

Hormone Replacement Therapy Is Associated with Lower Risk of Adenomatous Polyps of the Large Bowel: The Minnesota Cancer Prevention Research Unit Case-Control Study

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Abstract

Evidence of a role for steroid hormones and reproduction in colon neoplasia remains tantalizing but unclear. Hormone replacement therapy (HRT) has been reported in a number of recent studies to be associated with a reduced risk of colon cancer.

A case-control study was undertaken to establish whether HRT is associated with lower risk of adenomatous polyps. This case-control study was undertaken as a project of the Minnesota Cancer Prevention Research Unit. Cases ($n = 219$) were women, ages 30–74 years with colonoscopy-proven, pathology-confirmed, adenomatous polyps of colon and rectum recruited at Digestive Healthcare PA (Minneapolis, MN). Two control groups were selected: women without polyps at colonoscopy ($n = 438$) at Digestive Healthcare and age- and zip code-matched women selected from the general community ($n = 247$). Response rates were 68% among those colonoscoped and 65% among community controls.

Parity, age at first live birth, and oral contraceptive use did not distinguish cases from either control group. Multivariate adjusted odds ratios and 95% confidence limits for use of HRT for less than 5 years (compared with never use) among postmenopausal women were 0.52 (0.32–0.85) versus colonoscopy-negative controls and 0.74 (0.44–1.26) versus community controls. For 5 years of use or greater, the corresponding figures were 0.39 (0.23–0.67) and 0.61 (0.34–1.07). These results were not materially different when stratified on body mass index, oophorectomy, hysterectomy, aspirin use, or family history. There is no marked increase in risk even 5 years after cessation of HRT use.

HRT appears to lower risk of colorectal adenomatous polyps, suggesting that it acts quite early in the neoplastic process. Mechanisms remain unclear. Reduction of risk of colorectal neoplasia is an additional benefit of postmenopausal HRT.

Introduction

An association between reproductive variables and colorectal cancer was first noted by Fraumeni *et al.* (1), who showed that nuns, in addition to their higher risk of breast cancer, also had an elevated risk of colon cancer. In 1980, McMichael and Potter (2) drew together a variety of data on the changing patterns of colon cancer among men and women and on the relationship between steroid hormones and bile acid profiles, and some empirical observations on the association between parity and colon cancer (1, 3). We proposed that colon cancer risk was influenced by aspects of reproduction and hormonal status primarily as a result of effects on bile acid metabolism. We hypothesized specifically that higher parity, early age at first birth, and oral contraceptive use would lower risk of colon cancer. Subsequent studies have produced some inconsistent findings on reproductive variables (for a review, see Ref. 4).

The first investigation of a relationship between HRT³ and colon cancer risk was published in 1981 by Weiss *et al.* (5), who reported a null association between risk of colon cancer and non-OC hormone use. In 1983, Potter and McMichael (6) reported a lower risk of colon cancer with OC use and a marginally (and nonsignificantly) decreased risk (OR, 0.8; 95% CI, 0.4–1.5) with non-OC hormone use. Since that time, there have been a total of 13 other studies (7–19). Findings among these studies are not entirely consistent, although among the 10 that focused on colon cancer or provided separate data on colon cancer, 5 showed statistically significant lower risk with HRT or a less well-specified hormone variable (13–15, 18, 19), two showed nonsignificantly lower risks (6, 16), two were null (11, 17), and one study showed elevated risks among users (12). Of the five studies that reported on colorectal cancer as a single entity, four were null (5, 7, 9, 10), and one reported decreased risk (8).

Adenomatous polyps of the large bowel are precursor lesions in the pathway from normal epithelium to cancer. We present here an examination of reproductive and hormonal variables in relation to colorectal adenomatous polyps.

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³ The abbreviations used are: HRT, hormone replacement therapy; OC, oral contraceptive; OR, odds ratio; CI, confidence interval; CPRU, Cancer Prevention Research Unit; DH, Digestive Healthcare PA; ER, estrogen receptor; BMI, body mass index.

Table 1 Some female population characteristics

	Cases <i>n</i> = 219	Colonoscopy-negative controls <i>n</i> = 438	Community controls <i>n</i> = 247
Mean age (yr)	58.3	52.9	56.9
% currently married	79.8	72.6	79.3
Mean age at first live birth (yr)	23.2	23.0	23.8
Mean number of children (parity)	3.4	3.1	3.2
% ever OC users	50.7	59.9	49.4
% ever HRT users	39.2	49.8	44.1
Age at menopause-(postmenopausal women only; yr)	47.2 ^a	45.3 ^b	46.7

^a *n* = 177.^b *n* = 289.^c *n* = 188.

