnosis of colorectal cancer (from the pathology report or from the questionnaire if the pathology report was not retrieved), death from other causes, last contact, or return of the follow-up questionnaire. To assign dates of cancer diagnosis for cases identified by death certificates only, we used information requested during the earlier telephone interviews on whether subjects had been treated by a physician for conditions other than those of the breast, as well as information on the death certificate.

Age, as well as all of the hormone variables, was treated as time-dependent in the analyses. Periods of hormone use were reconstructed using interview dates. For subjects who died or who were known to be alive at the end of follow-up but who did not complete a mailed questionnaire, information on exposure to hormones was not ascertained between the last interview date and the exit date. Hormone status subsequent to the last interview was assumed to be the same as that last reported for

nonusers or past users of hormones. For 'current' users of menopausal hormones at their last annual interview who did not complete a mailed questionnaire, PYs subsequent to the last interview were classified as 'unknown' for currency and duration of use. PYs were assigned to hormone-use categories according to status one year prior to attained age. For example, a woman who first began using hormones at age 55 years would begin contributing PYs to the 'recent use' category at age 56. Consequently, cases who first began using hormones within a year prior to diagnosis would be classified as nonusers.

Hormone use other than birth control pills occurring more than five years before the date of menopause (reported by eight percent of the cohort) was considered unrelated to menopause and this person-time was not included in the hormone categories. Adjustment for hormone use occurring more than five years before menopause did not change the estimates associated with use of hormones within five years of menopause or later. Further, results of analyses excluding women who reported using hormones five or more years before their menopause were not different from those that included these women. Therefore, results including these women are presented.

Incidence relative risks (RR) and 95 percent confidence intervals (CI) were estimated by Poisson regression. Analyses using cases ascertained by self-report, and analyses using pathologically confirmed cases only were restricted to subjects who completed the follow-up questionnaire. RRs for menopausal hormone use were unaltered with adjustment for the variables in Table 1. Therefore, only the age-adjusted estimates are presented in the tables.

## **Results**

The mean duration of follow-up was 7.7 years, and the average age of subjects at the start of follow-up was 59 years (range = 41-80 years). Approximately equal proportions of person-time were associated with never- and ever-use of hormones. Table 1 presents the distribution of person-time for ever- and never-use of hormones by potential risk factors for colorectal cancer. Overall, menopausal hormone use did not vary substantially by these factors, although there was a slight tendency for ever-users to be more highly educated, leaner, taller, to have had fewer births, and to have used OCs.

As shown in Table 2, results observed for all colorectal cancer cases (ascertained by self-report and death certificate) were similar to those for cases that were self-reported on the follow-up questionnaire only. Ever-use of hormone replacement therapy was unrelated to colorectal cancer risk; however, recent use was associated with a slight reduction in risk that was not statistically signifi-

**Table 1.** Prevalence of postmenopausal hormone use according to selected factors, USA

	Never-used (%)	Ever-used (%)	Total person-years
Age (yrs)			
< 50	50	50	16,303
50-54	54	46	53,855
55-59	48	52	80,499
60-64	41	59	64,346
65-69	40	60	41,397
70-74	47	53	24,588
75+	58	42	17,048
Education			
< High school	52	48	42,291
High school	48	52	126,665
Some college	44	56	69,770
College graduate	47	53	33,052
Postgraduate	46	54	26,257
Weight (quintiles, lbs)			
< 121	47	53	61,276
121-131	46	54	59,488
132-142	47	53	56,418
143-158	49	51	55,405
159+	54	46	65,448
Height (inches)			
< 61	52	48	23,843
61 - < 63	49	51	62,051
63 - < 64	49	51	39,907
64 - < 65	49	51	47,239
65 - < 67	48	52	78,890
67+	48	52	46,106
Body mass index <sup>a</sup> (quintiles)			
< 21.0	44	56	57,044
21.0-22.5	43	57	57,163
22.6-24.2	46	54	60,024
24.3-27.0	48	52	61,961
> 27.0	54	46	61,842
Parity			
0	47	53	43,603
1	46	54	37,552
2	46	54	86,937
3	46	54	66,909
4+	51	49	63,034
Oral contraceptive use			
Never	48	52	229,487
Ever	43	57	68,548

<sup>a</sup> Weight(kg)/height(m)<sup>2</sup>.

cant. No significant associations were noted for time since last use among former users. Duration of hormone use was unrelated to colorectal cancer risk among ever-users or former users, although a slight reduction in risk was noted for recent users of five or more years' duration (Table 3).

