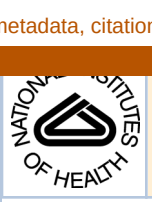

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Hormone Replacement Therapy, Oral Contraceptive Use and Distal Large Bowel Cancer: A Population-Based Case-Control Study

Millie D. Long, MD, MPH[1,2], **Christopher F. Martin, MSPH**[1,2], **Joseph A. Galanko, PhD**[1], and **Robert S. Sandler, MD, MPH**[1,2]

[1]University of North Carolina – Chapel Hill, Division of Gastroenterology and Hepatology

[2]University of North Carolina – Chapel Hill, Department of Epidemiology

Abstract

Objective—Lower incidence rates of distal large bowel cancer in women compared to men support the protective role of female hormones. We aimed to determine the associations between hormone replacement therapy, oral contraceptive use and distal large bowel cancer.

Methods—We conducted a population-based case-control study of incident distal large bowel cancer in North Carolina between 2001–2006. Data on hormone replacement therapy, oral contraceptive use, demographics and risk factors were obtained via in-person interviews. Odds ratios and 95% confidence intervals for the associations between oral contraceptive use, hormone replacement therapy and distal large bowel cancer were estimated via unconditional logistic regression models overall, by duration of use, and within strata of race.

Results—There were a total of 443 women with distal large bowel cancer and 405 controls. Ever use of hormone replacement therapy was strongly associated with a reduced risk of distal large bowel cancer (OR 0.52, 95% CI 0.38–0.72). Further reduction of distal large bowel cancer risk occurred with increased duration of use [<4 years (OR 0.77, 95% CI 0.44–1.35), 4–8 years (OR 0.64, 95% CI 0.37–1.10), 9–14 years (OR 0.47, 95% CI 0.27–0.81), ≥15 years (OR 0.34, 95% CI 0.20–0.58)]. Ever use of oral contraceptives was not associated with reduced incidence of distal large bowel cancer (OR 0.95, 95% CI 0.67–1.34), nor was duration of use. There were no differences by race.

Conclusions—Hormone replacement therapy is associated with a lower risk of distal large bowel cancer. This risk is further reduced with increased duration of use. Hormone replacement

Corresponding and Reprints Author: Millie D. Long MD, MPH, University of North Carolina – Chapel Hill, CB#7080, Chapel Hill, NC 27599-7080, millie_long@med.unc.edu, Phone 919-966-6000, Fax: 919-966-6842.

Guarantor of the Manuscript:
Millie D. Long MD, MPH

Author contributions
Millie D. Long MD, MPH designed the research question, performed the analyses, drafted the manuscript, and was involved in all stages of manuscript preparation and revision.
Robert S. Sandler MD, MPH designed the North Carolina Colon Cancer Study-II (the parent study from which our research question arises), he assisted with formulation of the research question, aided with analyses, and revised the manuscript.
Christopher F. Martin MSPH aided with the design of the North Carolina Colon Cancer Study-II, is the data manager for the study, assisted with analyses, and revised the manuscript.
Joseph A. Galanko PhD is the biostatistician who performed data programming, he aided with variable creation, oversaw the analyses and reviewed the manuscript.

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therapy may be partially responsible for the reduced incidence of distal large bowel cancer in women compared to men.

Introduction

Women have reduced rates of colorectal cancer compared to men (1). Epidemiologic studies have shown that exogenous hormones, such as oral contraceptives and hormone replacement therapy, are associated with a lower risk of colorectal cancer (2,3). The Women's Health Initiative showed that hormone replacement therapy significantly reduces the risk of colorectal cancer (4).

Although colorectal cancer is often considered a single entity, colon and rectal cancer are in fact distinct disease groups. When comparing colon and rectal cancer of similar stage, there are differences in histologic differentiation, gene expression and clinical outcomes such as prognosis and survival (5,6). Additionally, rectal and distal colonic tumors share similar mutational frequencies, which are different from those seen in proximal colonic tumors (7). The association between exogenous hormone use and distal large bowel cancer is less well defined than the association with colon cancer, although it also appears to be protective (8,9). Previous studies have not incorporated data on women using more contemporary doses of oral contraceptives. Previous work has also lacked the power to investigate racial differences in rectal cancer risk associated with hormone replacement therapy or oral contraceptive use.

