Short Communication

A Case-Control Study of Use of Postmenopausal Female Hormone Supplements in Relation to the Risk of Large Bowel Cancer[1]

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Abstract

Postmenopausal female hormone use has been associated with a reduced risk of colon cancer. We assessed the relation of use of these supplements to the risk of large bowel cancer. The data were collected in a case-control study of large bowel cancer conducted in Massachusetts. Control subjects were matched to incident cases of carcinoma of the colon or rectum on age, gender, and town precinct. The analysis was restricted to women who experienced a natural menopause or had had a hysterectomy with or without removal of the ovaries (292 colon cancer cases and 112 rectal cancer cases and their matched controls). Use of female hormone supplements was associated with a decreased risk of colon cancer among recent users (odds ratio, 0.6; 95% confidence interval, 0.4–1.0) and long duration (5+ years) of use (odds ratio, 0.5; 95% confidence interval, 0.3–0.9). The association with long duration of use appeared to be independent of recency of use and screening practices and was apparent for late-stage cancer. Hormone supplement use was not associated with a reduced risk of rectal cancer. Our results add to the evidence for a decreased risk of colon cancer associated with use of female hormone supplements.

Introduction

It has been suggested that exogenous estrogens may reduce the risk of large bowel cancer by decreasing bile acid concentration or by direct effects on colonic mucosa, *e.g.*, prevention of cell proliferation (1). Several epidemiological studies have suggested a decreased risk of colon cancer among users of postmenopausal female hormone supplements (2–10). For rectal cancer, most studies have observed no association or a slightly elevated risk (3, 5, 7, 11), but one study revealed an inverse association (10). Results concerning the timing and duration of use have been inconsistent.

In this study, we assess postmenopausal female hormone use in relation to large bowel cancer with data from a population-based case-control study conducted in Massachusetts (12). Factors associated with female hormone use that could confound an association of use with cancer risk, such as screening practices, are considered in the analyses.

Materials and Methods

Cases and Controls. A case-control study was conducted from July 1992 through December 1994 (12) to investigate the relation of use of nonsteroidal anti-inflammatory drugs to the risk of large bowel cancer. Incident cases of invasive large bowel carcinoma were ascertained at 1–2-month intervals from the tumor registrars of 71 collaborating Massachusetts hospitals that treated an estimated 90% or more of incident large bowel cancers in Massachusetts. Cases were included only if the diagnosis had been made within the past year and if the patient was a resident of Massachusetts, 20–69 years of age, and spoke English. Cases with a history of previous cancer other than nonmelanoma skin cancer were excluded.

After physician permission to contact patients was obtained, patients were sent an informational letter with an informed consent form and were then telephoned for an interview. Of 1847 potential cases for whom notifications were received, 1201 (65%) were interviewed: there were 72 physician refusals; 190 patient refusals; 154 patients who had died; 81 patients who could not be reached; and 149 patients who were too ill to participate or who could not understand the questions. The median interval between diagnosis and interview was 4.9 months, and 90% of cases were interviewed within 11 months. The diagnosis of colon or rectal cancer was confirmed by review of pathology reports and discharge summaries.

A control was matched to each case on 5-year age group, gender, and town precinct. Massachusetts town lists, which give the gender and age of all adult residents, were used as the source of controls. Completeness of the lists is supported by a recent study, in which over 90% of cases from three studies were found in the lists (13). Only controls who spoke English and had a listed telephone number were included, and those who reported a history of cancer other than nonmelanoma skin cancer were replaced. Among 1822 potential controls, 1201 (66%) were interviewed: 381 refused to participate; 40 had died; 166 could not be reached; and 34 were too ill to participate or could not understand the questions.

Data were collected from 515 female participants with large bowel cancer and their 515 matched controls. This report is based on women who had experienced a natural menopause or had had a hysterectomy with or without removal of the ovaries, a total of 404 cases (292 colon cancer and 112 rectal cancer cases) and their matched controls.

