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Postmenopausal Hormone Use and Risk for Colorectal Cancer and Adenoma

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Background: Accumulating evidence suggests that postmenopausal hormone use may decrease the risk for colorectal cancer.

Objective: To examine the relation of postmenopausal hormone therapy to colorectal adenoma and cancer.

Design: Prospective cohort and nested case–control studies.

Setting: Nurses' Health Study, a study of registered nurses recruited from 11 U.S. states.

Participants: 59 002 postmenopausal participants in the Nurses' Health Study.

Measurements: Self-reported data on hormone use and cases of distal colorectal adenoma and colorectal cancer obtained from biennial questionnaires completed from 1980 to 1994. Cases of colorectal adenoma and cancer were confirmed by medical record review.

Results: 470 women developed colorectal cancer, and 838 developed distal colorectal adenomas. Current use of postmenopausal hormones was associated with a decreased risk for colorectal cancer (relative risk [RR], 0.65 [95% CI, 0.50 to 0.83]). This association was attenuated in past users (RR, 0.84 [CI, 0.67 to 1.05]) and disappeared 5 years after hormone use was discontinued (RR, 0.92 [CI, 0.70 to 1.21]). Longer duration of current use did not afford greater protection (RR with ≥5 years of use, 0.72 [CI, 0.53 to 0.96]). Even after exclusion of women who reported having screening sigmoidoscopy, the relative risk for colorectal cancer seen with current hormone use was 0.64 (CI, 0.49 to 0.82). This suggests that the apparent protection is unlikely to be due to more intensive screening among hormone users. Current users also had a lower risk for large (≥1 cm) adenomas than did women who had never used hormones (RR, 0.74 [CI, 0.55 to 0.99]), although no overall material association was seen between colorectal adenoma and current hormone use (RR, 0.91 [CI, 0.77 to 1.08]).

Conclusions: The risk for colorectal cancer was decreased among women currently receiving postmenopausal hormone therapy, but the apparent reduction substantially diminished upon cessation of therapy. Hormone use was inversely associated with large colorectal adenomas but not small ones.

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Accumulating epidemiologic evidence suggests that the risk for colorectal cancer may be decreased by postmenopausal hormone use (1–8), but the data are not entirely consistent. Some studies reported similar effects for cancers of the colon and rectum (5); others observed that estrogen was primarily associated with decreased risk for colon cancer (2) or rectal cancer (6, 7), but not both. In addition, few studies have examined patterns of hormone use (for example, current use and duration of use). Available data, however, indicate that much of the effect on colorectal cancer is seen for current users (2, 3, 7, 8) and that long duration of use does not seem to afford further protection (2, 5, 6, 8). Furthermore, although few studies of colorectal adenoma (a precursor of cancer) have been conducted, three case–control studies have reported a decreased risk for adenoma in women receiving estrogen therapy (9–11).

Using information from the Nurses' Health Study, a large prospective cohort study, we examined whether postmenopausal hormone use decreased the risk for colorectal cancer and adenoma during a follow-up that lasted as long as 14 years. We specifically addressed the risks for colon and rectal cancers and distal colorectal adenomas. We evaluated the effect of current and past use of hormones, duration of use, and dose of estrogen taken.

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Methods

The Nurses' Health Study Cohort

The Nurses' Health Study began in 1976 when 121 700 female registered nurses in 11 states completed mailed questionnaires that included items about medical history and other health-related variables. Every 2 years, we mail follow-up questionnaires to update the information on risk factors and to identify newly diagnosed cases of major illnesses. Questionnaires on diet and physical activity were added in 1980; information on history of colonoscopy or sigmoidoscopy is requested for each time period. We repeatedly send questionnaires to participants who do not respond; after each 2-year mailing cycle, we search state and national vital statistics registries for deaths among the persistent nonrespondents. The total follow-up exceeds 92%, and follow-up for death is greater than 98%.

Identification of Colorectal Cancer

Nurses who reported a diagnosis of cancer of the colon or rectum were asked for permission to review their medical records. For cases ascertained through the mortality follow-up, we sought permission (subject to regulations of state registries) from the participants' families. We included only cases that were confirmed by pathology reports and were diagnosed after the return of the 1980 questionnaire and before 1 June 1994. Details of the histologic findings, cancer stage, and anatomic site were abstracted from the medical records of participants with colon or rectal cancer.

