
Hormone Replacement Therapy and Colorectal Adenoma Recurrence Among Women in the Polyp Prevention Trial

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For the Polyp Prevention Study Group

Background: Epidemiologic studies have suggested that estrogen may protect against the development of colorectal cancers and adenomatous polyps. We conducted a prospective study to evaluate the association between hormone replacement therapy (HRT) and adenoma recurrence among perimenopausal and postmenopausal women participating in the Polyp Prevention Trial, a randomized dietary intervention study of individuals with colorectal adenomas. **Methods:** We used a questionnaire and interviews to collect detailed information, at baseline and at each of four annual study visits, from 620 women regarding hormone use, menopausal status, diet, alcohol consumption, and other risk factors. Adenoma recurrence was ascertained by complete colonoscopy at baseline and after 1 and 4 years. Logistic regression models were used to evaluate the association between hormone use and adenoma recurrence after adjusting for intervention group and for age and body mass index at baseline. All statistical tests were two-sided. **Results:** Adenomas recurred in 200 women. There was no overall association between adenoma recurrence and either overall hormone use (odds ratio [OR] = 1.01; 95% confidence interval [CI] = 0.70 to 1.45), combined estrogen and progestin use (OR = 0.94; 95% CI = 0.57 to 1.56), or unopposed estrogen use (OR = 1.04; 95% CI = 0.68 to 1.59). HRT use was associated with a reduction in risk for recurrence of distal adenomas (OR = 0.56; 95% CI = 0.32 to 1.00) and a statistically nonsignificant increase in risk

for recurrence of proximal adenomas (OR = 1.39; 95% CI = 0.85 to 2.26). We observed a statistically significant interaction between the HRT-adenoma recurrence association and age ($P = .02$). HRT was associated with a 40% reduced risk of adenoma recurrence among women older than 62 years (OR = 0.58; 95% CI = 0.35 to 0.97) but with an increased risk among women younger than 62 years (OR = 1.99; 95% CI = 1.11 to 3.55). **Conclusions:** HRT was not associated with a reduced risk for overall adenoma recurrence in this trial cohort, although there was a suggestion of an age interaction. The effect of age on the association needs to be confirmed in other adenoma recurrence trials. [J Natl Cancer Inst 2001; 93:1799-805]

A hypothesis linking exogenous hormone use and the development of colorectal cancer was formulated after the observations of other investigators (1,2). These data include a higher than expected frequency of colorectal tumors among nuns, who also have elevated breast cancer risk, and descriptive data showing that, while women and men have a similar incidence of colorectal cancer before reaching age 50 years, women have a lower incidence than men after age 50 years. Given both the prevalence of hormone replacement therapy (HRT), with its potential benefits and risks, and the mortality and morbidity associated with colorectal cancer, the third leading cause of cancer death among women in the United States (3), the association between HRT and the risk of colorectal cancer and adenomatous polyps is of considerable public health significance.

One potential mechanism by which sex hormones could affect colon cancer risk is through the reduced production of secondary bile acids, which are thought to promote colon carcinogenesis (2). More recently, it has been hypothesized that estrogen may exert a more direct effect on colon cancer risk by inhibiting the growth of colon cancer cells in colonic mucosa (4,5), perhaps via its role in the modulation of vitamin D responsiveness and calcium absorption (6-9).

Numerous prospective and retrospective epidemiologic studies (10-16) have found inverse associations between HRT and risk for colorectal cancers. More recently, a few studies have evaluated associations between HRT and risk of adeno-

matous polyps, the latter of which are considered to be requisite precursors for most colorectal cancers. The evolution from an aberrant colonic crypt to the formation of a polyp is thought to take about 5 years (17). In three studies (18-20), inverse associations were observed between prevalent polyps and both the duration of HRT use and recent HRT use. A sigmoidoscopy-based prospective study of distal polyps found no association between HRT and prevalent polyps overall but did observe an inverse association between HRT and polyps larger than 1 cm (21). Thus, both experimental animal models and human epidemiologic studies suggest that estrogen may protect against the development of colorectal neoplasia and cancer.