As described in the methods section, the hormone analyses were based on exposure one year prior to diagnosis. The results for recent hormone use and colorectal cancer risk were roughly similar when the analyses were repeated categorizing cases on the basis of their use as of the date of diagnosis (RR = 0.84, CI = 0.60-1.2). When cases were categorized according to their use two years prior to diagnosis, the RR was 0.90 (CI = 0.64-1.7).

Risk associated with ever-use of menopausal hormones also was null for the combined sites of colon cancer among pathologically confirmed cases (Table 4). No pattern was noted for recency or time since last use of hormones. In the site-specific analyses, risk of proximal tumors was elevated to borderline significance among women who had ever used hormones compared with never-users. This excess risk was most evident for former users who had quit five or more years ago. In contrast, there was a nonsignificant reduction in risk of distal tumors associated with recent use of hormones. Among recent users of five or more years' duration (Table 5), there was a slightly lowered risk of total colon cancer as well as distal tumors, although based on relatively small numbers.

Ever-use of hormones was unrelated to rectal cancer, but a nonsignificant reduction in risk was associated with recent use of hormones. Risk among the subgroup of women who had quit within the past five years was elevated significantly compared with women who never used hormones (Table 6). Duration of hormone use appeared unrelated to risk of rectal cancer (Table 7).

Among postmenopausal women who answered the mailed follow-up questionnaire, use of unopposed estrogens accounted for 84 percent of follow-up time for ever-users while approximately 16 percent was accrued for combined estrogen and progestin therapy. The age-adjusted estimates for ever-use of unopposed estrogens were similar to those for any estrogen use: RR for colon = 1.1 (CI = 0.7-1.5); RR for proximal = 1.6 (CI = 1.0-2.7); RR for distal = 0.8 (CI = 0.5-1.5); RR for rectal = 1.2 (CI = 0.7-2.3). The RR associated with use of combined estrogen and progestin therapy for colon cancer was 1.4 (CI = 0.7-2.5); there were insufficient numbers of exposed cases to evaluate risk for colon subsites or the rectum.

A previous study<sup>6</sup> reported that colon cancer risk associated with use of menopausal hormones was modified by other factors, including age, parity and type of menopause. Our ability to assess effect modification was limited to analyses of total colon cancer; subsite analyses were not possible because of the small number of cases remaining after stratification. In general, associations with menopausal hormone use did not vary according to age, BMI, parity, type of menopause, or OC use (results not shown).

Given the slight excess of colon cancers observed among women with a family history of breast cancer,<sup>24</sup> the fact that this cohort consists, in part, of women at

**Table 2.** Age-adjusted relative risk (RR) estimates and 95% confidence intervals (CI) for postmenopausal hormone therapy and colorectal cancer, USA

	All colorectal <sup>a</sup>				Questionnaire only <sup>b</sup>			
	Person-years	No. of cases	RR	(CI)	Person-years	No. of cases	RR	(CI)
Status of hormone use								
Never	145,712	146	1.0	—	132,543	104	1.0	—
Ever	152,323	155	0.99	(0.79-1.2)	143,191	115	0.98	(0.75-1.3)
Recency of use								
Never	145,712	146	1.0	—	132,543	104	1.0	—
Recent <sup>c</sup>	58,752	40	0.78	(0.55-1.1)	56,252	29	0.74	(0.49-1.1)
Former	93,570	115	1.1	(0.85-1.4)	86,938	86	1.1	(0.82-1.5)
Years since cessation								
Never	145,712	146	1.0	—	132,543	104	1.0	—
< 5	33,681	37	1.2	(0.86-1.8)	31,456	27	1.2	(0.79-1.8)
5+	59,889	78	1.0	(0.78-1.4)	55,482	59	1.1	(0.76-1.5)

<sup>a</sup> Includes cases self-reported on the follow-up questionnaire and cases identified by death certificate. Excludes 12 cases and 14,948 person-years with uncertain hormone use.

<sup>b</sup> Includes cases self-reported on the follow-up questionnaire that were pathologically confirmed and for whom pathology reports were not retrieved. Excludes 10 cases and 14,269 person-years with uncertain hormone use.

<sup>c</sup> Defined as hormone use up to one year before diagnosis.