With data from the North Carolina Colon Cancer Study-II, a large population-based case-control study of distal large bowel cancer [defined as rectal, recto-sigmoid, or sigmoid cancer], we aimed to better determine the association of both hormone replacement therapy and oral contraceptive use with the risk of distal large bowel cancer among Caucasian and African American women in eastern North Carolina.

Methods

Study Cohort

The North Carolina Colon Cancer Study-II (NCCCS-II) was a population-based case-control study of incident distal large bowel cancer [defined as rectal, recto-sigmoid, or sigmoid cancer] in Caucasians and African Americans in 33 counties in the central and eastern part of North Carolina. Data for this study were collected by in-person interviews, conducted in the subject's home or in another convenient location, by trained nurse interviewers. Measurements of height, weight and abdominal circumference were obtained when possible. In order to confirm the diagnosis of invasive adenocarcinoma of sigmoid, rectosigmoid, or rectum, pathology reports were obtained and reviewed by the study pathologist for each case.

Assessment of distal large bowel cancer cases and controls

Between May 2001 and September 2006, a total of 1831 potentially eligible patients with a first diagnosis of invasive adenocarcinoma in sigmoid, rectosigmoid, and rectum were identified through the rapid ascertainment system of the North Carolina Central Cancer Registry. The procedure for case ascertainment has been described elsewhere (10). Cases were eligible for the study if they were residents of the selected counties, aged between 40 and 80 years, African American or Caucasian race, had a North Carolina driver's license or identification card, and were able to complete an interview in English. Of the 1,831 potentially eligible cases identified, 57 (3%) were excluded for physician refusal, and 357 (19%) were found ineligible. Of the remaining 1,417 eligible cases, 118 (8%) were not able

to be contacted, 242 (17%) refused to participate, and 1,057 (75%) completed an in-person interview. This population was then limited to women, resulting in 443 female cases of distal large bowel cancer. The specific response rate for women was not significantly different from the overall response rate, and not different by race (African American women 69%, Caucasian women 71 %).

Using the technique of randomized recruitment (11), controls were randomly selected from North Carolina Division of Motor Vehicle records (for controls age <65) or from Health Care Financing Administration (HCFA) records (for controls age ≥65), based on sampling probabilities within blocks defined by 5-year age group, sex and race. Initially, 2,345 subjects were identified as eligible controls, but 518 (22%) were later determined to be ineligible. Reasons for exclusion included lack of a North Carolina driver's license or identification card (if under age 65), not residing in the ascertainment area of 33 counties, any personal history of colorectal cancer, not speaking English, deaf or hard of hearing, too ill to be interviewed, legally incompetent or current incarceration. Of the 1,827 eligible controls identified, 325 (18%) were not able to be contacted, and 483 (26%) refused to participate. A total of 1,019 (56% of eligible controls) completed an interview. This population was then limited to women, resulting in 405 controls. The specific response rate for female controls was similar by race (54% for African American women and 56% for Caucasian women). Among controls, women were slightly less likely to respond than men, but these differences were not significant. The final dataset for analysis included 443 female cases and 405 female controls. The study was approved by the Institutional Review Board at University of North Carolina School of Medicine, and all subjects provided written informed consent.

Assessment of main exposures and other risk factors

We obtained information on hormone replacement therapy, oral contraceptive use and other reproductive factors during the in-person interview. Participants were asked whether they had ever used hormone replacement therapy, whether they had used these medications within the past year and the total duration of use at the time of diagnosis (case) or interview (control). The same questions were asked in regards to oral contraceptive use. Data on parity, gravidity, age at menarche, menopause and age at menopause were also obtained. Data on other factors associated with distal large bowel cancer including non-steroidal anti-inflammatory drug (NSAID) use, physical activity, red meat intake, smoking, and family history of colorectal cancer in a first degree relative were also included in the interview. Physical activity was assessed via a validated 7 day physical activity recall questionnaire (12,13). Dietary intake, including red meat, was assessed via a validated Diet History Questionnaire (14,15). All participants were asked their weight 1 year prior to diagnosis (case) or interview (control) in order to calculate body mass index from a weight unaffected by the cancer diagnosis or treatment. Demographic information such as education, marital status, income and insurance status was also collected.

