Published in final edited form as:
Cancer Detect Prev. 2007 ; 31(2): 161–165.

The Interaction of Age and Hormone Replacement Therapy on Colon Adenoma Risk

Harvey J. Murff, M.D., M.P.H.[1,2], **Martha J. Shrubsole, Ph.D.**[1,2,3], **Walter E. Smalley, M.D., M.P.H.**[2,4,5], **Haojie Wu, Ph.D.**[6,7], **Yu Shyr, Ph.D.**[4,6,7], **Reed M. Ness, M.D., M.P.H.**[2,5], and **Wei Zheng, M.D., Ph.D.**[1,2,3]

1*Division of General Internal Medicine and Public Health, Vanderbilt University Medical Center, Nashville TN*

2*Department of Veterans Affairs, Tennessee Valley Healthcare System, GRECC, Nashville TN*

3*Vanderbilt Center for Epidemiologic Research, Vanderbilt University Medical Center*

4*Department of Preventive Medicine, Vanderbilt University Medical Center*

5*Division of Gastroenterology, Vanderbilt University Medical Center*

6*Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center*

7*Department of Biostatistics, Vanderbilt University Medical Center*

Abstract

Background—Several studies have identified a possible interaction between age and hormone replacement therapy on colon neoplasm risk. We re-evaluated this interaction and determined if this interaction may be explained by the longer duration of estrogen use in older, rather than younger, women.

Methods—Included in the case-control study were 755 women (169 cases and 586 controls.) who were recruited from patients with no prior history of colorectal neoplasm and undergoing an elective colonoscopy examination.

Results—There was a significant interaction between age and hormone replacement therapy use (p = 0.03) with current estrogen users who were over 56 years of age having a reduced odds of colon adenoma (OR = 0.40, 95% CI 0.16-0.98) when compared to never users. Both older women who had used hormone replacement therapy for 3 or less years (OR = 0.07, 95% CI 0.006-0.81) and those reporting greater than 10 years of use (OR = 0.27, 95% CI 0.09-0.80) had a reduced adjusted odds for adenomas when compared to nonusers. No apparent association with estrogen replacement therapy was found among younger women (< 56 years).

Conclusions—Duration of use is not likely to explain the stronger association of hormone replacement therapy use with colon neoplasm in older women. Additional work is needed to better characterize the underlying mechanisms associated with this interaction.

Corresponding author: Harvey J. Murff, M.D., M.P.H., Department of Veterans Affairs, VA Tennessee Valley Healthcare System, GRECC, 1310 24th Avenue South, Nashville, TN 37212-5381, Work: 615 327-4751 ext 6823, Fax: 615 327-5381, Email: Harvey.murff@va.gov

Keywords

colon cancer; polyps; hormone replacement therapy; chemoprevention

Introduction

Case-control and cohort studies have suggested a protective effect for hormone replacement therapy (HRT) on colorectal neoplasm. (1-5) An intriguing observation has been a possible interaction between age and HRT use in colorectal neoplasm. Several studies have demonstrated that older women appear to derive a greater protective effect from HRT than younger women. (5-11) One possible explanation for this interaction is that age may represents a proxy for duration of HRT use. (12) Most studies, however, have been inconsistent regarding the association of colorectal neoplasm risk with the duration of HRT use (1). The purpose of this study was to evaluate the association of colorectal adenomas with HRT use, in particular, the interaction of HRT use and age in the risk of colorectal adenomas.

Materials and methods

Study participants were identified from consecutive patients undergoing elective colonoscopy at the Vanderbilt University Medical Center or the Tennessee Valley Healthcare System, Department of Veterans Affairs Hospital between February 2003 and December 2005. Eligible patients were invited to participate in the study prior to their scheduled colonoscopy. The results of patient colonoscopies were recorded using standardized data entry forms and information on the number, location, and size of any identified colonic polyp was collected. Cases included subjects diagnosed with one or more histologically confirmed adenomatous polyps. Controls were patients with normal polyp-free colons on complete colonoscopy. Exclusion criteria included patients with a known or suspected inherited colorectal cancer syndrome, a prior history of cancer, a history of inflammatory bowel disease, a prior adenoma diagnosis, and aged less than 40 years or greater than 75 years.

From a total of 4508 potentially eligible subjects, 3085 (68.4%) consented to participate and telephone interviews were completed on 2679 (87%). For the current analysis we included only postmenopausal females resulting in 172 cases and 630 controls. We also excluded one subject who indicated she had never had a menstrual period and 46 subjects with missing data on hormone replacement therapy resulting in an analytic sample consisted of 169 cases and 586 controls.