Identification of Colorectal Adenomas

More than 90% of the adenomas were diagnosed in women who underwent an endoscopic procedure for routine screening or for unrelated gastrointestinal conditions. These women were asked for permission to review their medical records. Because most procedures were sigmoidoscopies, we studied only adenomas of the distal colon and rectum; we excluded hyperplastic polyps, which are not precursors of colorectal cancer. Information on adenoma size was extracted from the endoscopy report or the pathology report; when both sources provided information, we used the size given on the endoscopy report.

Ascertainment of Hormone Use

At baseline, women were asked about their current (at the time of questionnaire response) and past (at any time before questionnaire response) use of postmenopausal hormone therapy, including duration (months of use, both currently and in the past), estrogen dose, and type of hormones used. All data on hormone use were subsequently updated on each biennial questionnaire, and data on duration of use were recalculated on the basis of updated hormone status. Approximately 75% of the person-time among hormone users was for estrogen alone; the remaining 25% was for estrogen combined with a progestin.

Sample for Analysis

We excluded women who provided no information on hormone use and those who did not respond to the 1980 dietary questionnaire. To identify a group of women without diagnosed cancer at each baseline period, we also excluded women who reported any cancer (except nonmelanoma skin cancer), polyposis coli, or ulcerative colitis before 1980 (the start of follow-up) and at the beginning of each time period. We classified women as postmenopausal from the time of natural menopause or hysterectomy with bilateral oophorectomy. Women who underwent hysterectomy without bilateral oophorectomy were considered postmenopausal when they reached the age at which natural menopause had occurred in 90% of the cohort (54 years for smokers and 56 for nonsmokers) (12). The women's reports of age at menopause and type of menopause were highly accurate (13).

A total of 29 264 women entered the analysis of colorectal cancer in 1980, and 29 738 women were added during follow-up as they became postmenopausal. During the 14 years of follow-up (from the return of the 1980 questionnaire until 1 June 1994), 601 503 person-years of follow-up were accrued. For each participant, person-years were allocated to the categories of hormone use according to the 1980 data and were updated at each 2-year interval by the information obtained subsequently.

Because colorectal adenomas have no symptoms and are diagnosed primarily in women who have undergone endoscopy for screening, analyses of colorectal adenoma were restricted to the participants who had had colonoscopy or sigmoidoscopy during the study period (21 153 postmenopausal women). This restriction eliminates potentially spurious associations caused by any relation between hormone use and the likelihood of undergoing endoscopy.

Statistical Analysis

The analysis of colorectal cancer is based on incidence rates in which person-months of follow-up were used as the denominator. We used relative risk (RR) as the measure of association, defined as the incidence of cancer among women in various categories of hormone use divided by the corresponding rate among women who never used hormones. Age-specific rates (with 5-year categories of age) were individually calculated and used to compute age-

Table 1. Relative Risk for Colorectal Cancer among Women According to Postmenopausal Hormone Use, 1980–1994*