Statistical Analysis

Odds ratios (OR) and 95% confidence intervals for the association between hormone replacement therapy and distal large bowel cancer were estimated from unconditional logistic regression models. Hormone replacement therapy use was defined as ever use for at least one year. All logistic regression models included indicator variables for the matched factors age and race as well as an offset term to adjust for sampling probability (11,16).

Other potential covariates and effect measure modifiers assessed for inclusion in multivariable models were: years of education (<high school, high school/GED or >high school), annual household income (<$25,000, ≥ $25,000), smoking status (ever > 100

cigarettes, never), marital status (married, previously married, never married), insurance status (any, none), gravidity (0, 1–3, >3 pregnancies), body mass index (BMI) calculated from weight 1 year prior measured in kg/m^2 (<25 normal/underweight, 25–30 overweight, ≥30 obese), menopausal status (yes, no), oral contraceptive use (ever, never), family history of colon cancer in a first degree relative (yes, no), physical activity measured in met-minutes/day (in quartiles), red meat consumption (total intake of luncheon meats, beef, pork, lamb and organ meats (g/day), continuous) and regular NSAID use (any NSAID >3 times a week for at least 3 months, yes, no). Presence of a prior colorectal polyp was thought to be an intermediate step on the causal pathway to distal large bowel cancer; therefore this variable was not included as a covariate in the analyses.

Interaction between the main exposure and each covariate was first assessed via likelihood ratio testing using a significance level of 0.10. No significant effect measure modifiers were identified. To determine which covariates should be entered in the final multivariable models, we constructed a full model with all potential confounders, and assessed the change in beta coefficients for hormone replacement therapy users versus non-users in relation to distal large bowel cancer when covariates were removed. Indicator variables for the strata of matched factors were retained in the model (age, race and a sampling probability offset term). Covariates were removed from the model using a backwards elimination technique using a threshold of <10% change in beta coefficients. The final model with hormone replacement therapy as the main exposure contained the outcome, exposure, educational level, smoking status, BMI, family history of colon cancer, oral contraceptive use, menopausal status, physical activity, red meat consumption and NSAID use.

The above modeling technique was repeated with oral contraceptive use as the main exposure. The final model contained the outcome, exposure, educational level, smoking status, BMI, family history of colon cancer, hormone replacement therapy use, menopausal status, physical activity, red meat consumption and NSAID use.

The effects of duration of use of both hormone replacement therapy and oral contraceptive use, each divided into quartiles, were also evaluated via logistic regression models with non-use of hormone replacement therapy or non-use of oral contraceptives respectively as the reference category.

The dataset was then stratified by race in order to determine the effects of ever versus never use of hormone replacement therapy or oral contraceptives in Caucasians and African Americans. The above modeling technique was repeated within each stratum of race for each main exposure.

Finally, a polytomous logistic regression model was used in order to determine the site-specific [rectal, recto-sigmoid, sigmoid] effects of ever use of hormone replacement therapy or oral contraceptives. Because polytomous models cannot incorporate weights, the offset term was not included for these analyses. A similar backwards elimination strategy based on <10% change in beta coefficients was used in these analyses. For all analyses, *p*-values were two-sided, and a p-value of 0.05 or less was considered statistically significant. All statistical analyses were performed using Stata version 9.0 (Texas Station, TX).

Results

Table 1 presents the baseline characteristics of the study population according to case or control status. For hormone replacement therapy, a significantly smaller percentage of cases than controls reported ever use of these agents. For the main exposure of oral contraceptive use, similar percentages of both cases and controls reported ever use. In regards to other characteristics of the population, the cases were slightly younger, had a higher BMI, and

were less educated. A slightly higher percentage of the cases were African American, fewer reported regular use of NSAIDS, and cases consumed more red meat. Of note, the populations were quite similar in regards to reproductive characteristics such as age of onset of menses, gravidity, parity and age of onset of menopause. Similar percentages in both groups were menopausal.

Ever use of hormone replacement therapy was associated with reduced risk of distal large bowel cancer in our multivariate analysis (OR 0.52, 95% CI 0.38–0.73) (table 2). Increased duration of use was associated with further reduction of distal large bowel cancer incidence. For women with <4 years of use, the odds ratio for distal large bowel cancer was 0.77 (95% CI 0.44–1.35). For each quartile of hormone replacement therapy use, the odds ratio for distal large bowel cancer continued to decrease. The highest quartile of use, ≥15 years, had an odds ratio of 0.34 (95% CI 0.20–0.58) for incident distal large bowel cancer (p for trend <0.001) (table 3). When site specific locations of the cancer were evaluated as the outcome, hormone replacement therapy reduced the risk of distal large bowel cancer in all three locations, with significant effects in the sigmoid and rectum (table 4).