A telephone survey was conducted for each consenting patient to collect information on demographic, family history and lifestyle factors, such as reproductive history and use of exogenous estrogen. Self-reported height and weight were collected and used to calculate body mass index (BMI), which was then categorized using the Centers for Disease Control classification scheme for BMI (normal < 25.0, overweight 25 – 30, obese > 30).

Differences between cases and controls were compared using the Student's *t* test for continuous variables or the χ^2 test for categorical variables. Unconditional logistic regression models were used to estimate the risk of colorectal adenomas associated with exogenous hormone use. Stratified analyses were used to evaluate effect modification by age and duration of use. Using the postmenopausal control distribution, age was dichotomized using the median value and duration of use was categorized into tertiles. All models were adjusted for age, race, family history of colorectal cancer or adenomatous polyps, body mass index, smoking status, alcohol use, educational attainment, physical activity level, and use of non-steroidal anti-inflammatory drugs. To test for an interaction between age and HRT use, an interaction term was created

using age as a continuous variable. Results were also stratifying by the age of initiation of HRT (in tertiles), timing of initiation of HRT (>1 year prior to menopause, 1 year before or after menopause, > 1 year after menopause) and type of menopause (natural, surgical). All statistical calculations were performed using SAS version 9 (SAS Institute, Cary, NC).

Results

Presented in Table 1 are major demographic characteristics and risk factors among cases and controls. Overall, current users of HRT had an adjusted odds ratio of 0.72 (95% CI 0.37 – 1.39) for colon adenomas when compared to never users. The interaction between age and current use of HRT was statistically significant (p = 0.03). Consistent with prior studies, the most pronounced effects for current users of HRT were in older women when compared to non-users. In neither older nor younger women was there a significant trend with respects to duration of HRT (Table 2). Older women who reported using HRT for 3 or less years or greater than 10 years both had a reduced odds for colon adenoma (OR = 0.07; 95% CI 0.006-0.81 and 0.27; 95% CI 0.09-0.80, respectively). Results stratified by age at initiation of HRT, timing of HRT with respects to menopause, and type of menopause are presented in Table 2. No consistent associations were found between age, HRT use, and adenoma risk when stratified by age at initiation of HRT as well as type of menopause. There was a significant trend (P = 0.01) suggesting a greater effect of HRT when initiated after menopause (OR = 0.15, 95% CI 0.02 – 1.01), as compared to peri-menopause (OR 0.33; 95% CI 0.11-1.00) or before menopause (OR = 0.67; 95% CI 0.19-2.29).

Discussion

We found that HRT use was associated with a reduced risk of colorectal adenoma only among older women and the interaction between age and HRT use was consistent in women using HRT for 3 or less years or those using HRT for greater than 10 years. Curiously, older women using HRT from 4 to 10 years had an increased odds, yet this was not statistically significant. Additionally, women under 56 years of age who noted greater than 10 years duration of HRT had an increased risk of colon adenomas. The confidence intervals however were quite large and this finding would need to be replicated in another sample. Age at initiation of HRT and type of menopause did not seem to impact the tendency towards greater protection in older women. There was a significant trend suggesting a stronger association of HRT with adenoma risk in older women who initiated HRT over 1 year after menopause compared to those who initiated HRT before menopause or at peri-menopause.

Our study does not support the hypothesis that older women benefit more from HRT therapy because they are likely to have used HRT for a greater duration when compared to younger women. As such, the beneficial effects of HRT may be more associated to when one begins estrogen replacement therapy rather than how long one is using HRT. It has been previously described that hypermethylation of the estrogen receptor (ER) is an age-related phenomena and that estrogen therapy reverses these changes with a subsequent increased in ER expression within colonic mucosa. (13,14) As most colorectal tumors arise from cells that no longer express ER, it has been hypothesized that HRT may be protective by limiting ER methylation and subsequently limiting the number of cells which may progress to colorectal cancer. (14, 15) Thus HRT may offer the greatest benefit for women who have both lost ER expression due to hypermethylation while concomitantly lost their ability to reverse these changes through physiological estrogen withdrawal. Alternatively, estrogen therapy may also reverse age-related decreases in calcium absorption and directly impact serum 25(OH)D and $1,25(OH)_2D$ levels.(16,17) Several studies have suggested that calcium may reduce colorectal polyp risk. (18,19) In our study the timing of initiation of HRT with respects to menopause (which could represent the duration of estrogen withdrawal) did appear to have an impact HRT protective

effects, however the study sample was small and we had limited power to detect effects in these subgroups.

In conclusion, our study supports previous studies, which have found an interaction between age and HRT use and risk for colon neoplasm. Duration of estrogen use did not appear to modify this relationship. Future research is needed to better characterize the underlying mechanisms associated with this interaction.