Data Collection. Trained interviewers used structured questionnaires in telephone interviews to collect information on demographic factors, anthropometric factors, physical activity, reproductive and menstrual history, nonsteroidal anti-inflam-

Received 8/5/99; revised 12/31/99; accepted 1/28/00.
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Table 1 Selected characteristics of postmenopausal women with colon or rectal cancer and their matched community controls

Characteristic	Colon cancer		Rectal cancer	
	Cases (n = 292)	Controls (n = 292)	Cases (n = 112)	Controls (n = 112)
	No. (%)[a]	No. (%)[a]	No. (%)[a]	No. (%)[a]
Age (yr)				
40–49	4 (1)	4 (1)	1 (1)	1 (1)
50–59	68 (23)	68 (23)	35 (31)	35 (30)
60–69	220 (75)	226 (76)	76 (68)	76 (68)
Education (yr)				
<12	51 (17)	43 (15)	15 (13)	13 (12)
12	145 (50)	161 (55)	56 (50)	57 (51)
13–15	48 (16)	47 (16)	19 (17)	19 (17)
16+	45 (15)	40 (13)	20 (18)	23 (20)
Body mass index (kg/m^2)				
<24	101 (35)	95 (32)	44 (39)	40 (36)
24–27	80 (27)	100 (34)	34 (30)	39 (35)
28+	105 (36)	87 (30)	32 (29)	32 (28)
Fat intake (g/day)				
<43	96 (33)	103 (35)	20 (18)	34 (30)
43–62	82 (28)	74 (25)	46 (41)	27 (24)
63+	71 (24)	51 (17)	32 (28)	23 (11)
Fiber intake (g/day)				
<15	91 (31)	75 (25)	33 (29)	29 (26)
15–20	92 (31)	75 (25)	33 (29)	24 (21)
21+	66 (23)	78 (27)	33 (29)	31 (28)
Fruit and vegetable intake (servings/day)				
<3	45 (15)	29 (10)	11 (10)	8 (7)
3–4	101 (34)	74 (25)	38 (34)	24 (21)
5+	103 (35)	123 (42)	49 (44)	53 (47)
Vigorous leisure-time physical activity (h/week)				
None	234 (80)	223 (76)	92 (82)	92 (82)
1–4	36 (12)	44 (15)	11 (10)	14 (12)
5+	17 (6)	21 (7)	7 (6)	4 (4)
Nonsteroidal anti-inflammatory drug use				
None	193 (66)	169 (58)	77 (69)	77 (69)
Regular use continuing into the year before index date	46 (16)	63 (22)	16 (14)	17 (15)
Other use	53 (18)	60 (20)	19 (17)	18 (16)
Oral contraceptive use				
Never	218 (75)	214 (73)	84 (75)	79 (71)
Ever	74 (25)	78 (27)	28 (25)	33 (29)
Ever pregnant				
No	40 (14)	25 (9)	22 (20)	11 (10)
Yes	252 (86)	267 (91)	90 (80)	101 (90)
History of colorectal cancer in parent or sibling				
No	245 (84)	258 (88)	92 (82)	98 (87)
Yes	47 (16)	34 (12)	20 (18)	14 (13)
Ever had screening for colorectal cancer				
Never	56 (19)	38 (13)	26 (23)	12 (11)
Rectal exam or fecal occult blood test only	188 (64)	185 (63)	73 (65)	67 (60)
Colonoscopy or sigmoidoscopy	48 (17)	69 (24)	13 (12)	33 (29)

[a] Percentage of total. Subjects with unknown values are not shown in the table.

matory drug use, oral contraceptive use, history of colorectal cancer in the parents or siblings, and history of colonoscopy, sigmoidoscopy, rectal examination, or fecal occult blood tests. Information on diet was obtained with a modification of the Willett food frequency questionnaire (14). Postmenopausal female hormone use was elicited by questions about the use of replacement female hormones such as Premarin or Provera; 97% of the use elicited was of oral preparations, and the remainder was of patches. For each episode of use, the month and year started, the duration, and the drug name were recorded. Women who used female hormones for less than 1 month were classified as never users.