Ever use of oral contraceptives was not associated with a reduction in distal large bowel cancer incidence in our multivariate analysis (OR 0.95, 95% CI 0.67–1.34) (table 5). There was no change in the association based on duration of use. Women with short term use (0–2 years) had an odds ratio of 0.63 (95% CI 0.38–1.03) for distal large bowel cancer, compared to non-users. With increasing duration of use, there was a slight increase in the odds of distal large bowel cancer, although this was not significant (p for trend 0.217) (table 6). There was no difference in the effect of oral contraceptives based on rectal, recto-sigmoid or sigmoid cancer location (table 7). We also stratified our analyses by age. Interestingly, there was a non-significant reduction in the risk of distal large bowel cancer in the oldest age group of women who reported prior use of oral contraceptive agents (≥ 70 years) (OR 0.52 95% CI 0.24–1.15).

The multivariate analyses of ever use of hormone replacement therapy or oral contraceptives and incident distal large bowel cancer were repeated within strata of race. There were no differences in the effects of these medications by Caucasian or African American ethnicity.

Discussion

In this population-based case control study, we observed a significant protective effect of hormone replacement therapy for incident distal large bowel cancer. Increasing duration of use appeared to convey further reduction in distal large bowel cancer risk. This reduction in risk was evident for both Caucasians and African Americans and in site specific locations of the cancer. Oral contraceptive use was not protective for the development of distal large bowel cancer, regardless of duration of use, race or site specific location of the cancer.

Previous studies have evaluated the relationship between hormone replacement therapy and colorectal cancer. Although there appears to be an overall protective effect, some studies have failed to yield a reduction in incidence of colorectal cancer. Randomized controlled trial data from the Women's Health Initiative (WHI) demonstrate a protective effect (HR 0.63, 95% CI 0.43–0.92) of combined estrogen and progesterone containing hormone replacement therapy for colorectal cancer (4). Also, several observational studies of colorectal adenomas have demonstrated a protective effect of hormone replacement therapy (17–19). However, a recent examination of combined data from the WHI clinical trial and observational study did not provide evidence of a clinically important benefit of hormone replacement therapy on the incidence of colorectal cancer over 7–8 years of treatment and follow-up (20). The relationship of these medications with distal large bowel [specifically

rectal] cancer has also been evaluated, again with mixed conclusions. Many of these studies showed a protective effect, but did not reach statistical significance (21–27). Other studies found non-significantly elevated odds ratios for the effect (28–30). Nichols did find a significant protective effect of hormone replacement therapy for rectal cancer in their population-based case-control study in Wisconsin (31). Grodstein performed a meta-analysis of the role of hormone replacement therapy in the development of rectal cancer and obtained an odds ratio of 0.81 (95% CI 0.72–0.92) (9). Our result is consistent with this protective effect. Other studies have also investigated whether there is a dose-response trend for the use of hormone replacement therapy, and have not demonstrated increased protection with increased duration of use (26). Our study did find further reduction in distal large bowel cancer incidence with prolonged duration of use. To our knowledge, no previous study has stratified analyses of hormone replacement therapy and distal large bowel cancer according to race. We found no difference in the effect based on Caucasian or African American ethnicity

