Estrogen Replacement Therapy and Risk of Fatal Colon Cancer in a Prospective Cohort of Postmenopausal Women

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Background: **The results of several recent epidemiologic studies suggest that estrogen replacement therapy (ERT) in postmenopausal women may decrease their risk of subsequently developing colon or colorectal cancer. However, the association is not clear, as other similar studies have failed to show this inverse relationship.** ***Purpose:*** **The present study attempts a more definitive analysis of the relationship between fatal colon cancer and use of ERT among women in a large prospective study of adults in the United States.** ***Methods:*** **Women were selected for study from the 676 526 female participants in Cancer Prevention Study II (CPS-II), a prospective mortality study of about 1.2 million American men and women (from all 50 states, the District of Columbia, and Puerto Rico), begun by the American Cancer Society in 1982. The median age of the female CPS-II participants was 56 years in 1982. Vital status was determined through December 31, 1989; 630 585 participants (93.2%) were still alive and 43 862 (6.5%) had died after 7 years of follow-up. Death certificates were obtained for 96.2% of participants known to have died. At the end of follow-up, 897 colon cancer deaths were observed in a cohort of 422 373 postmenopausal women who were cancer free at study entry. Cox proportional hazards modeling was used to compute rate ratios (RRs) and to adjust for other potential risk factors. The likelihood ratio test (two-sided) was used to determine the statistical significance of the interaction terms.** ***Results:*** **Ever use of ERT was associated with significantly decreased risk of fatal colon cancer (RR = 0.71; 95% confidence interval [CI] = 0.61-0.83). The reduction in risk was strongest among current users (RR = 0.55; 95% CI = 0.40-0.76), and there was a significant (P = .0001) trend of decreasing risk with increasing years of use among all users: Users of 1 year or less had an RR of 0.81 (95% CI = 0.63-1.03), while users of 11 years or more had an RR of 0.54 (95% CI = 0.39-0.76). These associations were not altered in multivariate analyses controlling for other risk factors.** ***Conclusions:*** **In our data, estrogen therapy, particularly recent and long-term use, was associated with a substantial decrease in risk of fatal colon cancer. These results were consistent with several published studies suggesting a protective role of exogenous estrogens in the development of colorectal cancer and merit further investigation. [J Natl Cancer Inst 87:517-523, 1995]**

It has been proposed that exogenous estrogens may act to reduce colorectal cancer risk (*1-3*). This could occur if exogenous estrogens reduce the concentration of bile acids in the colon or if estrogens act directly on colonic mucosa. Increased concentrations of secondary bile acids in the colon have been shown to promote colon cancer in animal models (*4,5*), and concentrations of fecal bile acids have been found to be higher in persons with colon cancer than in healthy control subjects (*6*). Exogenous estrogens decrease bile acid synthesis and secretion in animals (*7,8*) and humans (*9,10*), thus decreasing the ratio of bile acids to cholesterol. This increase in cholesterol saturation of bile results in increased gallstone formation in postmenopausal women on estrogen replacement therapy (ERT) (*11*), as well as in men treated with estrogens following myocardial infarction (*12*).

In addition to a possible hormonal influence on bile acid synthesis and composition, it is possible that exogenous estrogens exert a direct effect on colonic mucosa. Estrogen receptors occur in both human colorectal carcinomas and adjacent normal mucosa (*13-16*). Additional data suggest that estrogens may play an important role in the growth of colon carcinoma cells, inhibiting the growth of human colon cancer cells in vitro (*17,18*).

Several epidemiologic studies have suggested that postmenopausal use of estrogens may result in a decreased risk of colon or colorectal cancer (*19-27*), although other epidemiologic studies of this hormonal exposure have not shown an inverse relationship (*28-32*). We investigated the relationship between fatal colon cancer and ERT use among women in a large prospective study of U.S. adults.