Recurrence of adenomas among those screened is an important public health concern considering that, among the individuals screened, 40% will present with an adenoma, and these individuals are at higher risk for the development of subsequent adenomas and, possibly, colorectal cancer. We evaluated the association between HRT and colorectal adenoma recurrence among women participating in the Polyp Prevention Trial (PPT). To our knowledge, this is the first prospective study to evaluate this relationship using subjects enrolled in a well-designed intervention trial with detailed ascertainment of both adenomas (by complete colonos-

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See Appendix for members of the Polyp Prevention Study Group and their affiliations.

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copy) and hormone use (obtained yearly for 5 years by study interviewer).

SUBJECTS AND METHODS

Sample Population

The subjects of this study were the female participants of the PPT, a randomized, intervention trial designed to test whether a low-fat, high-fiber diet rich in fruit and vegetables inhibits the recurrence of colorectal adenomas. The PPT was a collaboration between eight study centers (listed in the "Appendix" section) and was approved by the institutional review boards of the National Cancer Institute and each of the participating centers. All study participants provided written informed consent. The overall design, rationale, dietary intervention and endpoint procedures, and trial results were reported previously (22–24). Briefly, women who were at least 35 years old and who had one or more histologically confirmed colorectal adenomas identified by complete colonoscopy within the 6 months before randomization in the PPT were recruited to our study. Eligibility criteria for the PPT were no history of either colorectal cancer, surgical resection of adenomas, inflammatory bowel syndrome, or the polypoid syndrome. At the baseline visit (T_0) and each of four subsequent annual visits (T_1 through T_4), each participant provided a venous blood specimen and answered an interviewer-administered questionnaire that assessed a variety of demographic, clinical, and behavioral characteristics, including drug/vitamin supplement use and menopausal status.

For the determination of menopausal status, women were asked if they had had a menstrual period in the last 6 months and, if they had not, the age they were when they had their last menstrual period. All participants who reported not having a menstrual period within 6 months of study entry were considered to be menopausal at baseline ($n = 536$). Women who reported both having menstrual periods at study entry and not having menstrual periods at a later study date were considered to be perimenopausal at baseline and were included in our analyses ($n = 26$). Women who did not report menopausal status (i.e., women who did not answer the question regarding their last menstrual period at any study visit) and who were older than 45 years at baseline were considered to be either perimenopausal or postmenopausal and were included in our study ($n = 58$). Women who did not report menopausal status and were 45 years old or younger at baseline were excluded from our study ($n = 57$). The final analytic set included 620 women whose ages ranged from 36 to 86 years.

Assessment of Adenomas

Eligible participants received a full colonoscopy (i.e., one that reached the cecum) at baseline (T_0), at the first annual visit (T_1), and at the end of the trial intervention period (either at the T_4 visit or at an unscheduled colonoscopy visit after the T_1 visit). The colonoscopy at the T_1 visit served to detect and remove any lesions missed by the baseline colonoscopy. The study endpoint was the recurrence of colorectal adenoma, which was defined as pathologically confirmed adenoma(s) discovered during any endoscopic procedure between the T_1 colonoscopy

and either the end of the trial colonoscopy (T_4) or, for subjects who missed the 1-year colonoscopy, any endoscopic procedure performed at least 2 years after randomization. Of the 677 women who completed the PPT, 60 (9%) did not undergo the T_1 colonoscopy. The use of HRT did not differ between those women who did undergo the T_1 colonoscopy and those who did not. Two pathologists reviewed samples of all adenomas removed during colonoscopy to determine the histologic features and degree of atypia of the lesions. Information about the size, number, and anatomic location of all adenomatous polyps within the large bowel was obtained from the endoscopists' reports.

Assessment of Menopausal Hormone Use

At the baseline and subsequent yearly visits, interviewers administered a detailed questionnaire to each participant that included questions about their use of prescription and nonprescription drugs. Participants were asked if they were currently taking any medication on a regular basis (defined as one or more times per month). At each annual visit, participants were also asked to bring all prescription and nonprescription medications that they were currently taking. Interviewers verified the name of each medication and determined the dosage and frequency of use. All drugs were categorized by use of the Pharmacologic-Therapeutic Classification Code of the American Hospital Formulary Service (25). Menopausal HRT included both unopposed estrogens (e.g., premarin) and estrogen/progestin combinations.