Materials and Methods

The Minnesota CPRU is a National Cancer Institute-funded program project that combines several units within the University of Minnesota and a large multiclinic private gastroenterology practice, DH, which undertakes approximately 60% of all colonoscopies in metropolitan Minneapolis. This "public-private" collaboration was established in 1988 and has functioned to support several studies on the etiology, prevention, and biology of adenomatous polyps.

Study Subjects. All patients of ages between 30 and 74 years who were scheduled for colonoscopy at DH clinics between April 1991 and April 1994, and who fulfilled specific eligibility criteria (see below), were recruited for the study prior to colonoscopy. The intent was to recruit subjects with both patient and recruiter blind to the ultimate diagnosis.

Eligibility criteria for cases were: first diagnosis of incident colon or rectal adenomatous polyps; resident of Twin Cities metropolitan area; age 30–74 years; English speaking; no known genetic syndrome associated with predisposition to colonic neoplasia; no individual history of cancer (except non-melanoma skin cancer); no history of inflammatory bowel disease. The clinic control group criteria were identical, with the single exception that they were found subsequently to be free of all polyps (hyperplastic or adenomatous) at colonoscopy.

The recruitment protocol was undertaken using staff and resources of DH and the University of Minnesota Divisions of Epidemiology and Biostatistics. Briefly, the DH patient coordinators scheduled a clinically indicated colonoscopy, did an initial eligibility screen, and mailed an introductory letter explaining the study with the questionnaires and the consent form. Two to 5 days later, a DH nurse called the study subject, confirmed the arrival of study materials, and sought verbal permission for the patient to be contacted by University of Minnesota staff. Eligibility was checked further. If permission was given, the University of Minnesota study staff called the subject to explain and answer any questions regarding the study. At colonoscopy, forms were collected and blood drawn. All polyps were examined histologically by the study pathologist using diagnostic criteria established for the National Polyp Study. The presence or absence of pathology was determined and assignment made to one of the following three groups: (a) adenomatous polyp group (*n* = 574); (b) hyperplastic polyp-only group; and (c) colonoscopy-negative group (*n* = 707). The hyperplastic polyp group was not included in the control group and is not considered further in this paper. Participation rate for all colonoscoped patients was 68%.

A second control group was recruited from the general population via a computer file of the State of Minnesota Drivers

Registry which includes all persons with a Minnesota Driver's License or Identification Card. The community controls were frequency matched on age (5-year intervals), sex, and zip code, with eligibility criteria identical to those of the clinic controls. The colonic-neoplasia status of the community controls was established by self-report only. The participation rate for the community controls was 65%. Prospective community controls were contacted via an initial phone call, and those eligible and giving consent were mailed an identical packet to that sent to clinic subjects. Subjects returned completed questionnaires by prepaid mail. No blood was collected.

Incomplete questionnaires resulted in call-backs to all participants for specific questions.

Data Collection. Study subjects completed an expanded Willett food frequency questionnaire and provided additional data on demographic characteristics, personal medical history, family history of cancer and polyps, usual physical activity, and reproductive history (women only). For OC and HRT, data on ever use and duration of use were obtained. Data collection on aspirin use was begun after the study was in the field and is available on just 59% (*n* = 530) of the study population.

Data Analysis. Standard techniques for case-control analyses were used; logistic regression analyses were used to assess the relationship of reproductive history, OC use, and HRT use to the incidence of adenomatous polyps, with appropriate control for confounding. Major results are presented as ORs with 95% confidence limits. Separate analyses are presented for cases *versus* colonoscopy-negative controls and cases *versus* community controls.

Results

Among the female respondents, there was a total of 219 cases, 438 colonoscopy-negative controls, and 247 community controls. Some relevant population characteristics are shown in Table 1.

The age-adjusted ORs associated with parity, age at first live birth, and hormone use are shown in Table 2. No obvious associations are suggested for any variable except HRT, which shows a relation between decreased risk of adenomatous polyps and HRT use, the association being stronger when the comparison is made with the colonoscopy-negative control group. The estimated ORs are similar when all women are considered, when premenopausal women are excluded, and when rectal polyps are excluded. Although numbers are very small, the ORs for rectal polyps alone are nearly identical (data not shown) to those reported for the colon.