Oral contraceptives have also been studied in regards to colorectal cancer risk. Two meta-analyses found a mild protective effect for ever versus never use (OR of 0.8) (3,32). One of these analyses found the effect to be most pronounced for recent users of oral contraceptives (OR 0.46, 95% CI 0.30–0.71) (3). In contrast to these studies, we found no risk reduction for incident distal large bowel cancer by oral contraceptives. Results of previous studies of oral contraceptive use and rectal cancer have been mixed, many have demonstrated a trend towards a mild protective effect, but have not reached statistical significance (3). The only meta-analysis that specifically evaluated oral contraceptive use and rectal cancer yielded an OR of 0.74 (95% CI 0.59–0.93) (3). Several studies in this meta-analysis were published in the 1980's and may have disproportionately contained women who used higher-dose estrogen formulations than are predominantly used today. Higher dose formulations of oral contraceptives were prevalent before 1976 (33). The lack of a protective effect seen in our study may be because modern-day formulations of oral contraceptives contain very low dose estrogen and progesterone (between 20 and 35 mcg of ethinyl estrodiol compared to 50 mcg or greater). We performed additional analyses supporting this hypothesis that showed a trend for risk reduction in the oldest strata of women, who would likely have been exposed to higher doses of estrogen and progesterone containing oral contraceptives. Some forms of oral contraceptives used today also are progestin-only, although traditionally progestin-only users represent a very small proportion of overall users (33). Our study population was accrued between 2001–2006, and the average age of women in our study was approximately 63. These women may therefore represent a mixed population of both high and low dose oral contraceptive users, which may explain our lack of an association. Even in previous studies where a protective effect was found, often there was no dose-response trend with increased duration of use (2,3,31). This lack of a dose-response effect with oral contraceptives argues against a substantial causative risk reduction.

The mechanism behind the association between exogenous hormone therapy and distal large bowel cancer is uncertain. Female hormones may protect against cancers of the large bowel as a result of changes in bile synthesis and secretion. This can result in reduced concentration of bile acids in the colon (34). Other biological mechanisms have been proposed, including the potential inhibition of colon cancer cells by estrogen (35) and the reduction of serum insulin-like growth factor (36). Recently it has also been proposed that progesterone may enhance the inhibitory effect of estrogen on colon cancer cells (37). Newcomb at al performed a case-control study where pathology from cases was tested for microsatellite instability (MSI). For women with MSI-low or MSI-stable tumors, there was a significant (40%) reduction in colorectal cancer risk associated with combined estrogen-progesterone hormone replacement therapy use. In contrast, no association was found with MSI-high tumors (37). Additional data show that estrogen exposure in women may protect

against MSI, and the lack of estrogen in older women increases the risk of unstable tumors (38). Rates of MSI differ between proximal and distal location of the tumor. Slattery et al found MSI in 23.7% of proximal and only 3.8% of distal and 2.0% of rectal tumors (7). While it is unknown whether the mechanism of action of female hormones differs based on proximal versus distal location of the cancer, our data support that the protection continues in the distal large bowel.

There were many strengths to this study, including a large sample size, the in-person data collection, the confirmation of pathology by a study pathologist, and the ability to control for many risk factors. The associations between exposures and distal large bowel cancer were similar to other studies of distal large bowel cancer suggesting external validity. For example, the distal large bowel cancer cases in our study had a significantly greater BMI, consumed more red meat, and also used NSAIDS less frequently. These risk factors are consistently seen throughout the literature in association with distal large bowel [specifically rectal] cancer (39–42). There were also several limitations to this population-based case control study. First, use of hormone replacement therapy and oral contraceptives was by self-report. Certainly, there is potential for recall bias with any self-reported data. However, previous studies have demonstrated good agreement between self-report of hormone replacement therapy and medical records (43–45). While we did have information on whether women had used hormone replacement therapy within the one year prior to diagnosis, we did not have information on time since their last dose in order to determine whether the effect diminished over time. Specifically, this study cannot answer the question of whether or not there is a rebound increase in risk of distal large bowel cancer after withdrawal of these medications or continued protection after the medication is discontinued. It has also been previously argued that women who use oral contraceptives and hormone replacement therapy represent “healthy users (46).” This healthy user effect could contribute to the protective association we found. However, in an attempt to account for this, we statistically controlled for many associated risk factors for distal large bowel cancer including socioeconomic status information and dietary consumption patterns. Finally, specific formulations and dosages of hormone replacement therapy and oral contraceptives were not available within our dataset. Specific doses of estrogen or progesterone may have differing effects on the risk of distal large bowel cancer.