The data were collected with reference to an index date. This was the date of diagnosis for cases. For the matched control, the index date was chosen so that the interval between index date and interview date was the same as the interval from diagnosis date to interview date for the case.

Analysis. We used ORs[3] (and test-based 95% CIs) derived from conditional logistic regression to estimate the relative risk of large bowel cancer for female hormone use relative to never use (15). For risk factors for large bowel cancer that were associated with female hormone use among the controls, we

[3] The abbreviations used are: OR, odds ratio; CI, confidence interval.

Table 2 Risk of colon cancer and rectal cancer in relation to recency and duration of postmenopausal female hormone use

Hormone use	Colon cancer			Rectal cancer		
	Cases (n = 292)	Controls (n = 292)	OR (95% CI)	Cases (n = 112)	Controls (n = 112)	OR (95% CI)
Never	212	188	Ref.[a]	76	81	Ref.[a]
Ever	80	104	0.8 (0.5–1.2)	36	31	1.7 (0.8–3.6)
Interval since last use (yr)						
<1	40	67	0.6 (0.4–1.0)	16	17	1.5 (0.5–4.0)
1+	36	34	1.1 (0.6–1.9)	19	12	2.2 (0.8–6.3)
Unknown	4	3	1.0 (0.2–4.7)	1	2	
Duration of use (yr)						
<5	43	46	1.0 (0.6–1.7)	19	16	1.5 (0.6–3.7)
5–9	14	18	0.7 (0.3–1.9)	7	5	1.6 (0.4–6.7)
10+	14	34	0.4 (0.2–0.8)	7	6	2.0 (0.5–8.4)
Unknown	9	6	1.1 (0.3–3.5)	3	4	2.9 (0.4–19.5)
Duration of use within interval since last use						
<1 year since last use						
<5 years duration	15	21	0.8 (0.4–1.7)	5	9	0.6 (0.1–3.8)
5+ years duration	23	44	0.5 (0.3–1.0)	11	8	2.3 (0.7–7.2)
1+ years since last use						
<5 years duration	28	25	1.2 (0.6–2.2)	14	7	2.3 (0.7–7.5)
5+ years duration	5	8	0.5 (0.1–1.7)	3	3	0.4 (0.0–4.7)

[a] Ref., reference category.

compared the OR estimate obtained with and without the factor in the logistic regression. In the final model, we included factors that changed the estimate by 10% or more: (*a*) fat, fruit, and vegetable intake; (*b*) vigorous leisure time physical activity; (*c*) body mass index; and (*d*) history of screening for colorectal cancer. We conducted tests for trend across duration of use considered as a continuous variable.

Results

As shown in Table 1, colon cancer cases had a higher body mass index; a greater fat intake; a lesser intake of fiber, fruits, and vegetables; and less continuing use of nonsteroidal anti-inflammatory drugs than their matched controls. Also, colon cancer cases had a higher prevalence of family history of colorectal cancer and were less likely to have undergone a screening procedure such as colonoscopy. Rectal cancer cases had a higher fat intake, a higher prevalence of family history of colorectal cancer, and were less likely to have undergone a screening procedure than their matched controls. Both colon cancer and rectal cancer cases had a higher prevalence of nulliparity than controls.

For colon cancer, the OR for ever use of postmenopausal female hormones was 0.8 (95% CI, 0.5–1.2; Table 2). Among women last exposed less than 1 year before the index date (recent use), the OR was 0.6 (95% CI, 0.4–1.0). No association was found among women whose interval since last use was at least a year. Duration of hormone use was inversely related to risk: the OR was 0.5 (95% CI, 0.3–0.9) for women who used hormones for 5 or more years (long duration use) and 0.4 (95% CI, 0.2–0.8) among women with at least 10 years of use (P for trend = 0.02). Hormone use was not associated with a reduced risk of rectal cancer: for ever use, the OR was 1.7 (95% CI, 0.8–3.6).