To focus on a homogeneous group, Tables 3–5 are confined to postmenopausal women (74% of all women); both

Table 2 Age-adjusted ORs associated with reproduction and hormone use

	Cases		vs. colonoscopy-negative controls		vs. community controls		
	N ^a	N ^a	OR	95% CI	N ^a	OR	95% CI
Parity							
0	28	65	1.00		34	1.00	
1-2	77	152	1.25	0.73-2.15	86	1.10	0.61-1.99
3-4	75	157	0.93	0.56-1.60	98	0.91	0.51-1.63
≥5	39	64	0.93	0.50-1.73	29	1.53	0.76-3.09
Age at first live birth (yr)							
<20	34	87	1.00		31	1.00	
20-24	102	177	1.23	0.76-1.98	104	0.86	0.49-1.51
25-29	43	78	1.33	0.76-2.32	58	0.67	0.36-1.25
≥30	12	31	0.88	0.40-1.96	20	0.53	0.22-1.27
OC use							
Never	108	175	1.00		125	1.00	
<5 yr	73	154	1.25	0.82-1.91	73	1.42	0.88-2.31
≥5 yr	34	106	0.84	0.51-1.39	46	1.05	0.59-1.84
OC use (postmenopausal women only)							
Never	105	152	1.00		118	1.00	
<5 yr	54	87	1.23	0.77-1.97	42	1.42	0.84-2.43
≥5 yr	21	58	0.68	0.38-1.23	28	0.83	0.43-1.60
HRT Use							
Never	132	220	1.00		138	1.00	
<5 yr	48	119	0.63	0.42-0.95	56	0.90	0.57-1.41
≥5 yr	30	85	0.47	0.29-0.76	44	0.68	0.40-1.15
HRT use (postmenopausal women only)							
Never	102	114	1.00		92	1.00	
<5 yr	42	92	0.57	0.36-0.91	48	0.79	0.48-1.29
≥5 yr	30	83	0.43	0.26-0.71	43	0.64	0.37-1.09
HRT use (colon polyps in postmenopausal women only)							
Never	87	114	1.00		92	1.00	
<5 yr	35	92	0.56	0.35-0.90	48	0.78	0.46-1.31
≥5 yr	26	83	0.44	0.26-0.74	43	0.66	0.37-1.16

^a Numbers may not sum to total study sample because of missing data for some variables.

point estimates and 95% confidence limits are changed very little by this exclusion (data not shown).

Because it is plausible that hormonal milieu would vary by degree of obesity and history of hysterectomy or oophorectomy and because hysterectomy or oophorectomy might represent a different indication for HRT use, separate analyses were carried out for relevant strata. Table 3 shows the age-adjusted ORs associated with HRT among postmenopausal women with high and low BMI (stratified at the median), and among those with and without a history of bilateral oophorectomy and hysterectomy. Stratification on BMI suggests that, compared with colonoscopy-negative controls, there may be a more marked association with lower risk among the more obese. However, compared with community controls, whose polyp status is, of course, unknown, there is no association between HRT use and risk of polyps among the more obese. The association between HRT and those with low BMI is consistent across the comparisons with the two control groups. Neither hysterectomy nor oophorectomy status appears to modify greatly the association between HRT and risk of adenomatous polyps.

Table 4 shows the association between HRT use and risk of adenomatous polyps among postmenopausal women stratified on family history. Among those without a family history, the lower risk finding remains when comparison is made with either control group. Among the family history positive, HRT remains associated with lower risk when a comparison is made among those whose polyp status is established, but not when a comparison is made with community controls.

Because aspirin use is associated inversely with risk [in

this study, the OR for ever *versus* never use compared with colonoscopy-negative controls is 0.72 (0.52-0.99)], and because it is plausible that aspirin use and HRT use may be associated behaviors among more health-conscious women, we examined the association between HRT and risk among postmenopausal women, stratifying on history of aspirin use. Table 5 shows that the overall pattern of lower risk with HRT use is essentially independent of aspirin use.

The data for time since ceasing HRT use among all women ever taking HRT do not suggest that there is any marked increase in risk with the passage of time after cessation of use (Table 6).

A variety of potential confounders were explored for their influence on the age-adjusted ORs reported above, including family history, smoking, alcohol, BMI, waist-to-hip ratio, physical activity, aspirin use, and a variety of dietary variables (energy intake, fat as a percentage of calories, fiber, and intake of vegetables and fruit). A multivariate model including age, smoking status, alcohol use, family history, and waist-to-hip ratio produced the following ORs for use of less than 5 years (*versus* never use): 0.52 (0.32-0.85; colonoscopy-negative controls), and 0.74 (0.44-1.26; community controls). For HRT use of 5 years or more, the corresponding figures were 0.39 (0.23-0.67) and 0.61 (0.34-1.07).