Our work on hormone replacement therapy is important in that it demonstrates a protective dose-response effect for distal large bowel cancer with increased duration of use. After publication of the results from the Women’s Health Initiative, there has been a decline in overall prescriptions for hormone replacement therapy in the United States and in England (47,48). In fact, hormone therapy prescribing has fallen by about 50% since 2002 (49). It remains to be seen whether alterations in prescribing patterns for these medications may affect the incidence of distal large bowel cancer. Much of the reduced incidence of distal large bowel cancer seen in the last two decades may have been partially related to long-term hormone replacement therapy use which is no longer recommended based on the risk-benefit ratio observed in the Women’s Health Initiative (4). However, women continue to use hormone replacement therapy for short-term perimenopausal symptom control (50,51). If practice patterns permanently change from long-term use to short-term perimenopausal use, further work is necessary to characterize the duration of distal large bowel cancer risk reduction associated with these medications. Studies have found that former users of hormone replacement therapy do not retain the protective effects (17). Grodstein demonstrated that the risk reduction seen with hormone replacement therapy disappears at approximately 5 years after cessation of these medications (26). Further work should evaluate women after cessation of these medications to determine if there is a “rebound” effect of an increase in polyp formation. It may become important in the future to tailor timing of women’s colorectal screening based on cessation of hormone replacement therapy.

In conclusion, this study suggests that women who use hormone replacement therapy are at reduced risk for the development of distal large bowel cancer, regardless of race. Longer duration of use is associated with increased protection. It is possible that widespread use of hormone replacement therapy is partially responsible for the reductions we have seen in distal large bowel cancer incidence over time.

Study Highlights

1. What is current knowledge
    a. Women have reduced incidence of distal large bowel cancer compared to men
    b. Hormone replacement therapy and oral contraceptive use may reduce the risk of distal large bowel cancer
2. What is new here
    a. Increased duration of use of hormone replacement therapy is associated with increased reduction of distal large bowel cancer incidence
    b. Oral contraceptives, when modern-day formulations are included, do not reduce the risk of distal large bowel cancer
    c. The effects of hormone replacement therapy and oral contraceptives on incident distal large bowel cancer do not vary by race

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Table 1

Characteristics of women in the North Carolina Colon Cancer Study-II by case-control status, matched characteristics include age by 5 year block and race.*

Characteristics	n	Case Distal large bowel cancer*	n	Control No distal large bowel cancer*	P value
Main Exposures					
Hormone replacement therapy use †					
% Yes	156	35.3	197	49.0	<0.01
Oral contraceptive use ‡					
% Yes	218	49.6	187	46.5	0.38
Risk Factors					
Age	443	62.5 (10.3)	405	64.5 (10.5)	0.01
Age of onset of menses	437	12.7 (1.6)	399	12.7 (1.6)	0.84
Age at first birth	388	22.4 (4.8)	365	22.6 (4.8)	0.59
Age at last birth	317	29.8 (5.8)	305	29.7 (5.6)	0.86
Gravidity	442	3.0 (2.1)	404	3.1 (1.9)	0.55
Parity	443	2.5 (1.9)	404	2.5 (1.7)	0.94
Menopause					
% Yes	410	92.8	358	89.1	0.06
Age at menopause	398	45.4 (7.7)	351	45.5 (8.4)	0.98
BMI (kg/m2) §	424	30.1 (7.5)	395	28.3 (6.7)	<0.01
Smoking status					
%Yes	223	50.3	192	47.4	0.39
Health insurance					
% Yes	419	95.2	390	96.8	0.25
Educational level					
% <High School	98	22.1	58	14.3	
% High School/GED	137	30.9	131	32.4	0.01
% >High School	208	47.0	216	53.3	
Race					

Characteristics	n	Case Distal large bowel cancer*	n	Control No distal large bowel cancer*	P value
% Caucasian	317	72.1	320	80.0	0.01
% African American	123	27.9	80	20.0	
Marital status					
% Married/living as married	237	53.5	242	59.7	0.15
% Divorced/ Separated/Widowed	184	41.5	149	36.8	
% Single/Never married	22	5.0	14	3.5	
Regular NSAID use //					
%Yes	205	46.3	226	55.8	0.01
Family History of CRC ¶					
%Yes	58	13.5	42	10.7	0.22
Red meat consumption (g/day)**	436	60.1 (43.3)	403	49.2 (32.8)	<0.01
Physical activity (met-minutes/day) ††	421	2142.0 (545.3)	396	2079.5 (400.5)	0.06

*Mean(standard deviation) for continuous variables by Student's t-test and % for categorical variables by Pearson's chi squared test statistic

†Hormone replacement therapy use defined as ever versus never for at least one year

‡Oral contraceptive use defined as ever vs. never for at least one year

§Body Mass Index calculated as kg/m^2 or (weight in lbs *703)/(height in $inches^2$)