Hormone Use	Patient-Years of Follow-up	Colorectal Cancer		Colon Cancer		Rectal Cancer	
		Cases	RR (95% CI)	Cases	RR (95% CI)	Cases	RR (95% CI)
		n		*n*		*n*	
Never	289 589	262		203		59	
Current	170 170	90		69		21	
Age-adjusted			0.62 (0.49–0.79)		0.62 (0.47–0.81)		0.64 (0.39–1.06)
Multivariate-adjusted†			0.65 (0.50–0.83)		0.64 (0.48–0.85)		0.67 (0.40–1.12)
<5 years	75 299	30		20		10	
Age-adjusted			0.53 (0.36–0.78)		0.45 (0.29–0.72)		0.80 (0.40–1.59)
Multivariate-adjusted†			0.56 (0.39–0.83)		0.49 (0.31–0.77)		0.83 (0.42–1.64)
≥5 years	90 903	59		48		11	
Age-adjusted			0.69 (0.52–0.91)		0.71 (0.52–0.98)		0.59 (0.31–1.11)
Multivariate-adjusted†			0.72 (0.53–0.96)		0.75 (0.54–1.04)		0.59 (0.30–1.16)
Past	141 744	118		94		24	
Age-adjusted			0.82 (0.66–1.02)		0.84 (0.65–1.08)		0.76 (0.47–1.23)
Multivariate-adjusted†			0.84 (0.67–1.05)		0.86 (0.67–1.11)		0.76 (0.47–1.24)
<5 years	99 458	77		61		16	
Age-adjusted			0.79 (0.61–1.03)		0.83 (0.62–1.12)		0.78 (0.44–1.38)
Multivariate-adjusted†			0.79 (0.61–1.03)		0.81 (0.60–1.08)		0.75 (0.43–1.31)
≥5 years	36 029	34		27		7	
Age-adjusted			0.88 (0.61–1.27)		0.89 (0.59–1.34)		0.84 (0.38–1.86)
Multivariate-adjusted†			0.90 (0.62–1.30)		0.91 (0.60–1.39)		0.83 (0.37–1.90)

* Information on duration of hormone use was missing for 8 cases (1 current user and 7 past users) and 10 225 person-years of follow-up (3968 person-years of current use and 6256 person-years of past use). RR = relative risk.
† Adjusted for age, body mass index, past use of oral contraceptives, family history of colorectal cancer, calcium intake, folate intake, methionine intake, red meat intake, aspirin use, alcohol intake, previous polyps, cigarette smoking, exercise, and age at menopause.

adjusted relative risks with 95% CIs (14). Proportional hazards models (15) were used to calculate relative risks, adjusting for age; age at menopause (<43 years, 43 to 48 years, 49 to 50 years, and >50 years); body mass index (quintiles of kg/m^2); cigarette smoking (number of pack-years before 35 years of age); previous use of oral contraceptives (never, <3 years of use, and ≥3 years of use); dietary calcium (quintiles); intake of red meat, folate, and methionine (quintiles); alcohol use (quintiles); aspirin use (none, 1 to 3 tablets per week, 4 to 6 tablets per week, 7 to 10 tablets per week, 11 to 14 tablets per week, and ≥14 tablets per week); family history of colorectal cancer (yes or no); leisure-time physical activity (quintiles); and history of polyps (yes or no). Adjustment for additional dietary variables, such as fiber intake, did not influence the model; thus, these variables were not included.

For the nested case–control analysis of colorectal adenomas, we compared hormone use in case-patients and controls who had endoscopy during the study period. Women who had had a positive result on endoscopy at any time during the study period were considered case-patients, and those who had consistently negative endoscopic results were designated as controls. Hormone status and the presence of potentially confounding variables were established by responses to the questionnaire returned immediately before diagnosis of an adenoma (for case-patients) or before negative results on endoscopy (for controls). We used multiple logistic regression (16) to derive relative risks and 95% CIs (estimated by odds ratios) for the relation of hormone use to adenoma, after adjusting for the above confounders and the performance of endoscopy (yes or no) before the start of the study.

Role of Funding Source

This research was completely funded by the National Institutes of Health. The funding source had no part in collecting, analyzing, or interpreting the data.

Results

From 1980 to 1994, we identified 470 women with colorectal cancer (366 with colon cancer and 104 with rectal cancer) and 838 women with adenomas (617 with sigmoid colon adenomas and 221 with rectal adenomas). Women who had never used hormones represented 48.1% of the total follow-up time; current users, 28.3%; and past users, 23.6%.