Discussion

The data presented here suggest that there is a halving or more of risk of adenomatous polyps of the colon and rectum associated with the use of HRT. The data are derived from a

Table 3 Age-adjusted^a ORs associated with HRT use, stratified on BMI, hysterectomy, and bilateral oophorectomy: postmenopausal women only

	Cases		vs. colonoscopy-negative controls		vs. community controls		
	N ^a	N	OR	95% CI	N	OR	95% CI
Low BMI (<27)							
Never	55	61	1.00		43	1.00	
<5 yr	31	50	0.87	0.48–1.57	35	0.71	0.38–1.32
≥5 yr	19	42	0.59	0.30–1.15	35	0.44	0.22–0.87
High BMI (≥27)							
Never	46	49	1.00		48	1.00	
<5 yr	10	39	0.29	0.13–0.64	12	0.86	0.34–2.18
≥5 yr	10	37	0.29	0.13–0.65	8	1.30	0.47–3.55
Oophorectomy: Yes							
Never	19	22	1.00		11	1.00	
<5 yr	12	27	0.77	0.30–1.98	10	0.73	0.23–2.24
≥5 yr	19	52	0.54	0.24–1.22	17	0.70	0.27–1.84
Oophorectomy: No							
Never	83	92	1.00		81	1.00	
<5 yr	30	65	0.53	0.32–0.90	38	0.76	0.43–1.34
≥5 yr	11	31	0.39	0.19–0.83	26	0.41	0.19–0.89
Hysterectomy: Yes							
Never	25	35	1.00		17	1.00	
<5 yr	13	40	0.52	0.23–1.17	16	0.66	0.26–1.68
≥5 yr	19	63	0.45	0.22–0.93	22	0.74	0.32–1.72
Hysterectomy: No							
Never	77	79	1.00		75	1.00	
<5 yr	29	52	0.60	0.34–1.06	32	0.85	0.47–1.54
≥5 yr	11	20	0.56	0.25–1.24	21	0.49	0.22–1.09

^a Adjustment for other factors (see text) did not materially modify the findings presented here.

Table 4 Age-adjusted ORs associated with HRT use, stratified on family history of colorectal neoplasia: postmenopausal women only

	HRT use among:						
	Cases		vs. colonoscopy-negative controls		vs. community controls		
	N	N	OR	95% CI	N	OR	95% CI
Family history positive							
Never	30	47	1.00		18	1.00	
<5 yr	15	33	0.82	0.38–1.78	8	1.27	0.44–3.69
≥5 yr	12	37	0.65	0.29–1.46	6	1.25	0.39–4.03
Family history negative							
Never	72	67	1.00		74	1.00	
<5 yr	27	59	0.44	0.25–0.79	39	0.71	0.39–1.28
≥5 yr	18	46	0.36	0.19–0.67	37	0.50	0.26–0.95

case-control study, and bias and confounding need to be considered.

The response rate among all groups in this study was 65–68%. Although there is a real possibility that those who refused participation had a different pattern of HRT use from the study subjects themselves, to eliminate the association completely, it would require bias of the following order: approximately 75% of the nonrespondent cases would have to be HRT users (among existing cases the proportion is approximately 39%), and the nonrespondent colonoscopy-negative controls would have to be distributed approximately 1:1 (users:nonusers), as is true of the existing controls. A response bias of this magnitude is extremely unlikely.

The inverse relation between HRT and polyps did not appear to be confounded by other factors. Indeed, inclusion of measured confounders in the model actually strengthened the association between HRT and reduced risk in analyses using either set of controls.

There is evidence of misclassification bias in these data;

the associations reported are all marginally weaker in the analyses using community controls where there are at least some undiagnosed adenomatous polyps.

The association reported here is an important finding. Consider, for example, postmenopausal women with high BMI. The relative risk of developing polyps with any history of HRT is 0.29 in this group of women. Among DH patients in this group, the prevalence of polyps is 35–48% among never users and 21% among ever users. The attributable benefit of 27% is substantial.