Acknowledgements

The authors would like to thank the Tennessee Colorectal Polyp Study participants and staff. The authors would like to thank William Wu, Ming Li, and Heidi Chen for their assistance in data preparation. The authors would like to acknowledge the Department of Veterans Affairs, Tennessee Valley Healthcare System, GRECC for it administrative support in the preparation of the manuscript. This study was supported through the National Cancer Institute grant CA 95103 (Vanderbilt-Ingram Cancer Center SPORE in GI Cancer Grant), R01 CA97386 and the Tennessee Valley Healthcare System Veterans Affairs Clinical Research Center of Excellence.

Sources of support: This study was supported through the National Cancer Institute grant CA 95103 (Vanderbilt-Ingram Cancer Center SPORE in GI Cancer Grant), R01 CA97386 and the Tennessee Valley Healthcare System Veterans Affairs Clinical Research Center of Excellence.

References

1. Grodstein F, Newcomb PA, Stampfer MJ. Postmenopausal hormone therapy and the risk of colorectal cancer: a review and meta-analysis. Am J Med 1999;106(5):574–82. [PubMed: 10335731]
2. Nanda K, Bastian LA, Hasselblad V, Simel DL. Hormone replacement therapy and the risk of colorectal cancer: a meta-analysis. Obstet Gynecol 1999;93(5 Pt 2):880–8. [PubMed: 10912438]
3. Hebert-Croteau N. A meta-analysis of hormone replacement therapy and colon cancer in women. Cancer Epidemiol Biomarkers Prev 1998;7(8):653–9. [PubMed: 9718216]
4. Troisi R, Schairer C, Chow WH, Schatzkin A, Brinton LA, Fraumeni JF Jr. A prospective study of menopausal hormones and risk of colorectal cancer (United States). Cancer Causes Control 1997;8 (2):130–8. [PubMed: 9134236]
5. Kampman E, Potter JD, Slattery ML, Caan BJ, Edwards S. Hormone replacement therapy, reproductive history, and colon cancer: a multicenter, case-control study in the United States. Cancer Causes Control 1997;8(2):146–58. [PubMed: 9134238]
6. Fernandez E, La Vecchia C, Braga C, Talamini R, Negri E, Parazzini F, et al. Hormone replacement therapy and risk of colon and rectal cancer. Cancer Epidemiol Biomarkers Prev 1998;7(4):329–33. [PubMed: 9568789]
7. Terry MB, Neugut AI, Bostick RM, Sandler RS, Haile RW, Jacobson JS, et al. Risk factors for advanced colorectal adenomas: a pooled analysis. Cancer Epidemiol Biomarkers Prev 2002;11(7):622–9. [PubMed: 12101109]
8. Purdue MP, Mink PJ, Hartge P, Huang WY, Buys S, Hayes RB. Hormone replacement therapy, reproductive history, and colorectal adenomas: data from the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial (United States). Cancer Causes Control 2005;16(8):965–73. [PubMed: 16132805]
9. Prihartono N, Palmer JR, Louik C, Shapiro S, Rosenberg L. A case-control study of use of postmenopausal female hormone supplements in relation to the risk of large bowel cancer. Cancer Epidemiol Biomarkers Prev 2000;9(4):443–7. [PubMed: 10794491]
10. Jacobs EJ, White E, Weiss NS. Exogenous hormones, reproductive history, and colon cancer (Seattle, Washington, USA). Cancer Causes Control 1994;5(4):359–66. [PubMed: 8080948]
11. Newcomb PA, Storer BE. Postmenopausal hormone use and risk of large-bowel cancer. J Natl Cancer Inst 1995;87(14):1067–71. [PubMed: 7616598]
12. Woodson K, Lanza E, Tangrea JA, Albert PS, Slattery M, Pinsky J, et al. Hormone replacement therapy and colorectal adenoma recurrence among women in the Polyp Prevention Trial. J Natl Cancer Inst 2001;93(23):1799–805. [PubMed: 11734596]

13. Woodson K, Weisenberger DJ, Campan M, Laird PW, Tangrea J, Johnson LL, et al. Gene-specific methylation and subsequent risk of colorectal adenomas among participants of the polyp prevention trial. Cancer Epidemiol Biomarkers Prev 2005;14(5):1219–23. [PubMed: 15894675]

14. Issa JP, Ottaviano YL, Celano P, Hamilton SR, Davidson NE, Baylin SB. Methylation of the oestrogen receptor CpG island links ageing and neoplasia in human colon. Nat Genet 1994;7(4):536–40. [PubMed: 7951326]

15. Slattery ML, Potter JD, Curtin K, Edwards S, Ma KN, Anderson K, et al. Estrogens reduce and withdrawal of estrogens increase risk of microsatellite instability-positive colon cancer. Cancer Res 2001;61(1):126–30. [PubMed: 11196149]