**Table 3.** Age-adjusted relative risk (RR) estimates and 95% confidence intervals (CI) for duration of postmenopausal hormone therapy and colorectal cancer, USA

	All colorectal <sup>a</sup>				Questionnaire only <sup>b</sup>			
	Person-years	No. of cases	RR	(CI)	Person-years	No. of cases	RR	(CI)
Duration (yrs) among ever-users								
Never-use	145,712	146	1.0	—	132,543	104	1.0	—
< 5	80,315	83	1.1	(0.82-1.4)	75,358	61	1.1	(0.77-1.5)
5+	72,008	72	0.90	(0.68-1.2)	67,832	54	0.89	(0.64-1.3)
Duration (yrs) among recent users <sup>c</sup>								
Never-use	145,712	146	1.0	—	132,543	104	1.0	—
< 5	20,910	12	0.83	(0.46-1.5)	20,023	10	0.90	(0.47-1.8)
5+	37,842	28	0.75	(0.50-1.1)	36,228	19	0.65	(0.40-1.1)
Duration (yrs) among former users								
Never-use	145,712	146	1.0	—	132,543	104	1.0	—
< 5	59,404	71	1.1	(0.85-1.5)	55,334	51	1.1	(0.78-1.5)
5+	34,166	44	1.0	(0.74-1.5)	31,604	35	1.1	(0.75-1.6)

<sup>a</sup> Includes cases self-reported on the follow-up questionnaire and cases identified by death certificate. Excludes 12 cases and 14,948 person-years with uncertain hormone use.

<sup>b</sup> Includes cases self-reported on the follow-up questionnaire that were pathologically confirmed and for whom pathology reports were not retrieved. Excludes 10 cases and 14,269 person-years with uncertain hormone use.

<sup>c</sup> Defined as hormone use up to one year before diagnosis.

high risk of breast cancer raises some concern about the generalizability of our findings. We performed an analysis restricted to the sample of women who had neither surgery nor recommendation for surgical consultation during the screening phase. A total of 63 cases of colorectal cancer occurred among these women; 31 were nonusers and 32 were ever-users. The age-adjusted RR of colorectal cancer was 1.1 (CI = 0.7-1.8) for ever-use of menopausal hormones.

## Discussion

In this large prospective study of women, ever-use of menopausal hormones was not associated with risk of colorectal cancer. Risk among recent users, however, was reduced nonsignificantly for total colorectal cancers, most notably for distal colon and rectal tumors. Our results are consistent with a slight protective effect of recent use on risk of colorectal cancer, and agree in magnitude with

**Table 4.** Age-adjusted relative risk (RR) estimates and 95% confidence intervals (CI) for postmenopausal hormone therapy and colon cancer,<sup>a</sup> USA

	Person-years	Colon <sup>b</sup>			Proximal <sup>c</sup>			Distal <sup>d</sup>		
		No. of cases	RR	(CI)	No. of cases	RR	(CI)	No. of cases	RR	(CI)
Status of hormone use										
Never	132,543	61	1.0	—	25	1.0	—	26	1.0	—
Ever	143,191	78	1.1	(0.81-1.6)	45	1.7	(1.0-2.7)	30	0.98	(0.58-1.7)
Recency of use										
Never	132,543	61	1.0	—	25	1.0	—	26	1.0	—
Recent <sup>e</sup>	56,252	21	0.90	(0.54-1.5)	14	1.5	(0.80-3.0)	7	0.68	(0.29-1.6)
Former	86,938	57	1.3	(0.88-1.8)	31	1.7	(1.0-2.9)	23	1.1	(0.65-2.0)
Years since cessation										
Never	132,543	61	1.0	—	25	1.0	—	26	1.0	—
< 5	31,456	15	1.1	(0.63-2.0)	6	1.1	(0.47-2.8)	7	1.2	(0.51-2.7)
5+	55,482	42	1.3	(0.89-2.0)	25	2.0	(1.1-3.5)	16	1.1	(0.59-2.1)

<sup>a</sup> Includes only the pathologically confirmed cases.

<sup>b</sup> Excludes 7 cases and 14,269 person-years with uncertain hormone use.

<sup>c</sup> Excludes 4 cases and 14,269 person-years with uncertain hormone use.

<sup>d</sup> Excludes 1 case and 14,269 person-years with uncertain hormone use.

<sup>e</sup> Defined as hormone use up to one year before diagnosis.

**Table 5.** Age-adjusted relative risk (RR) estimates and 95% confidence intervals (CI) for duration of postmenopausal hormone therapy and colon cancer,<sup>a</sup> USA