Statistical Analyses

Our analysis was limited to perimenopausal and postmenopausal women and to women with unknown menopausal status who were older than 45 years at baseline for whom we had complete information on HRT use, gathered during the baseline or the first annual visit, before ascertainment of adenoma recurrence status. We used the detailed information on hormone use obtained yearly to establish prospective overall hormone use, dose, and duration of use. Prospective overall use was defined by whether a participant was a current user or nonuser of hormones at T_0 and/or at T_1 . Hormone dose was evaluated as a continuous variable and was categorically based on the median split of reported daily doses among the hormone users (0.62 mg for estrogen and 2.5 mg for progesterone). Continuous use was evaluated as a dichotomous variable and defined as those participants who reported using HRT at every study visit (T_0 through T_4). We used logistic regression models to estimate the association (odds ratios [ORs] and 95% confidence intervals [CIs]) between HRT and adenoma recurrence. Potential confounders were evaluated by assessing their associations with HRT and adenoma recurrence. HRT was not associated with other indicators of healthy behaviors, such as physical activity and vitamin and aspirin use. Final models were adjusted for age and body mass index (BMI) at T_0 and intervention assignment. Associations between HRT and adenoma multiplicity were evaluated by logistic regression analysis, with the outcome variable being women with more than one adenoma, using women with a

single adenoma or no adenoma as the reference group. Associations between HRT and advanced adenomas were evaluated by use of logistic regression analysis, with the outcome variable being women with advanced adenomas (defined as adenomas with either villous histologic subtype, dysplasia, or ≥ 1 cm in size), using women with nonadvanced adenomas or no adenoma as the reference group. Logistic regression analysis was used to estimate the OR of adenoma recurrence for each anatomic subsite within the bowel (i.e., proximal, distal, or a combination of distal and proximal) relative to the no adenoma reference group (women with recurrent adenomas at locations other than the subsite being evaluated were not included in this analysis). Effect modification by age was determined by including age as a continuous variable, by dichotomizing age at the median, and by using quartiles of age in an interaction term with HRT use in the regression model and evaluating the significance of the cross-product term. All three of these models yielded statistically significant interaction terms between age and HRT use. All statistical tests were two-sided and P values were considered to be statistically significant if less than .05.

RESULTS

The general characteristics of the 620 women according to colorectal adenoma recurrence status are described in Table 1. Thirty-two percent of the women had one or more recurrent adenomas by the end of the study period. Except for age and years since menopause, there were essentially no differences in study characteristics between the women who had a recurrence of adenoma and those that did not.

Forty percent of the women in our study used estrogen or hormone replacement drugs at the time of their T_0 or T_1 visits; 60% used unopposed estrogen and 40% used estrogen-progestin combination therapy. Because the proposed mechanisms for the role of estrogen in colon carcinogenesis involve cell growth and proliferation and earlier studies have demonstrated that the duration of HRT use is associated with colon cancer risk, we also evaluated hormone use over the duration of the study. Among the women in our study, 28% reported current HRT use at each annual visit. Of those women who used HRT at T_0 or T_1 , approximately 70% took hormones throughout the course of the study. The median length of follow-up time did not differ by HRT use (2.98 and 3.06 years for HRT users and nonusers, respectively).

Associations between HRT use and adenoma recurrence are presented in Table 2. All ORs were adjusted for age, BMI, and intervention assignment. There was no association between HRT use and ad-

Table 1. Selected baseline characteristics according to recurrence status of perimenopausal and postmenopausal women enrolled in the Polyp Prevention Trial*

Baseline characteristic	All study participants (n = 620)	Any adenoma recurrence (n = 200)	No adenoma recurrence (n = 420)	P†
Mean age, y (SD)	61.5 (9.3)	63.7 (9.0)	60.5 (9.2)	<.001
Mean age at menopause, y (SD)	46.1 (7.7)	46.2 (7.5)	46.1 (7.7)	.60
Mean years since menopause (SD)	15.9 (10.1)	17.7 (9.6)	15.1 (10.2)	.003
Natural menopause, %	46.0	45.5	46.2	.87
Mean body mass index, kg/m ² (SD)	26.9 (4.4)	27.0 (4.4)	26.8 (4.4)	.57
Race, % Caucasian	90.2	90.0	90.2	.88
Education, % high school or less	31.5	31.0	31.7	.57
Current drinker, %	47.4	47.5	47.4	.98
Current smoker, %	13.9	13.0	14.3	.69
Family history of colorectal cancer, %	31.3	31.5	31.2	.94
No. of children, %				
None	12.7	8.5	14.8	.05
1–3	64.4	70.0	61.7	
≥4	22.9	21.5	23.6	
HRT current use (at T ₀ and T ₁), %	40.2	37.5	41.5	.35
HRT use at all follow-up visits	27.9	24.0	29.8	.14