Subjects and Methods

Women in this study were selected from the 676 526 female participants of Cancer Prevention Study II, a prospective mortality study of about 1.2 million American men and women begun by the American Cancer Society in 1982. Participants were identified and enrolled by more than 77 000 American Cancer Society volunteers in all 50 states, the District of Columbia, and Puerto Rico. They completed a four-page questionnaire in 1982 that included personal iden-

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See "Notes" section following "References."

tifiers, demographic characteristics, personal and family history of cancer and other diseases, and various behavioral, environmental, occupational, and dietary exposures. The median age of female study participants in 1982 was 56 years; 75% of the women were between 45 and 70 years of age, and none was younger than 30.

The vital status of study participants was determined using two approaches from the month of enrollment through December 31, 1989. Volunteers made personal inquiries in September 1984, 1986, and 1988 to determine whether their enrollees were alive or dead and to record the date and place of all deaths. Automated linkage using the National Death Index was used to extend follow-up through December 31, 1989 (*33*) and to identify deaths among 13 219 (2.0%) women lost to follow-up between 1982 and 1988. At completion of mortality follow-up in December 1989, 630 585 women (93.2%) were still living, 43 862 (6.5%) had died, and 2079 (0.3%) had follow-up truncated on September 1, 1988, because of insufficient data for National Death Index linkage. Death certificates were obtained for 96.2% of all women known to have died.

Colon cancer deaths were defined as those deaths occurring among women through December 31, 1989, with colon cancer [International Classification of Diseases, Ninth Revision, i.e., ICD-9, codes 153.0-153.9 (*34*)] as the underlying cause. We excluded from the analysis 3275 women with incomplete information on race, 56 861 who had prevalent cancer (except nonmelanoma skin cancer) at study entry in 1982, 119 471 who were premenopausal, 14 915 who had unknown menopausal status at study entry, and 59 631 who had missing data on estrogen use. After 7 years of follow-up, 897 eligible cases of fatal colon cancer were observed among 422 373 postmenopausal women who were cancer free at study entry. The deaths occurred by follow-up year as follows: 62 deaths in year 1; 92 deaths in year 2; 130 deaths in year 3; 136 deaths in year 4; 150 deaths in year 5; 172 deaths in year 6; and 155 deaths in year 7.

In addition to analyzing colon cancer cases, we examined the association between ERT and rectal cancer mortality. Rectal cancer deaths were defined as deaths with ICD-9 codes 154.0-154.8 as the underlying cause. There were 112 eligible cases of fatal rectal cancer in this cohort.

In the base-line questionnaire, women were asked whether they had "ever used female hormones (estrogens) other than oral contraceptives," the reason for their use, age at first use, years of use, and method of use (i.e., injection, cream, or pill). Three measures of hormone use were investigated for their potential relationship with fatal colon cancer: 1) ever use, 2) current and former use, and 3) total years of use. Women with missing years of use who indicated they were "still using" hormones at the time of interview (1.4% of ever users) were assigned the difference between their age at enrollment and the age at first use as their years of use. Current users were defined as those women who said they were still using, as well as those women whose total years of use, added to their age at first use, was equal to (within 1 year) their age at enrollment. Former users were defined as those women whose total years of use, added to their age at first use, was less than their age at enrollment. Women who were unclassifiable as to current or former use or duration of use were excluded from those analyses and so noted in all tables.

When assessing the association between ERT and fatal colon cancer, we used Cox proportional hazards modeling (*35*) to compute rate ratios (RRs) and to adjust for other potential risk factors. All Cox models stratified on exact year of age at enrollment and race (white, black, or other). Potential confounders included in multivariate models were a history of colon cancer in a parent (yes or no), body mass index (BMI) [BMI = weight in kilograms/(height in meters)^2; <26, ≥26 and <29, ≥29], consumption of citrus fruit, vegetables, and grains [the frequency per week of consuming 14 items, divided into quintiles (*36*)], total fat consumption [estimated grams per week categorized into quintiles (*36*)], current physical activity at work or play (none, slight, moderate, or heavy), parity (parous or nulliparous), type of menopause (natural, surgical, or perimenopausal), age at menopause (<45 years or ≥45 years), oral contraceptive use (ever or never), aspirin use (none, occasional, 1-15 times per month, or ≥16 times per month), and smoking (current, former, or never).