Colorectal Cancer

Current use of postmenopausal hormones was associated with a decreased risk for colorectal cancer compared with no previous use (age-adjusted RR, 0.62 [95% CI, 0.49 to 0.79]); adjustment for multiple risk factors only slightly attenuated this estimate (multivariate-adjusted RR, 0.65 [CI, 0.50 to 0.83]) (**Table 1**). The inverse relation was similar for cancers of the colon and rectum (multivariate-adjusted RR, 0.64 for colon cancer and 0.67 for rectal cancer). The risk for proximal tumors apparently decreased (RR, 0.56 [CI, 0.35 to 0.91]), and a decrease in the risk for distal tumors was suggested

Table 2. Relative Risk for Colorectal Cancer among Women Who Previously Received Postmenopausal Hormone Therapy According to Time since Last Use, 1980–1994*

Time since Last Hormone Use	Patient-Years of Follow-up	Colorectal Cancer		Colon Cancer		Rectal Cancer	
		Cases	RR (95% CI)	Cases	RR (95% CI)	Cases	RR (95% CI)
		n		*n*		*n*	
<5 years	51 365	31		26		5	
Age-adjusted			0.68 (0.47–0.99)		0.74 (0.49–1.11)		0.48 (0.20–1.18)
Multivariate-adjusted†			0.69 (0.48–0.98)		0.73 (0.49–1.09)		0.53 (0.23–1.23)
≥5 years	77 065	74		58		16	
Age-adjusted			0.88 (0.67–1.15)		0.88 (0.65–1.19)		0.86 (0.48–1.54)
Multivariate-adjusted†			0.92 (0.70–1.21)		0.91 (0.67–1.25)		0.93 (0.52–1.68)

* Information on time since last use was missing for 13 cases and 13 314 person-years of follow-up. Reference group is women who never used hormones. RR = relative risk.
† Adjusted for age, body mass index, past use of oral contraceptives, family history of colorectal cancer, calcium intake, folate intake, methionine intake, red meat intake, aspirin use, alcohol intake, previous polyps, cigarette smoking, exercise, and age at menopause.

(RR, 0.79 [CI, 0.50 to 1.25]); the latter finding, however, was not statistically significant. Among past hormone users, we observed a modest, nonsignificant reduction in the risk for colorectal cancer (RR, 0.84 [CI, 0.67 to 1.05]).

Protection against colon cancer did not increase with longer duration of current hormone use (**Table 1**). Compared with women who had never received hormones, the relative risk for colon cancer among current hormone users who had received hormones for less than 5 years was 0.56 (CI, 0.39 to 0.83); for those who had used hormones for 5 or more years, the relative risk was 0.72 (CI, 0.53 to 0.96). Similarly, no substantial inverse relation was seen for long-term past users (RR, 0.90 [CI, 0.62 to 1.30]).

When we examined the time since last use of hormones (**Table 2**), we found a decrease in the risk for colorectal cancer among women who had recently (<5 years) stopped taking hormones (RR, 0.69 [CI, 0.48 to 0.98]). However, no association was seen among women who had last used hormones 5 or more years before completion of the questionnaire (RR, 0.92 [CI, 0.70 to 1.21]) compared with women who had never used hormones.

Moderate evidence suggested a trend for increasing protection with increasing estrogen dose (P for trend = 0.07). For women who received 0.3 mg of estrogen, we found no relation between current hormone use and colorectal cancer (RR, 0.99 [CI, 0.57 to 1.70]); for women taking 1.25 mg or more, the relative risk was 0.48 (CI, 0.25 to 0.90). However, because the most prevalent estrogen dose in this cohort was 0.625 mg, we have little statistical power with which to distinguish effects of different doses.

Because women with the highest body mass index have higher levels of endogenous estrogen, we explored whether body mass index modified estrogen's effect on risk for colorectal cancer. We expected that exogenous estrogen would be most important for the thinnest women. However, we found that women in the highest quintile of body mass index (>29 kg/m^2; n = 12 women with cancer who were current estrogen users) had the greatest apparent protection against colorectal cancer (age-adjusted RR, 0.51 [CI, 0.28 to 0.93]); no relation was seen between current hormone use and cancer among women in the lowest quintile of body mass index (<21 kg/m^2; RR, 1.10 [CI, 0.55 to 2.18]). We also explored the interaction between folate and methionine intake and hormone use; if estrogen influences DNA methylation, as has been hypothesized (17), one might expect that women with low folate or methionine intake would particularly benefit from hormone use. However, reduction in the rate of colorectal cancer for current hormone users did not vary by folate or methionine intake.