*SD = standard deviation; HRT = hormone replacement therapy; T₀ = baseline visit; T₁ = first annual visit.

†P value for differences by recurrence status in means determined by Student's *t* test and differences in proportions determined by chi-squared test.

Table 2. Association between HRT and adenoma recurrence in perimenopausal and postmenopausal women enrolled in the Polyp Prevention Trial*

HRT	Any adenoma recurrence, No. (%)	No adenoma recurrence, No. (%)	OR (95% CI)†
HRT use (T ₀ or T ₁)			
Current	75 (30.1)	174 (69.9)	1.01 (0.70 to 1.45)
Not currently using‡	125 (33.7)	246 (66.3)	1.00
HRT use at all follow-up visits			
Yes	48 (27.7)	125 (72.2)	0.85 (0.57 to 1.27)
No‡	152 (34.0)	295 (66.0)	1.00
HRT dose, mg/day			
>0.65	16 (33.3)	32 (66.7)	1.31 (0.67 to 2.55)
0.1–0.65	59 (29.4)	142 (70.6)	0.95 (0.65 to 2.55)
Not currently using‡	125 (33.7)	246 (66.3)	1.00
Estrogen and/or progestin§			
Currently using combination therapy	28 (28.3)	71 (71.7)	0.94 (0.57 to 1.56)
Currently using unopposed estrogen	47 (31.3)	103 (68.7)	1.04 (0.68 to 1.59)
Not currently using either‡	125 (33.9)	244 (66.1)	1.00

*HRT = hormone replacement therapy; OR = odds ratio; CI = confidence interval.

†ORs and 95% CIs for adenoma recurrence were adjusted for age, body mass index (kg/m²), and intervention group assignment.

‡Reference category.

§Two participants using progestin only were not included in this analysis.

enoma recurrence for women who were current users of HRT at T₀ or T₁ (OR = 1.01; 95% CI = 0.70 to 1.45) or for women who were continuous HRT users from T₀ through T₄ (OR = 0.85; 95% CI = 0.57 to 1.27). We also assessed the risk of adenoma recurrence associated with either unopposed estrogen use or combined estrogen–progestin therapy and found that neither was related to overall adenoma recurrence status.

A large proportion (38%) of our study

participants underwent menopause as a consequence of surgery. We, therefore, assessed whether the reason for menopause had an effect on the HRT association and found no difference in the risk associations between women who underwent natural menopause versus those who became menopausal as a consequence of surgery (data not shown). In other subgroup analyses, we observed associations of similar magnitude between HRT use and adenoma recurrence when we re-

stricted our analyses to only those women known to be postmenopausal at T₀ (n = 536) or to women who had colonoscopies at both T₁ and T₄ (n = 569).

In another subgroup analysis, we evaluated the association between HRT use and anatomic location of the recurrent adenomas (Table 3). We observed that HRT use was associated with a reduction in risk for recurrence of distal adenomas (OR = 0.56; 95% CI = 0.32 to 1.00). However, we observed a statistically non-

Table 3. Association between HRT and anatomic location of recurrent adenoma in perimenopausal and postmenopausal women enrolled in the Polyp Prevention Trial*

Anatomic site†	HRT use at T ₀ or T ₁		OR (95% CI)‡
	Current user, No. (%)	Nonuser, No. (%)	
Proximal	41 (44.6)	51 (55.4)	1.39 (0.85 to 2.26)
Distal or rectal	19 (27.1)	51 (72.9)	0.56 (0.32 to 1.00)
Combined	12 (35.3)	22 (64.7)	1.12 (0.51 to 2.45)
No adenomas§	174 (41.4)	246 (58.6)	1.00

*HRT = hormone replacement therapy; T₀ = baseline; T₁ = first yearly visit; OR = odds ratio; CI = confidence interval.