To test whether other risk factors modified the association between ERT and colon cancer, we entered multiplicative interaction terms between estrogen use (ever or never) and each potential confounder into the multivariate models. Using the likelihood ratio test (*37*), we assessed the statistical significance of the interaction terms at the $P = .05$ level. All statistical tests performed were two-sided tests of significance.

Results

Table 1 describes the distribution of selected characteristics at study entry for both colon cancer case patients and non-case subjects. Case patients were older and more likely to be black than non-case subjects. Case patients were also heavier and were more likely to have a parental history of colon cancer and to be nulliparous than non-case subjects.

Estrogen use was less prevalent among colon cancer case patients than non-case subjects (Table 2). Case patients were less likely to be ever estrogen users, and among the ever users, case patients were less likely to be current users or to have used estrogens for more than 5 years. The average age at first use among case patients was 46.0 years compared with 44.8 years among non-case subjects. For both case patients and non-case subjects, the reason given for estrogen use was overwhelmingly menopausal symptoms, hysterectomy, or both, and the method of use was primarily oral estrogen.

A negative association was observed between ever using estrogen and colon cancer mortality (RR = 0.71; 95% confidence interval [CI] = 0.61-0.83) (Table 3). This effect was most pronounced for current estrogen users, who experienced approximately half the colon cancer risk of never users (RR = 0.55; 95% CI = 0.40-0.76). There was also a significant trend of decreasing risk with increasing years of use (P for trend = .0001); users of 1 year or less had an RR of 0.81 (95% CI = 0.63-1.03), while users of 11 years or more had an RR of 0.54 (95% CI = 0.39-0.76). These estimates of risk were virtually

Table 1. Characteristics of colon cancer case patients and non-case subjects at study entry, Cancer Prevention Study II, United States, 1982-1989

Characteristic	Colon cancer case patients	Non-case subjects
No. of women	897	421 476
Age, mean, y	65.8	59.2
Age, %		
<50 y	3.2	12.6
50-59 y	25.1	43.1
60-69 y	36.7	30.9
70-79 y	27.2	11.1
≥80 y	7.8	2.3
Race, %		
White	92.2	95.0
Black	7.1	4.2
Other	0.7	0.8
BMI, %		
<26	61.4	68.2
26 to <29	16.4	15.1
≥29	18.7	14.7
Unknown	3.5	2.1
Parental history of colon cancer, %		
Yes	4.2	3.5
No	95.8	96.5
Parity		
0	15.5	11.5
1-2	38.2	37.3
≥3	40.5	48.3
Unknown	5.8	2.9

Table 2. Characteristics of estrogen use among colon cancer case patients and non-case subjects, Cancer Prevention Study II, United States, 1982-1989

Estrogen use	Colon cancer case patients	Non-case subjects
	Among all women	
No. of women	897	421 476
Ever use, %		
Ever	33.3	44.7
Never	66.7	55.3
	Among ever users of estrogen	
No. of women	299	188 578
Use status, %		
Current	14.7	26.7
Former	62.9	53.6
Missing	22.4	19.7
Years of use, %		
≤1	25.1	23.2
2-5	30.8	28.7
6-10	12.0	16.3
≥11	13.0	15.5
Missing	19.1	16.3
Age at first use, %		
<35 y	6.7	8.4
35-39 y	9.0	10.4
40-44 y	18.1	19.9
45-49 y	24.4	27.5
50-54 y	22.1	19.9
55-59 y	7.0	5.1
≥60 y	3.3	1.9
Missing	9.4	6.9
Reason for use, %		
Menopausal symptoms	50.2	42.9
Hysterectomy	33.8	40.0
Menopausal symptoms and hysterectomy	4.3	7.7
Other	9.0	7.3
Missing	2.7	2.1
Method of use, %		
Pill only	66.6	73.6
Pill and other	5.7	6.9
Injection only	14.7	9.8
Cream, cream and injection	4.3	3.8
Don't know and missing	8.8	5.8
Brand, %.		
Premarin only	18.4	30.0
Premarin and other	1.3	1.3
Other	6.7	8.9
Don't know and missing	73.5	59.7