Finally, we were concerned that hormone users might have undergone screening more frequently and that this explained some of the apparent protection against colorectal cancer. To address this issue, we excluded all women who reported ever having undergone screening sigmoidoscopy (15% of person-years). After exclusion, we still observed a strong relation between hormone use and colorectal cancer (RR, 0.64 [CI, 0.49 to 0.82]) in this subgroup.

Colorectal Adenoma

We found no overall association between risk for adenoma and either current or past hormone use relative to no previous use (**Table 3**) (RR, 0.91 [CI, 0.77 to 1.08] and 1.06 [CI, 0.89 to 1.26], respectively). This seemed to be true for both sigmoid and rectal adenomas. After we distinguished small (<1 cm) and large colorectal adenomas, however, current hormone users had a reduced risk for large adenomas (RR, 0.74 [CI, 0.55 to 0.99]).

As was seen with colorectal cancer, duration of hormone use had no effect on risk for adenoma. After 5 or more years of current use, the relative risk for colorectal adenoma was 0.97 (CI, 0.79 to 1.18) compared with no previous use; the relative risk for large adenomas was 0.81 (CI, 0.57 to 1.15). High doses of estrogen did not seem to alter these

associations; among women whose estrogen dose was 1.25 mg or more, no association was seen between colorectal adenoma and current hormone use (RR, 1.03 [CI, 0.74 to 1.41]) and no evidence showed additional protection against large adenomas (RR, 0.90).

Discussion

In this large prospective study, the risk for colon and rectal cancers was decreased by 35% among women currently using postmenopausal hormones; a smaller apparent reduction was noted for past users. However, long duration of use did not seem to provide any additional protection. There did seem to be a trend of increasing protection with increasing estrogen dose. We also found an inverse association between the risk for large adenomas and current hormone use, although no relation was observed for small adenomas.

We previously reported data after a preliminary analysis with 8 years of follow-up in this study (18). Although the observed relative risk (0.8 [CI, 0.5 to 1.6]) did not indicate significant protection for hormone users, there were few cases of colorectal cancer (15 cases in women who received hormone therapy) and the CI was consistent with our current findings. Although we do not validate self-reported hormone use, we believe the reports to be accurate because all study participants are registered nurses with a demonstrated interest in medical research. Validation of several other self-reported exposures in these nurses, such as diet (19), alcohol intake (20), and body mass index (21), have substantiated this belief. Moreover, the prospective design of our study eliminates recall bias, which can be a problem in case–control studies.

Several epidemiologic studies done in the past two decades have investigated the relation between estrogen and the risk for colorectal cancer (1–8, 22–31); our current investigation is one of three large prospective studies (3, 7) to find an inverse association between colorectal cancer and current use of postmenopausal estrogen.

In their prospective study, Calle and colleagues (3) reported the strongest protection against colon cancer in current hormone users (RR, 0.55 [CI, 0.40 to 0.76]); the end point in that study was death from colon cancer, whereas our end point was all cases of diagnosed colorectal cancer. In a study of 40 464 postmenopausal women followed for an average of 8 years, Troisi and colleagues (7) found a decreased risk for colorectal cancer in women who had recently used hormones (RR, 0.78 [CI, 0.6 to 1.1]). In a large case–control study, Newcomb and Storer (2) showed an inverse association between postmenopausal hormones and colorectal cancer, especially among women who had recently received estrogen therapy (RR, 0.54 [CI, 0.36 to 0.81]). Kampman and associates (8) reported a similar finding in their case–control study of 894 women with colon cancer (RR, 0.71 [CI, 0.56 to 0.89]). In a prospective study, Risch and Howe (22) found no significant association between estrogen and colorectal cancer. However, women who had used hormones for 3.5 years or less were included in the reference group of women who did not take hormones; given that short-term hormone use seems to decrease risk for colorectal cancer, this categorization could explain the researchers' null results.

Our study shows that increased duration of postmenopausal estrogen use does not yield additional protection against colorectal cancer. Although few other studies have examined this issue, several have reported similar results (2, 5, 6, 8). Newcomb and Storer (2) initially identified a stronger protective effect with long duration of use, but this occurred because long-term hormone users were also the most recent users; after adjustment for time since last use, duration no longer had any effect. Jacobs (4) and Calle (3) and their coworkers reported increased protection for long-term hormone users but did not control for time since last use.