†Proximal is defined as the portion of the large bowel from the cecum up to, but not including, the splenic flexure. Distal is defined as the portion of the large bowel from the splenic flexure and including the rectum. Four subjects for whom anatomic location was unknown were not included in the analysis.

‡ORs and 95% CIs for each anatomic subsite were adjusted for age, body mass index (kg/m²), and intervention group assignment. For each anatomic site, only women with recurrent adenomas at that site were included in the analysis.

§Reference category.

significant association between HRT use and an increase in risk for recurrence of proximal adenomas (OR = 1.39; 95% CI = 0.85 to 2.26). We also evaluated the association between HRT and several characteristics of recurrent adenomas. We observed no relationship between HRT use and either adenoma multiplicity (OR = 0.91; 95% CI = 0.52 to 1.61) or the recurrence of advanced adenomas (OR = 0.67; 95% CI = 0.29 to 1.53). However, inferences from this latter analysis were limited because of the small number of recurrent advanced adenomas (n = 35) among women in the trial.

Because previous studies have demonstrated age modification of the association between HRT and colon cancers (14–16), we evaluated whether age modified the HRT–adenoma recurrence association for the women in our study. We observed a statistically significant interaction with

age ($P = .02$) (Table 4). Women who used hormones and were older than 62 years, the median age of our study sample, had an approximately 40% reduced risk for adenoma recurrence (OR = 0.58; 95% CI = 0.35 to 0.97), whereas women 62 years old and younger had a nearly 100% increased risk for adenoma recurrence (OR = 1.99; 95% CI = 1.11 to 3.55). Hormone use varied with age, in that use was statistically significantly lower among older women (e.g., 58% of women from 55 to 62 years were current users of hormones compared with 19% of women over the age of 69 years; Table 4). The association between HRT and adenoma recurrence was not modified by a number of other covariates, including age at menopause, BMI, parity, family history of colorectal cancer, educational level, calcium supplementation, and nonsteroidal anti-inflammatory drug use.

DISCUSSION

We evaluated the effect of HRT on adenoma recurrence among women who presented with one or more adenomatous polyps at the baseline screening colonoscopy. We found no association between current hormone use, either as unopposed estrogen or estrogen–progestin combination therapy, and adenoma recurrence overall. HRT use was, however, associated with a 40% reduction in risk for recurrence of distal polyps. Because age has been shown to modify the association between HRT use and colon cancer (14–16), we evaluated age modification of the association between HRT use and adenoma recurrence. We found an interaction between HRT use and age, with a decreased risk for adenoma recurrence among older women (>62 years) and an increased risk among younger women (≤62 years).

Table 4. Effect modification by age of the relationship between HRT and adenoma recurrence in perimenopausal and postmenopausal women enrolled in the Polyp Prevention Trial*

Age, y†	% using hormones	HRT use at T ₀ or T ₁	Any adenoma recurrence, No. (%)	No adenoma recurrence, No. (%)	OR (95% CI)‡	P§
<55	45.5	Yes	22 (31.0)	49 (69.0)	1.49 (0.71 to 3.13)	.02
		No	18 (21.2)	67 (78.8)	1.00	
55–62	58.5	Yes	32 (33.3)	64 (66.7)	2.29 (1.06 to 4.97)	
		No	14 (20.6)	54 (79.4)	1.00	
63–69	35.5	Yes	12 (22.2)	42 (77.8)	0.50 (0.23 to 1.13)	
		No	36 (36.7)	62 (63.3)	1.00	
>69	18.9	Yes	9 (32.1)	19 (67.9)	0.58 (0.23 to 1.44)	
		No	57 (47.5)	63 (52.5)	1.00	

*HRT = hormone replacement therapy; T₀ = baseline; T₁ = first annual visit; OR = odds ratio; CI = confidence interval.

†Age categorized into quartiles based on the age distribution among women without adenomas.

‡ORs and 95% CIs were adjusted for age, body mass index (kg/m²), and intervention group assignment. Stratified analysis of the HRT–adenoma recurrence association by age was based on median split: OR = 1.99 (95% CI = 1.11 to 3.55) for women 62 years and younger, and OR = 0.58 (95% CI = 0.35 to 0.97) for women older than 62 years (P value for interaction with dichotomous age variable; $P < .001$).