identical and remained significant after adjustment for other potential confounders (Table 3).

We further examined duration of use separately among current estrogen users and former users to see whether the observed trend with increasing duration could be due to longer duration of use among current users than among former users. The data indicate that both recency of use (current versus former) and duration of use were important predictors of risk (Table 4). The negative association between estrogen use and colon cancer was more pronounced in current users than in former users at each level of duration. Similarly, in both current and former users, increased duration of use was associated with a greater reduction in risk. Among current users of 11 years or more, the RR was 0.45 (95% CI = 0.28-0.71).

Among former estrogen users, we examined years since last use to see if recency of use influenced risk of colon cancer. Among former users who took estrogens within the last 10 years, the adjusted RR was 0.62 (95% CI = 0.48-0.80); for those with former use 11 years or more ago, the RR was 0.85 (95% CI = 0.69-1.05). No consistent patterns of risk were observed for duration of use within years since last use categories.

The association between ERT and fatal rectal cancer was similar to that between ERT and fatal colon cancer (Table 5). There was an inverse association between ever using estrogens and rectal cancer mortality (RR = 0.71; 95% CI = 0.49-1.04), although the magnitude of the association did not differ for current users and former users. As with colon cancer, there was a significant trend (P for trend = .0263) of decreasing risk with increasing years of use; users of 6 years or more had an RR of 0.46 (95% CI = 0.23-0.93).

There were no significant interactions between ever use of ERT and any of the other potential risk factors included in the analysis. In other words, the negative association between ever use of estrogen and colon cancer was consistently observed across levels of the other risk factors.

Discussion

These prospective data support the hypothesis that postmenopausal ERT may decrease the risk of fatal colon cancer. There are several reasons to suspect that this association may be causal. These reasons include the strength of the association, the statistically significant dose–response trend with duration of use, the persistence of the decreased risk after control for other risk factors, and the similarity between these findings and those in several previously published studies (*19,21-24*).

The 14 studies listed in Table 6 represent all currently published investigations of colon cancer risk and hormone replacement therapy. All were based on incident colon or colorectal cancer cases. Nine of the 14 suggest an inverse association between colon cancer risk and hormone use (*19-27*), and five show a significant reduction in risk (*19,21-24*). With one exception (*32*), none shows an estimate of risk that is significantly greater than 1.0. The one study showing a significant increased risk (*32*) was conducted in a high-risk region for colorectal cancer in China. No analysis of duration could be done because 90% of the women using hormones had used them for 1 year or less. The results of the most recent study (*19*), a population-based, case–control study conducted in western Washington State, were similar to those of the current study. The investigators (*19*) found that the reduction in risk of colon cancer associated with hormone use was greatest for current users (odds ratio [OR] = 0.53; 95% CI = 0.29-0.96) and for users of more than 5 years' duration (OR = 0.47; 95% CI = 0.24-0.91). Taken together, these studies (*19,21-24*) and the current study suggest the possibility of a true inverse association between colon cancer and exogenous hormone use.