When the joint effects of recency and duration of use were considered (Table 2), long-duration use was associated with a reduced risk of colon cancer, both for recent use (OR, 0.5; 95% CI, 0.3–1.0) and use that ended a year or more before the index date (OR, 0.5; 95% CI, 0.1–1.7). For recent use of less than 5 years in duration, the OR was 0.8 (95% CI, 0.4–1.7). Results for rectal cancer did not reveal any consistent pattern for the joint effect of duration and recency of use.

Data on recent female hormone use and long-duration use among colon cancer cases and their matched controls are shown in Table 3 according to age, site, family history of large bowel cancer, screening practices, cancer stage, and female hormone regimen used. The ORs were less than 1.0 for all categories of recent and long-duration use, with the following exceptions: the OR was 1.0 for recent use among women under age 60 years and for recent and long-duration use among women with a positive family history of large bowel cancer. CIs were generally wide. The ORs were significantly reduced for long-duration use among women 60–69 years of age, women who had had a rectal examination or fecal occult blood test, and women without a family history of large bowel cancer. In addition, for use of unopposed estrogen only, which accounted for most of the female hormone use, the ORs for recent use and for long-duration use were both 0.5 (95% CI, 0.2–0.9). For stage II–IV cancer, which would have been less susceptible to detection bias than earlier stage cancer, the OR estimate for long-duration use was 0.5 (95% CI, 0.2–1.2).

Discussion

The present results are compatible with a 50% reduction in the risk of colon cancer among women who used female hormones for 5 or more years. The association with long-duration use appeared independent of recency of use. There was a suggestion of a reduced risk among women who had used hormones for less than 5 years if they had used them less than 1 year previously. The inverse association with colon cancer risk was statistically significant for use of unopposed estrogen, which accounted for about two-thirds of female hormone use. The association was not apparent among women with a positive family history of large bowel cancer, but numbers were small, and the CIs were compatible with an inverse association as well as no association. Postmenopausal female hormone use was not associated with a reduced risk of rectal cancer.

A major concern in the interpretation of the present results is the possibility of confounding from correlates of female

Table 3 Risk of colon cancer in relation to recency and duration of postmenopausal female hormone use by age, site, family history of large bowel cancer, screening practices, cancer stage, and female hormone regimen[a]

Factor	Female hormone use					
	Interval since last use < 1 year			Duration 5+ years		
	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)
Age (yr)						
<60	18	22	1.0 (0.4–2.8)	12	16	0.8 (0.2–2.7)
60–69	22	43	0.5 (0.3–1.0)	16	35	0.4 (0.2–0.9)
Site						
Proximal colon	8	20	0.4 (0.1–1.1)	8	17	0.4 (0.1–1.1)
Distal colon	28	36	0.9 (0.4–1.8)	17	27	0.6 (0.2–1.4)
Family history						
Yes	9	8	1.0 (0.3–3.3)	6	6	1.0 (0.2–3.9)
No	31	59	0.5 (0.3–1.0)	22	46	0.4 (0.2–0.8)
Screening						
None	2	4	0.3 (0.0–2.9)	1	4	0.2 (0.0–2.2)
Rectal exam or fecal occult blood test	29	42	0.7 (0.4–1.2)	19	35	0.5 (0.2–0.9)
Sigmoidoscopy/colonoscopy	9	21	0.5 (0.2–1.4)	8	13	0.7 (0.3–3.6)
Stage						
I	9	13	0.9 (0.2–3.3)	5	12	0.4 (0.1–2.1)
II–IV	25	42	0.6 (0.3–1.2)	18	31	0.5 (0.2–1.2)
Regimen						
Unopposed estrogen only	22	43	0.5 (0.2–0.9)	17	35	0.5 (0.2–0.9)
Combination use only	13	15	0.9 (0.4–2.2)	7	9	0.7 (0.2–2.5)
Both	5	9	0.7 (0.2–2.6)	4	8	0.6 (0.1–2.8)