//Regular NSAID use defined as >3 times a week for a period of at least 3 months

¶Family history of colorectal cancer in first degree relative

**Red meat consumption calculated from luncheon meats, beef, pork, lamb and organ meats over the 1 year prior to interview or diagnosis of rectal cancer

††Physical activity in met-minutes/day from a validated 7 day physical activity recall questionnaire

Table 2

Multivariate-adjusted odds ratios* of distal large bowel cancer by hormone replacement therapy use in women, North Carolina Colon Cancer Study-II

	Distal large bowel cancer		
	No of cases	**OR**	**95% CI**
HRT use, all women			
Never	286	1.0	
Ever	156	0.52	0.38, 0.73

* adjusted for age, race, family history of colorectal cancer, education level, smoking status, oral contraceptive use, physical activity and body mass index

Table 3

Multivariate-adjusted odds ratios of distal large bowel cancer by hormone replacement therapy duration compared to non-users of hormone replacement therapy, North Carolina Colon Cancer Study-II

	Distal large bowel cancer		
	No of cases	**OR**	**95% CI**
No HRT use		1.0 (referent)	
HRT duration			
<4 years	43	0.77	0.44, 1.35
≥4 to <9 years	38	0.64	0.37, 1.10
≥ 9 to <15 years	32	0.47	0.27, 0.81
≥15 years	35	0.34	0.20, 0.58
p for trend <0.001			

*adjusted for age, race, family history of colorectal cancer, education level, smoking status, oral contraceptive use, physical activity and body mass index

Table 4

Multivariate-adjusted odds ratios using polytomous logistic regression estimating site-specific incidence of distal large bowel cancer* by hormone replacement therapy use, base outcome for comparison is controls, North Carolina Colon Cancer Study-II**

	Site specific distal large bowel cancer								
	Sigmoid			Recto-sigmoid			Rectum		
	No of cases	OR	95% CI	No of cases	OR	95% CI	No of cases	OR	95% CI
HRT use	75	0.54	0.36, 0.82	27	0.62	0.34, 1.16	51	0.47	0.29, 0.74

* 8 cases classified only as distal cancer without a site specific location were not included in analyses (3 of whom had a history of HRT use)

** adjusted for age, race, family history of colorectal cancer, education level, smoking status, oral contraceptive use, physical activity and body mass index

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Table 5

Multivariate-adjusted odds ratios* of distal large bowel cancer by oral contraceptive use in women, North Carolina Colon Cancer Study-II

	Distal large bowel cancer		
	No of cases	**OR**	**95% CI**
OC use			
Never	222	1.0	
Ever	218	0.95	0.67, 1.34

* adjusted for age, race, family history of colorectal cancer, education level, smoking status, hormone replacement therapy use, physical activity and body mass index

Table 6

Multivariate-adjusted odds ratios* of distal large bowel cancer by oral contraceptive duration, comparing women by duration of oral contraceptive use in quartiles to non-users of oral contraceptives, North Carolina Colon Cancer Study-II

	Distal large bowel cancer		
	No of cases	**OR**	**95% CI**
No OC use	222	1.0 (referent)	
OC use			
0–2 years	55	0.63	0.38, 1.03
>2 to <5 years	42	1.11	0.61, 2.00
>=5 to <10 years	59	1.18	0.70, 2.00
>=10 years	56	1.32	0.79. 2.21
p for trend: 0.217			

* adjusted for age, race, family history of colorectal cancer, education level, smoking status, hormone replacement therapy use, physical activity, and body mass index

Table 7

Multivariate-adjusted odds ratios using polytomous logistic regression estimating site-specific incidence of distal large bowel cancer* by oral contraceptive use, base outcome for comparison is controls, North Carolina Colon Cancer Study-II**

	Site specific distal large bowel cancer								
	Sigmoid			**Recto-sigmoid**			**Rectum**		
	No of cases	OR	95% CI	No of cases	OR	95% CI	No of cases	OR	95% CI
HRT use	108	0.96	0.63, 1.48	38	1.06	0.56, 1.99	69	0.92	0.58, 1.47

* 8 cases classified only as distal cancer without a site specific location were not included in analyses (3 of whom had a history of OCP use)

** adjusted for age, race, family history of colorectal cancer, education level, smoking status, hormone replacement therapy use, physical activity and body mass index