Because our study examined mortality rather than incidence, the observed inverse association with estrogen use could reflect increased survival among estrogen users because of the association of estrogen use with other attributes of a healthy lifestyle. Women who use postmenopausal estrogens differ from nonusers

Table 3. Colon cancer mortality by categories of estrogen use, Cancer Prevention Study II, United States, 1982-1989

Estrogen use	Colon cancer case patients	Non-case subjects	RR* (95% CI)	RR† (95% CI)
Never	598	232 898	1.00 (—)	1.00 (—)
Ever	299	188 578	0.69 (0.60-0.79)	0.71 (0.61-0.83)
Recency of use‡				
Current	44	50 347	0.52 (0.38-0.70)	0.55 (0.40-0.76)
Former	188	101 111	0.73 (0.62-0.86)	0.75 (0.63-0.89)
Years of use§				
≤1	75	43 755	0.80 (0.63-1.02)	0.81 (0.63-1.03)
2-5	92	54 189	0.75 (0.60-0.93)	0.76 (0.61-0.95)
6-10	36	30 669	0.53 (0.38-0.74)	0.55 (0.39-0.77)
≥11	39	29 164	0.51 (0.37-0.71)	0.54 (0.39-0.76)
			P for trend = .0001	*P* for trend = .0001

*RR estimates adjusted for age and race.
†RR estimates adjusted for age, race, parental history of colon cancer, BMI, two diet variables, exercise, parity, type of menopause, age at menopause, oral contraceptive use, aspirin use, and smoking.
‡Excludes 67 case patients and 37 120 non-case subjects with unclassifiable recency of estrogen use.
§Excludes 57 case patients and 30 801 non-case subjects with unclassifiable years of estrogen use.

Table 4. Colon cancer mortality by duration of estrogen use and recency of use, Cancer Prevention Study II, United States, 1982-1989

Estrogen use	Colon cancer case patients	Non-case subjects	RR* (95% CI)
Never	598	232 898	1.00 (—)
Current estrogen users			
Years of use†			
≤1	6	8304	0.63 (0.28-1.42)
2-5	11	11 821	0.74 (0.41-1.36)
6-10	8	12 405	0.40 (0.20-0.81)
≥11	19	17 767	0.45 (0.28-0.71)
			P for trend = .0001
Former estrogen users			
Years of use			
≤1	64	33 779	0.81 (0.62-1.05)
2-5	78	40 639	0.75 (0.59-0.96)
6-10	28	17 304	0.60 (0.41-0.88)
≥11	18	9389	0.62 (0.38-0.99)
			P for trend = .0001

*RR estimates adjusted for age and race.
†Includes 50 non-case subjects with unclassified years of estrogen use.

Table 5. Rectal cancer mortality by categories of estrogen use, Cancer Prevention Study II, United States, 1982-1989

Estrogen use	Rectal cancer case patients	Non-case subjects	RR* (95% CI)
Never	80	233 416	1.00 (—)
Ever	42	188 835	0.71 (0.49-1.04)
Recency of use†			
Current	9	50 382	0.74 (0.37-1.49)
Former	23	101 276	0.67 (0.42-1.07)
Years of use‡			
≤1	11	43 819	0.85 (0.45-1.60)
2-5	13	54 268	0.77 (0.43-1.40)
≥6	9	59 899	0.46 (0.23-0.93)
			P for trend = .0263

*RR estimates adjusted for age and race.
†Excludes 10 case patients and 37 177 non-case subjects with unclassifiable recency of estrogen use.
‡Excludes nine case patients and 30 849 non-case subjects with unclassifiable years of estrogen use.

with regard to a number of possible confounding factors that could influence health and survival. Estrogen users tend to be better educated, to be white, to be leaner, to exercise more often, to be nonsmokers, and to use preventive health services more often than nonusers (*38-40*). While we can be reasonably sure that diet, physical activity, obesity, aspirin use, smoking, and race are unlikely sources of bias, we have no information with which to control for the use of sigmoidoscopy or other screening procedures.