§ P value for differences in hormone use by age was determined by chi-squared test ($P < .01$). P value for interaction based on inclusion of the cross-product terms (age as a continuous variable and HRT) into the logistic regression model ($P = .02$).

||Reference category.

Prospective and retrospective epidemiologic studies (10–21) have consistently demonstrated a protective role for menopausal hormone use in the development of both colon cancers and adenomatous polyps. A recent meta-analysis of colorectal cancer occurrence (26) found an overall reduction of 20% in colon cancer risk and a 19% reduction in rectal cancer risk for ever versus never users of HRT across studies. Many of the studies analyzed in the meta-analysis produced similar observations. Specifically, much of the risk reduction observed was restricted to current hormone users, who had a 34% risk reduction, and in every study there was greater protection against colon cancer associated with current hormone use than with ever use. Most of the studies in the meta-analysis also found that the risk protection was attenuated several years after hormone use was discontinued and that longer duration of hormone use offered no greater risk reduction than recent use. Two studies (11,13), however, found no differences in risk for unopposed estrogen use and combined estrogen–progestin use. In summary, there is consistency among observational studies for an inverse association between HRT use and the development of adenomas and colorectal cancer. Observational studies of polyp risk, such as those included in the meta-analyses, are usually prevalence studies or cohort studies, in which the endpoint is the presence of polyps among the entire population. Because our study evaluated associations with adenoma recurrence among a subset of individuals who were screened by endoscopy and diagnosed with at least one adenomatous polyp, the generalizability of our findings to the overall population is limited.

Neither the specific biologic effect of estrogen on colonic mucosa nor the point in colon carcinogenesis at which estrogen most likely plays a role is known. Administration of estrogen to cell lines inhibits cell growth and proliferation (27) and, in rodents, estrogen suppresses chemically induced tumor formation (6,7). Exogenous estrogens are believed to decrease secondary bile acid production and can alter intestinal microflora and, therefore, could protect against colorectal cancer. The demonstration that estrogen receptors and the products of other estrogen-related genes are expressed in the gastrointestinal tract suggests that estrogen may have a direct role in inhibiting cancer cell growth (4,28–30). Estrogen has been proposed to

inhibit cell proliferation in colonic mucosa and to stimulate intestinal calcium absorption, perhaps via its effect on vitamin D (6–8). In rats, administration of estrogen increased the level of the vitamin D receptor gene transcript level, protein level, and endogenous calcitriol bioactivity in colonic mucosa (6).

We cannot entirely exclude chance as an explanation for our findings of an interaction between HRT and age in the risk of adenoma recurrence. In addition, we know of no published data that provide a biologic rationale for our observation of increased risk of polyp recurrence among younger women using HRT. However, the risk reduction that we observed among the older women in our study is supported by three previous studies of colorectal cancer (11,12,16). There are several potential explanations for this finding. First, older age may be a proxy for duration of hormone use. Second, exogenous estrogens may reverse age-related decreases in estrogen receptor expression observed in the colonic mucosa (31). Third, estrogen may reverse age-related decreases in calcium absorption in the gut (32,33) via the vitamin D–endocrine system (6–9). In this regard, epidemiologic studies in humans (34–36) have demonstrated that calcium protects against the recurrence of polyps.

To our knowledge, our study is the first to evaluate the association between menopausal hormone use and recurrent adenomatous polyp formation in the distal versus proximal colon. The data in the literature regarding associations between HRT and anatomic location of polyps or cancer are somewhat inconsistent. In a prospective study of colorectal cancers, Troisi et al. (13) found that HRT use was associated with a more pronounced risk reduction for distal colon and rectal tumors than proximal tumors. In the four case–control studies, in which the association between HRT use and anatomic location of colorectal cancer has been explored, two (10,15) found that HRT use was associated with a greater reduction in the number of proximal cancers, and two (11,14) found no differences in anatomic location-specific associations. In a large sigmoidoscopy-based prospective study, although Grodstein et al. (21) found no overall association between current hormone use and distal adenomas, they did observe a decreased risk for large (>1 cm) adenomas. In a sigmoidoscopy-based study of prevalent polyps, Peipins et al.