Table 3. Relative Risk for Colorectal Adenomas among Women According to Postmenopausal Hormone Use, 1980–1994*

Hormone Use	All Adenomas		Sigmoid Adenomas		Rectal Adenomas		Small Adenomas†		Large Adenomas†	
	Cases	RR (95% CI)	Cases	RR (95% CI)	Cases	RR (95% CI)	Cases	RR (95% CI)	Cases	RR (95% CI)
	n		*n*		*n*		*n*		*n*	
Never	352	1.0	255	1.0	97	1.0	155	1.0	128	1.0
Current	252		190		62		136		73	
Age-adjusted		0.89 (0.78–1.05)		0.94 (0.77–1.13)		0.79 (0.58–1.09)		1.10 (0.87–1.39)		0.72 (0.54–0.96)
Multivariate-adjusted‡		0.91 (0.77–1.08)		0.95 (0.78–1.16)		0.82 (0.59–1.13)		1.07 (0.84–1.35)		0.74 (0.55–0.99)
Past	234		172		62		118		80	
Age-adjusted		1.08 (0.91–1.29)		1.08 (0.89–1.32)		1.08 (0.78–1.49)		1.26 (0.98–1.61)		1.00 (0.75–1.33)
Multivariate-adjusted‡		1.06 (0.89–1.26)		1.06 (0.87–1.30)		1.06 (0.76–1.46)		1.21 (0.94–1.54)		0.99 (0.74–1.31)

* RR = relative risk.
† Information on size of adenoma was missing for 148 cases.
‡ Adjusted for age, cigarette smoking, body mass index, past use of oral contraceptives, calcium intake, red meat intake, aspirin use, alcohol intake, folate intake, methionine intake, exercise, family history of colorectal cancer, previous endoscopy, and age at menopause.

Current theories of carcinogenesis view adenomatous polyps as precursors of colon cancer. To our knowledge, only three other investigations have examined colorectal adenomas and estrogen use. On the basis of 17 exposed cases, Jacobson and colleagues (9) reported a nonsignificant inverse association (RR, 0.7 [CI, 0.3 to 1.2]) with hormone use. Potter and associates (10) compared 174 postmenopausal women who had colorectal polyps with 289 colonoscopy-negative controls and with 183 community controls; the odds ratios were 0.43 (CI, 0.26 to 0.71) and 0.64 (CI, 0.37 to 1.09), respectively, after 5 or more years of hormone use. In a recent small case–control study of 74 postmenopausal women with adenoma diagnosed at colonoscopy and 137 colonoscopy-negative controls, Peipins and colleagues (11) reported a reduced risk for colorectal adenoma in women who had ever used hormones (RR, 0.39 [CI, 0.15 to 0.97]). Our prospective study found a decreased risk for large adenomas, although no association was seen between small adenomas and hormones.

An important concern is that women who receive postmenopausal hormones may differ from women who do not in ways that influence risk for colorectal cancer. Women taking hormones must visit their physicians regularly and may more frequently undergo endoscopic procedures; removal of precancerous adenomas that are identified by these procedures could decrease the risk for cancer. In 1990, we asked participants about screening practices; women taking hormones reported undergoing screening sigmoidoscopy (15.6%) more frequently than did women who had never used hormones (11.4%), but the proportion was identical for current (15.4%) and past users (15.8%). If more frequent endoscopy completely explained the decreased risk for colorectal cancer, we would expect to see similar reductions in the risk for cancer among both current and past hormone users; however, we found a greater decrease in the risk for colorectal cancer with current than with past use. Furthermore, the strong inverse relation between postmenopausal use of hormones and proximal tumors, which are less likely to be detected by sigmoidoscopy, also indicates that the association we observed cannot be totally attributable to differences in screening habits. Finally, even when we excluded all women who reported ever having undergone screening sigmoidoscopy, the relative risk for colorectal cancer among current postmenopausal hormone users was still 0.64.