Perhaps the most likely alternative explanation, other than a causal relationship with estrogens, is that women who receive estrogens may have more intensive medical surveillance and may thus be diagnosed earlier, when survival from colon cancer is better. While we cannot rule out the possibility that surveillance bias might have affected our results, the reduction in risk associated with estrogen use appears too large to be explained fully by such a bias. One study of postmenopausal, upper middle class women (*40*) noted a 16% difference in reported screening behavior (for fecal occult blood test and rectal examination) between current estrogen users and never users. If we assume that the reduction in mortality due to early diagnosis of colon cancer is 50%, the differential screening behavior of the two groups would result in an overall reduced mortality risk among current estrogen users of 8.0% (0.16×0.50) and an RR of 0.92. This calculation strongly suggests that increased screening surveillance on the part of estrogen users cannot completely explain the observed magnitude of risk reduction.

One limitation of our study is the relatively short follow-up, so that fatal cases that progress from diagnosis to death in 7 years or less may not be representative of all colon cancer cases. Another limitation is the absence of data on colon cancer subsite. Subsites within the colon have developmental and biological differences that may result in differing susceptibilities to disease (*41*). Estrogen use was established at enrollment and may not exactly reflect use status at the time of disease occurrence. However, the prospective design of our study and the exclusion of women with cancer at base line minimize the potential that disease status might bias reporting of hormone use.

Table 6. Hormone replacement therapy and colorectal cancer: results from available studies

Study	Location	Design	Study size*	Site†	Use	RR‡	95% CI
Jacobs et al. (*19*), 1994	King, Pierce, and Snohomish Counties, Wash.	Population-based, case–control	193/194	C	Ever	0 60	0.35-1.01
					Current	0.53	0.29-0.96
					Former	0.73	0.36-1.49
					1-5 y	0.72	0.39-1.32
					>5 y	0.47	0.24-0.91
				PC	Ever	0.46	0.23-0.91
					Current	0.33	0.15-0.76
					Former	0.71	0.30-1.72
					1-5 y	0.69	0.32-1.48
					>5 y	0.23	0.09-0.61
				DC	Ever	0.74	0.39-1.39
					Current	0.73	0.36-1.49
					Former	0.75	0.32-1.78
					1-5 y	0.73	0.35-1.53
					>5 y	0.74	0.34-1.60
Bostick et al. (*20*), 1994	Iowa	Cohort	212/167 447	C	Former	0.93	0.68-1.27
					Current	0.82	0.50-1.32
Gerhardsson de Verdier and London (*21*), 1992	Stockholm, Sweden	Population-based, case–control	299/276	C	Ever§	0.6	0 4-1.0
				PC		0.4	0.2-0.8
				DC		1.0	0.5-1.9
				R		0.7	0.4-1.3
Newcomb et al. (*22*), 1992	Wisconsin	Population-based, case–control	—	C and R	Ever	0.78	0.62-0.97
					Current	0.53	0.36-0.79
Chute et al. (*23*), 1991	United States (Nurses Health Study)	Cohort	91/195 950	C	Ever	0.7	0.4-1.1
					Current	0.8	0.5-1.6
					Former	0.5	0.3-1.0
				PC	Ever	0.6	0.2-1.7
				DC	Ever	0.7	0.4-1.2
					Current	0.9	0.5-1.9
					Former	0.4	0.2-1.0
				R	Ever	1.4	0.6-3.3
Wu-Williams et al. (*32*), 1991	Chinese women, North America	Population-based, case–control	189/494	C	Everll	2.1	$P = .14$
				R	Everll	0.5	$P = .23$
	Chinese women, China	Population-based, case–control	206/618	C	Everll	2.9	$P = .01$
				R	Everll	1.3	$P = .56$
Peters et al. (*28*), 1990	Los Angeles County, Calif.	Population-based, case–control	327/327	C	<5 y	1.32	0 88-1.98
					5-14 y	1.08	0.64-1.82
					≥15 y	1.05	0.58-1.89
				PC	<5 y	1 44	0.80-2.62
					5-14 y	1.09	0.47-2.56
					≥15 y	1.19	0.51-2.78
				DC	<5 y	1.25	0.69-2 28
					5-14 y	1.10	0.55-2.21
					≥15 y	0.75	0.30-1.85
Furner et al. (*24*), 1989	Chicago, Ill	Hospital-based, case–control	90/208	C and R	Ever	0.5	0 27-0.90
				PC		0.8	0 27-2.63
				DC		0.6	0.27-1.31
				R		0.2	0.03-0.77
Davis et al. (*29*), 1989	Alberta, Canada	Registry-based, case–control¶	720/349	C and R	Current	1.5	0.8-2.7
					Former	1.1	0.7-1.9
Rosenberg et al. (*25*), 1987	Boston, Mass.	Hospital-based, case–control	—	DC	Long-term	↓#	—
				R		↓#	—
Wu et al. (*30*), 1987	Laguna Hills, Calif. (Leisure World)	Cohort	68/27 017	C and R	<8 y	0.98	0.5-1.8
					≥8 y	1 02	0.6-1.8
Potter and McMichael (*26*), 1983	Adelaide, Australia	Population-based, case–control	155/311	C	Ever	0.8	0.4-1.5
				R		1.5	0.8-3.0
Weiss et al. (*31*), 1981	King and Pierce Counties, Wash.	Population-based, case–control	143/707	C and R	<6 y	1.1	0 7-1.9
					≥6 y	1.0	0 6-1 6
Burch et al (*27*), 1975	Nashville, Tenn.	Case series**	3/11 026	C	≥5 y	0.5	—