(19) found that a statistically significantly reduced risk for distal adenomas was associated with ever use of hormones. In a colonoscopy-based study, Potter et al. (20) found that 5 or more years of hormone use was inversely associated with prevalent polyps, but no anatomic subsite data were reported.

Although we cannot exclude the possibility that the difference in adenoma recurrence risk by anatomic site that we observed could be due to chance, it is worth mentioning that there is controversy in this field about possible differences in the etiology of large bowel cancer by anatomic location. Carcinogenesis in the proximal and distal bowel may occur by different molecular mechanisms. In addition, some cancers appear to be influenced by sex-related factors. For example, mutations in the tumor suppressor gene p53 are found predominantly in tumors of the distal bowel, with no differences by sex, whereas mutations in k-ras, microsatellite instability, and DNA hypermethylation of specific genes were found at a higher prevalence in tumors of the proximal versus distal bowel among women but not among men (37–42). One could speculate that differences in etiologies by anatomic subsite might be due to differences in the hormonal milieu in the distal versus proximal bowel.

The strengths of our study lie in its prospective design as well as in its extensive ascertainment of both hormone exposure and adenoma recurrence status. At baseline and at T₁, all participants were examined thoroughly by complete colonoscopy, and all adenomas were removed. All participants received another colonoscopy after 4 years at the end of the trial (hypothetically, enough time for adenoma recurrence), allowing for complete ascertainment of adenoma recurrence status. Study interviewers recorded information regarding menopausal hormone use when participants brought all prescribed and nonprescribed drugs that they were taking to the clinic during their yearly visits.

This study is limited in that we collected information pertaining to current, but not past, hormone use. Although we evaluated the association between current use and adenoma recurrence within a 4-year period, it is possible that hormone use before enrollment in our study may have influenced adenoma formation. Among the participants of our study, hormone use varied with age, with fewer of

the older women reporting current HRT use compared with the younger women. It is possible that the women who did not respond to hormone therapy, or those who had more therapy-related side effects, had discontinued their use of HRT, which might result in greater misclassification of hormone use among older women. Another study limitation is the generalizability of our findings, given that the study population consisted of women who already had adenoma(s). These women are "predisposed" to develop subsequent adenomas, and the putative effect of hormones in our study population may differ compared with that of the general population.

In conclusion, we did not find a protective relationship between HRT and adenoma recurrence overall; however, HRT use was associated with a reduced risk of polyp recurrence among older women and the suggestion of an increased risk for recurrence among younger women. Given the high prevalence of HRT use in the United States and the morbidity and mortality associated with colon cancer, further prospective studies in screened populations are necessary to fully evaluate the public health implications of our findings.

APPENDIX

The members of the Polyp Prevention Study Group participated in the conduct of the Polyp Prevention Trial. However, the data presented in this report and the conclusions drawn from them are solely the responsibility of the coauthors. The members of the Polyp Prevention Study Group and their affiliations are as follows: Schatzkin A, Lanza E, Corle D, Freedman LS, Clifford C, and Tangrea JA (National Cancer Institute, Bethesda, MD); Cooper MR, Paskett E, Quandt S, DeGraffinreid C, Bradham K, Kent L, Self M, Boyles D, West D, Martin L, Taylor N, Dickenson E, Kuhn P, Harmon J, Richardson I, Lee H, and Marceau E (Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, NC); Lance MP, Marshall JR (currently at the University of Arizona, Tucson), Hayes D, Phillips J, Petrelli N, Shelton S, Randall E, Blake A, Wodarski L, Deinzer M, and Melton R (University of New York at Buffalo); Iber FL, Murphy P, Bote EC, Brandt-Whittington L, Haroon N, Kazi N, Moore MA, Orloff SB, Ottosen JM, Patel M, Rothschild RL, Ryan M, Sullivan WJ, and Verma A (Edwards Hines, Jr. Hospital, Department of Veterans Affairs Medical Center, Hines, IL); Caan B, Selby JV, Friedman G, Lawson M, Taff G, Snow D, Belfay M, Schoenberger M, Sampel K, Giboney T, and Randel M (Kaiser Foundation Research

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NOTES

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