	Person-years	Colon <sup>b</sup>			Proximal <sup>c</sup>			Distal <sup>d</sup>		
		No. of cases	RR	(CI)	No. of cases	RR	(CI)	No. of cases	RR	(CI)
Duration (yrs) among ever-users										
Never-use	132,543	61	1.0	—	25	1.0	—	26	1.0	—
< 5	75,358	45	1.3	(0.90-2.0)	24	1.8	(1.0-3.1)	19	1.3	(0.71-2.3)
5+	67,832	33	0.95	(0.62-1.5)	21	1.5	(0.86-2.8)	11	0.70	(0.34-1.4)
Duration (yrs) among recent users										
Never-use	132,543	61	1.0	—	25	1.0	—	26	1.0	—
< 5	20,023	9	1.3	(0.65-2.7)	6	2.3	(0.91-5.8)	3	0.99	(0.29-3.3)
5+	36,228	12	0.70	(0.37-1.3)	8	1.2	(0.54-2.7)	4	0.53	(0.18-1.5)
Duration (yrs) among former users										
Never-use	132,543	61	1.0	—	25	1.0	—	26	1.0	—
< 5	55,334	36	1.3	(0.88-2.0)	18	1.7	(0.93-3.1)	16	1.3	(0.71-2.5)
5+	31,604	21	1.2	(0.71-1.9)	13	1.9	(0.95-3.7)	7	0.85	(0.36-2.0)

<sup>a</sup> Includes only the pathologically confirmed cases.

<sup>b</sup> Excludes 7 cases and 14,269 person-years with uncertain hormone use.

<sup>c</sup> Excludes 4 cases and 14,269 person-years with uncertain hormone use.

<sup>d</sup> Excludes 1 case and 14,269 person-years with uncertain hormone use.

<sup>e</sup> Defined as hormone use up to one year before diagnosis.

the findings of other studies that have evaluated the relation of menopausal hormone therapy to the risk of colorectal<sup>15,14</sup> and colon<sup>4,9,14,16-18</sup> cancers. Two recent studies<sup>6,15</sup> have reported greater reductions in risk, on the order of 50 percent, among current users of menopausal hormones. Other studies, however, have found no association for ever or current use of menopausal hormones,<sup>11,12</sup> or a

slight elevation in risk.<sup>7,8,13</sup> Our results for the proximal colon also were elevated slightly with ever-use of menopausal estrogens.

Several limitations inherent to observational studies must be considered in interpreting our results. Since cases were ascertained at the end of follow-up and by death certificate, it is possible that some cases may have been

**Table 6.** Age-adjusted relative risk (RR) estimates and 95% confidence intervals (CI) for postmenopausal hormone therapy and rectal cancer,<sup>a</sup> USA

	Person-years	No. of cases	RR	(CI)
Status of hormone use				
Never	132,543	20	1.0	—
Ever	143,191	25	1.1	(0.59-1.9)
Recency of use				
Never	132,543	20	1.0	—
Recent <sup>b</sup>	56,252	5	0.64	(0.24-1.7)
Former	86,938	20	1.3	(0.68-2.4)
Years since cessation				
Never	132,543	20	1.0	—
< 5	31,456	10	2.3	(1.1-4.9)
5+	55,482	10	0.88	(0.41-1.9)

<sup>a</sup> Includes only pathologically confirmed cases. Excludes 2 cases and 14,269 person years with uncertain hormone use.

<sup>b</sup> Defined as hormone use up to one year before diagnosis.

missed if they survived to the end of follow-up but did not respond to the follow-up questionnaire. If underascertainment of cases were related to exposure, particularly if the undetected cases were less likely to be using estrogens, an artificially increased RR could result. The women in the cohort study, however, participated both in the initial screening program and responded to the baseline follow-up interview, making it less likely that subsequent response by cases would be related to whether they were using hormones. Further, the difference in response to the follow-up questionnaire between hormone users and nonusers at the start of follow-up was only six percent (87 percent and 81 percent, respectively). To affect appreciably an estimate of the true RR, the proportion of cases ascertained would have to differ considerably by exposure status.

Random misclassification in exposure to menopausal hormones would tend to bias estimates of RR toward one. Our previous analysis of menopausal hormone use and breast cancer risk in this cohort,<sup>25</sup> however, is consistent with the small increased risk noted in other studies. This finding lends support to the accuracy of self-reported use, since misclassification due to inaccurate reporting would obscure the association with breast cancer as well as colorectal cancer. Moreover, in our study, hormone use was updated at intervals of approximately one year.