*Number of case patients/control subjects (case–control studies) or number of case patients/person-years (cohort studies).

†C = colon; R = rectum; PC = proximal colon; DC = distal colon.

‡In references (*19,22,24,29,32*), values represented ORs. In reference (*27*), value represented observed/expected.

§Hormone use includes both oral contraceptives and postmenopausal estrogens.

‖Approximately 90% of hormone users had used the hormone for ≤1 year. Use of non-oral contraceptive hormones was reported by 6% and 8% of control subjects in North America and China, respectively.

¶Controls were women with "non-endocrine related cancers" selected from the cancer registry that generated the cases.

#The authors note that "long-term use of estrogen-containing drugs was inversely associated with left-sided colon cancer and with rectal cancer."

**A series of 735 hysterectomized women, given estrogen therapy and observed for 11 026 person-years. Expected number of cancers were obtained from external population data.

A potential bias, which is of less concern in prospective studies than in retrospective ones, might arise from our exclusion of cohort members who had missing data on estrogen use. We found no evidence that women for whom data were missing were at higher risk than nonusers of estrogen with complete data. It is therefore unlikely that the exclusion of these women could have biased our findings.

If estrogen does influence mortality due to colon cancer, it might do so either by improving survival or by reducing the incidence of cancer. The latter possibility has been suggested by the earlier reports (*19,21-24*) that studied incident cases. A beneficial effect on survival is also plausible, given that exogenous estrogens have been shown to decrease concentrations of secondary bile acids (*7-10*), thus potentially reducing the ability of these bile acids to promote tumors in the colon (*4-6*).

Our study seems compatible with either hypothesis. Since the follow-up period was only 7 years long, most of the colon cancers, or their precursor lesions, may have been present but undiagnosed at enrollment; thus, it is possible that there was a treatment effect. This treatment effect may explain why the risk reduction was greater for current users of estrogen than for former users.

In summary, women using ERT, particularly long-term users and current users, were at substantially decreased risk of fatal colon cancer. These results are consistent with several published studies (*19,21-24*) that suggest a protective role of exogenous hormones in the development of colorectal cancer. Given the limited number of studies of this association, the results of the current study should be interpreted cautiously. However, a true protective effect of postmenopausal hormone use against colon cancer would be of considerable public health importance and merits further investigation.

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Notes

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