16. Peters U, Hayes RB, Chatterjee N, Shao W, Schoen RE, Pinsky P, et al. Circulating vitamin D metabolites, polymorphism in vitamin D receptor, and colorectal adenoma risk. Cancer Epidemiol Biomarkers Prev 2004;13(4):546–52. [PubMed: 15066918]

17. Bullamore JR, Wilkinson R, Gallagher JC, Nordin BE, Marshall DH. Effect of age on calcium absorption. Lancet 1970;2(7672):535–7. [PubMed: 4195202]

18. Whelan RL, Horvath KD, Gleason NR, Forde KA, Treat MD, Teitelbaum SL, et al. Vitamin and calcium supplement use is associated with decreased adenoma recurrence in patients with a previous history of neoplasia. Dis Colon Rectum 1999;42(2):212–7. [PubMed: 10211498]

19. Baron JA, Beach M, Mandel JS, van Stolk RU, Haile RW, Sandler RS, et al. Calcium supplements for the prevention of colorectal adenomas. Calcium Polyp Prevention Study Group. N Engl J Med 1999;340(2):101–7. [PubMed: 9887161]

Table 1

Selected characteristics among female cases and controls

Characteristic	Cases (N = 169)	Controls (N = 586)	P-value
Age (mean yrs)	59.5	57.3	0.0004
Ethnicity, % white	82.0	86.1	0.20
Body mass index,			
≤ 24.9 kg/m^2	39.1	39.3	
25.0 – 29.9 kg/m^2	30.8	29.7	0.96
≥ 30.0 kg/m^2	30.2	31.1	
Family history, %			
Colorectal cancer or adenomatous polyp	21.7	17.4	0.21
Education, %			
≤ High school	24.9	23.1	
Some college	30.8	28.9	0.61
College graduate	23.7	22.2	
> College	20.7	25.8	
Smoking status, %			
Never	51.5	62.5	
Former	27.8	27.6	0.0006
Current	20.7	9.9	
Alcohol use, %			
Never	75.2	75.6	
Former	11.2	10.6	0.97
Current	13.6	13.9	
Physical activity, %			
Regularly exercise	56.8	59.6	0.52
Non-steroidal anti-inflammatory drugs, %			
Current user	43.0	41.5	0.79

Table 2

Association of age and current hormone replacement therapy use with adenoma risk in postmenopausal women stratified by duration of use, age at beginning HRT, age at menopause, and timing of initiation of HRT

	Participant Age, yrs					
	< 56			≥ 56		
	Controls/Cases	OR[1]	95% CI	Controls/Cases	OR[1]	95% CI
HRT Use						
Never	98/15	1.00	1.00	53/27	1.00	1.00
Current	123/27	1.38	0.47-4.02	141/31	0.40	0.16-0.98
Test for interaction						P = 0.03
Duration of HRT Use						
Never used	98/15	1.00		53/27	1.00	
≤ 3 yrs	37/10	1.04	0.24–4.53	20/4	0.07	0.006-0.81
4 to 10 yrs	37/5	0.51	0.09-2.90	23/9	1.24	0.31-4.91
> 10 yrs	23/9	8.41	1.37-51.58	66/15	0.27	0.09-0.80
Test for trend			P = 0.24			P = 0.08
Age at initiation of HRT						
Never used	98/15	1.00		53/27	1.00	1.00
≤ 43 yrs	45/14	2.23	0.58-8.62	34/7	0.24	0.06-0.89
44 to 49 yrs	32/5	0.77	0.16-3.62	31/9	0.24	0.05-1.13
> 49 yrs	20/5	1.27	0.20-8.02	44/12	0.57	0.57-1.75
Test for trend			P = 0.81			P = 0.36
Menopause status at HRT initiation						
Never used	98/15	1.00		53/27	1.00	
Pre-	38/6	0.67	0.20-2.26	50/12	0.67	0.19-2.29
Peri-	77/19	1.63	0.51-5.19	69/13	0.33	0.11-1.00
Post-	8/2	4.25	0.31-59.25	22/6	0.15	0.02-1.01
Test for trend			P = 0.24			P = 0.01
Type of menopause in HRT users						
Never used	98/15	1.00		53/27	1.00	
Natural	35/9	0.96	0.22-4.17	55/14	0.31	0.09-1.07
Surgical/medical	62/15	1.59	0.46-5.48	54/14	0.44	0.16-1.22
Test for trend			P = 0.60			P = 0.07

[1] OR adjusted for age (continuous), family history of colorectal tumor (yes, no), body mass index (≤ 24.9, 25.0 – 29.9, and ≥ 30.0 kg.m^2), smoking status (never, current, former), alcohol use (never, current, former), ethnicity (white, non-white), education (≤ high school, > high school), physical activity (regular exercise, no regular exercise) and NSAID use (current user, not current user).