Adjusting for several potential confounders made little difference in our estimates of effect. Although we lacked data on diet and physical activity, other studies that had information to evaluate possible confounding by these factors have noted little difference between the adjusted and unadjusted risks.<sup>6,14</sup> In addition, adjustment for BMI, which seems a reasonable surrogate for excess caloric

**Table 7.** Age-adjusted relative risk (RR) estimates and 95% confidence intervals (CI) for duration of postmenopausal hormone therapy and rectal cancer,<sup>a</sup> USA

	Person-years	No. of cases	RR	(CI)
Duration (yrs) among ever-users				
Never	132,543	20	1.0	—
< 5	75,358	12	1.1	(0.52-2.2)
5+	67,832	13	1.1	(0.53-2.2)
Duration (yrs) among recent users <sup>b</sup>				
Never	132,543	20	1.0	—
< 5	20,023	0	—	—
5+	36,228	5	0.83	(0.31-2.2)
Duration (yrs) among former users				
Never	132,543	20	1.0	—
< 5	55,334	12	1.3	(0.64-2.7)
5+	31,604	8	1.3	(0.57-3.0)

<sup>a</sup> Includes only pathologically confirmed cases. Excludes 2 cases and 14,269 person years with uncertain hormone use.

<sup>b</sup> Defined as hormone use up to one year before diagnosis.

intake and/or low physical activity, did not affect the risk estimates for hormone use in our study.

It has been argued that a 'healthy hormone user' bias could explain a seemingly protective effect of current use on cancer risk, since women may stop using hormones upon experiencing preclinical symptoms. In an attempt to avoid this bias, we assigned cases to hormone categories according to use one year prior to diagnosis, and found an RR of 0.78 for recent use and colorectal cancer risk. Repeating the analyses, we found RR estimates of 0.84 and 0.90, respectively, when cases were categorized according to their use at diagnosis, and two years prior to diagnosis. Former users who had quit within five years of diagnosis had a slight elevation in risk of colon cancer compared with never-users (ranging from 1.1-1.2), although these estimates were not significant and could have been due to chance. Interestingly, rectal cancer risk associated with recent cessation was doubled. Taken together, these results indicate the possibility of a small effect on the risk estimates of women stopping hormone use prior to diagnosis.

In evaluating the effects of menopausal hormones, it is possible that women who use hormones are under more intensive medical surveillance than women who do not. We have no data regarding screening for colorectal cancer, although hormone users in our cohort were more likely to undergo mammographic screening for breast cancer than nonusers.<sup>24</sup> Further, others have reported that users of exogenous hormones are more likely to undergo fecal

occult blood tests (FOBT) than nonusers.<sup>26</sup> Although we are unaware of any data on the relation of screening sigmoidoscopy to hormone use, it seems reasonable to assume a positive association exists. Assessing the impact of differential screening on our results is complex given that screening could either increase or decrease the incidence rate for colorectal cancer, at least in the short term. Increased incidence would result from the earlier detection of cancer, and decreased incidence from the detection and removal of premalignant polyps, which may reduce up to 90 percent the subsequent risk of colorectal cancer.<sup>27</sup>

In attempting to quantify the effect of screening bias, we focused on a possible reduction in incidence, since any potential increase in incidence is likely to be small.<sup>28</sup> Barrett-Connor<sup>26</sup> reported that the prevalence of FOBT was 56 percent in hormone users and 44 percent in nonusers. Assuming a 90 percent reduction in colorectal cancer incidence after screening, the effect of screening in hormone users would be to reduce incidence by approximately 50 percent  $[(1-0.56) + (0.56 \times 0.1) = 0.5; 1-0.5 = 0.5]$ . Similarly, in nonusers, incidence would be reduced by approximately 40 percent  $[(1-0.44) + (0.44 \times 0.1) = 0.6; 1-0.6 = 0.4]$ . Removing the effect of screening would result in a bias-corrected RR of 0.95  $[0.78 / (0.5/0.6)]$ . This estimate suggests little or no impact of hormone use on colorectal cancer risk in our study. A lower efficacy of screening would reduce the magnitude of the bias and not preclude a small protective effect of hormone use. For example, assuming a 50 percent decrease in incidence after screening results in a bias-corrected RR of 0.85  $(0.78 / 0.92)$ .

However, to evaluate with precision the impact of colorectal screening on our results would require data that was unavailable in this survey. In the only other study that has considered screening,<sup>15</sup> a reduced risk of colon cancer among current hormone users remained after adjusting for history of screening sigmoidoscopy. Some of the variability across studies of hormone use and colorectal cancer risk thus may reflect differences in screening patterns and efficacy.

In summary, our cohort study revealed no association between ever-use of menopausal hormones and colorectal cancer risk, but a slight reduction in risk was noted for recent users that was less pronounced than that observed in some recent studies.<sup>6,15</sup> The question of whether recent use of menopausal hormones lowers the risk of colon cancer has substantial public health significance, given the high prevalence of hormone replacement therapy and the importance of colorectal cancer as a cause of morbidity and mortality among older women. However, given the inconsistent findings to date and the potential for screening bias in studies of hormone use, more definitive studies are needed to determine whether menopausal hormones are protective against the development of colorectal cancer.

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