The findings are consistent with much of the data available from recent studies of colon cancer (13–16, 18, 19). Indeed, the approximate halving of risk with longer use is also consistent. They are also consistent with the findings of the study of Jacobson *et al.* (20), although, perhaps because of small numbers, their estimates of risk reduction were not statistically significant. It might be argued that if HRT lowers the risk of polyps, this is not compatible with its fairly early (short duration of exposure) impact on colon cancer itself. One way to

Table 5 Age-adjusted ORs associated with HRT use, stratified on aspirin use: postmenopausal women only^a

	HRT use among:						
	Cases	vs. colonoscopy-negative controls			vs. community controls		
		N	N	OR	95% CI	N	OR
Aspirin users							
Never	17	23	1.00		18	1.00	
<5 yr	6	23	0.37	0.12–1.09	12	0.54	0.17–1.76
≥5 yr	6	18	0.46	0.15–1.40	7	0.71	0.19–2.67
Aspirin nonusers							
Never	41	45	1.00		32	1.00	
<5 yr	19	36	0.66	0.32–1.33	16	0.99	0.44–2.23
≥5 yr	14	28	0.56	0.26–1.22	23	0.49	0.22–1.09

^a Aspirin data available only on 59% (n = 530) of study population.

Table 6 Age-adjusted ORs associated with time since cessation of use of HRT

	HRT use among:						
	Cases	vs. colonoscopy-negative controls			vs. community controls		
		N	N	OR	95% CI	N	OR
Current use	56	144	1.00		60	1.00	
Time since cessation							
≤5 years	7	33	0.76	0.49–1.17	12	0.79	0.48–1.31
>5 years	21	33	1.43	0.75–2.73	36	0.63	0.32–1.21

reconcile these is to argue that HRT has an overall impact on the balance between proliferation and apoptosis. The tendency to prevent the growth of polyps and to inhibit promotion (growth of cancer) could be the consequence of similar controls on nonmutational changes in colon neoplasia across the spectrum of disease development.

What remains to be elucidated is the mechanism. The original explanation for the role of hormones (2) was based on the bile acid hypothesis, as follows. Increased fat in the diet increases hepatic bile acid secretion; bile acids, particularly secondary bile acids produced by colonic bacteria, are trophic, toxic, and cocarcinogenic to colonic epithelium; and bile acid profile is rendered somewhat more benign by pregnancy and steroid hormones (2). Although the physiologically focused bile acid hypothesis has become less popular with the development of clear evidence for specific somatic (or germline) changes in a variety of tumor suppressor genes, DNA repair genes, and one oncogene (21, 22), the fact remains that not one active DNA-interacting agent has been clearly identified. Roles for cell signaling, hormones, and growth factors still appear to be plausible. Bile acids may be relevant (23).

Two other marginally more direct mechanisms for hormones have been proposed. ERs have been described in colorectal cancers (2, 24, 25), but their function is not understood. More intriguingly, Issa *et al.* have shown recently, in all 45 tumor specimens that they examined, that abnormal methylation patterns exist in the *ER* gene (26). These authors argue that the silencing of the *ER* gene (via hypermethylation of CpG islands in the promoter region) in normal tissue is consistent with an age-induced epithelial field defect. They further argue that the *ER* gene on 6q25 is a tumor suppressor gene both because of parallels with nonmutational loss of function of retinoblastoma (*Rb*) and Von Hippel Lindau (*VHL*) tumor suppressor genes and because of the capacity of an introduced unmethylated ER construct to reduce proliferation and malignant potential in colon cell lines (26).

If, as other data show, ER expression is dependent on estrogens, this provides a clear molecular mechanism for the

role of replacement estrogens in reducing polyp formation and colon cancer in women.

The possible differences by BMI are intriguing. Although the strongest association is seen in the comparison with colonoscopy-negative controls among women with high BMI, the more consistent observation (*i.e.*, the story is similar in comparison with either control group) is seen for women with low BMI. This might argue that high-BMI women already have a higher level of endogenous (adipose-derived) estrogens and that therefore the HRT is more potent or beneficial among the low-BMI individuals. This latter is also what we see in our separate case-control study of colon cancer.⁴

The appropriately conservative interpretation of the possible differences by family history seen in Table 4 is that this is just a consequence of small numbers; the findings are inconsistent across the two control groups, and all the confidence limits overlap extensively. A much larger study is needed to test adequately for such differences.

This is one of the first reports of an association between colorectal adenomatous polyps and HRT. The findings are consistent with a series of studies that suggest that HRT lowers risk of colon cancer. What is new is that these data suggest that, in whatever manner HRT exerts its influence, it does so early in the neoplastic process.

There is an increasing disparity in the rates of colon cancer between men and women beginning in the last 20 years (27). Women in the United States are now clearly doing something different from men. A plausible candidate is HRT use. It may be one sex-specific chemopreventive agent with, by and large, beneficial effects for women against a variety of disorders. One of those appears to be colonic neoplasia.

⁴ E. Kampman, J. Potter, M. Slattery, B. Caan, and S. Edward, Hormone replacement therapy, reproductive history, and colon cancer: a U. S. multi-center case-control study, submitted for publication.

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