Hormone users also tend to have rectal and pelvic examinations and fecal occult blood tests more often than women who do not visit a physician regularly. In 1990, 48% of women in our study who never used hormones, 52% of past users, and 64% of current users reported that they had recently undergone a rectal examination. Regular pelvic examinations and fecal occult blood testing follow similar patterns. However, such screening tests lead to earlier diagnosis but do not prevent cancer occurrence. If the relation between colon cancer and postmenopausal hormone use were completely due to better general screening among hormone users, we would expect to see a much greater decrease in the risk for advanced cancers than in the risk for all colon cancers. However, the relative risk seen for stage C and D cancers (0.65 [CI, 0.45 to 0.94]; 217 of all cases of cancer) was similar to that seen for all colon cancers.

A final concern is the possibility that women may discontinue hormone use when symptoms of a disease develop (31), leaving mostly healthy women in the category of current users. If so, women who recently discontinued taking hormones would be those in whom cancer is most likely to be diagnosed. However, our data suggest that women who have stopped postmenopausal hormone therapy in the past 5 years have a decreased risk for colorectal cancer that is similar to that of current users.

Long-standing hypotheses about the biological mechanism of estrogen in colorectal cancer have focused on variations in bile acid metabolism in response to sex hormones, as proposed by McMichael and Potter (32). Secondary bile acids are believed to initiate or promote malignant change in the colonic epithelium, and exogenous estrogens (which decrease secondary bile acid production) could therefore protect against colorectal cancer. An additional hypothesis attributes the influence of estrogens to intestinal microflora that require bile acids to produce diacylglycerol; this activates a key enzyme in growth stimulation and tumor production (32). Suppression of diacylglycerol by way of decreased bile acid production may also explain estrogen's apparent ability to suppress the growth of colonic epithelial cells (33).

More recent hypotheses focus on steroid hormone receptors in normal colonic mucosa as well as colorectal tumor cells (34–37). However, in vitro experiments have shown contradictory effects of estrogen on cell growth. A promotional growth effect was seen in some mouse (38) and human (39) adenoma- and carcinoma-derived colonic cell lines, but growth inhibition by estrogen has also been demonstrated in studies of human colonic (40) and noncolonic (41) cell lines.

Issa and colleagues (17) found age-related hypermethylation of the promotor region of the estrogen receptor gene. Methylation-associated loss of expression of the estrogen-receptor gene resulted in deregulated growth in colonic mucosa, and these authors suggest that the receptor may have a tumor suppressor role. Methylation was found to be pro-

gressive with age of colonic mucosa; as a result, the mucosa may be at increased risk for neoplastic transformation. The mechanism of methylation is unclear, but the authors demonstrated that with natural decline of circulating estrogens, several tissues exhibited decreased expression of estrogen receptor and reduced rates of transcription; these changes predispose the tissues to methylation. Exogenous estrogens may maintain transcription and expression of the receptor gene, thereby protecting it from methylation. Indeed, Issa and colleagues demonstrated that overexpression of the estrogen receptor gene suppressed growth in cultured neoplastic colon cells. This growth suppression was accentuated by added estrogen, a finding that supports a possible inverse association between postmenopausal hormones and the risk for colon cancer.

In conclusion, we found that recent or current use of postmenopausal hormones seems to reduce the risk for colorectal cancer; this result is consistent with substantial epidemiologic and biological data. Colorectal cancer is the fourth leading cause of cancer-related death and the second leading cause of all-cancer death in the United States (42). The rate of colorectal cancer development in our study was 85/100 000 person-years among 55- to 59-year-old women and 121/100 000 person-years among 60- to 64-year-old women. On the basis of our data, we would expect that 30 cases of colorectal cancer would be prevented per 100 000 person-years of hormone use among women 55 to 59 years of age. This number would increase to 58 cases prevented in the higher-risk group of women 60 to 64 years of age; the benefit would be similarly increased among other high-risk groups, such as women with a family history of colorectal cancer. Nonetheless, these reductions must be considered in light of other major risks and benefits of estrogen use (43), including decreases in risk for coronary disease and fractures and an increased risk for breast cancer.

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