[a] Reference category for all ORs is never use.

hormone use. The results of a recent randomized trial of the secondary prevention of coronary heart disease by female hormone supplements underscore the difficulty of controlling for these factors (16). Whereas numerous observational studies that controlled for important correlates of female hormone use have suggested that these supplements reduce the incidence of both primary and recurrent heart disease by 35–50% (17, 18), the randomized trial found no overall difference in coronary heart disease occurrence between women randomized to treatment (combination female hormone therapy) or placebo. Healthy behaviors, such as participation in vigorous physical activity and consumption of fruits and vegetables, are related to female hormone use (19), and they are also related to a reduced risk of colon cancer. Although we controlled for usual diet and physical activity in the present study, control was necessarily incomplete. To the extent that residents of the same town precincts may share certain lifestyle factors, matching controls to cases on town precinct may have provided some additional control for difficult-to-measure factors. Nonetheless, confounding cannot be ruled out as having contributed to the observed inverse association.

In our study, we found that women who took hormone supplements were more likely to have had a colonoscopy, sigmoidoscopy, or fecal occult blood test than were nonusers. It has been shown that treatment of precancerous lesions reduces colon cancer risk (20–22), and we found that colorectal cancer was inversely associated with these procedures. However, the inverse association of hormone use with colon cancer remained after control for these procedures, and inverse associations were observed across categories of screening status. Moreover, inverse associations were observed among women whose colon cancer was detected at stages II–IV, which would have been less prone to detection bias than stage I cancer.

Recall bias is an unlikely explanation for our findings because, if anything, cases would be expected to recall their hormone use more fully than controls. This would bias the data in the direction of a positive association. About 35% of potential controls either refused to participate or could not be located. If controls of higher socioeconomic status had been more likely to participate, this could have led to a bias in the direction of an inverse association because hormone use is more common among women of higher socioeconomic status.

Several previous studies have found an inverse association of postmenopausal female hormone use with colon cancer risk (2–10). Most found that the reduction was related to recent use (2–4, 6–9) or long-duration use (3, 4, 6, 10). Of three studies that examined the combined effect of recency and duration, one found an association with long-duration use among former users (3), one did not find a greater reduction in risk with longer duration of use among recent users (9), and one found that recency and duration were both important, but that there was a more striking inverse association with duration of use among current users (4). A meta-analysis of hormone replacement therapy and colon cancer found that colon cancer was inversely related to current use and use lasting 5 or more years (23).

A role of female hormone supplements in reducing the risk of colon cancer has some biological plausibility. Secondary bile acids may play a role in colorectal carcinogenesis. Secondary bile acids are presumably cytotoxic to colonocytes, which may lead to increasing cell proliferation (24). Higher secondary bile acid concentrations have been found in patients with colon cancer (25) and in patients with familial polyposis (26). Exogenous estrogen alters bile composition by increasing cholesterol secretion and decreasing bile acid secretion (27).

Our results are in agreement with most previous studies in finding an association with colon cancer but not with rectal cancer. McMichael and Potter (28) suggested that there may be a difference between colon cancer and rectal cancer because bile acids are reabsorbed in the proximal bowel. Previous results on site have been mixed: there has been a stronger inverse association of female hormone use with proximal colon cancer (5, 6); a stronger association with distal colon cancer (3); and no difference (7). The point estimates of OR in the present

study were smaller for proximal cancer than distal cancer, but they were compatible with no difference.

In summary, the present study suggests an inverse association between female hormone use and risk of colon cancer and suggests that bias related to screening practices and detection does not account for the association.

Acknowledgments

We thank Drs. Theodore Colton and Arthur Schatzkin for comments on the manuscript.

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