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Reproductive factors and risk of colorectal polyps in a colonoscopy based study in western Washington State

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Abstract

Background—Oral contraceptives (OC) are associated with a decreased risk of colorectal cancers; however a recent study reported an increased risk of small colorectal adenomas associated with OC use. To determine if these results were replicable in a different study population, we investigated the relationship between OC use and other reproductive factors and risk of colorectal polyps in a case-control study in western Washington.

Methods—Study participants were 24–79 year old female enrollees at an integrated health care system in western Washington who were diagnosed as having adenomas (n=299), serrated polyps (n=337), both types of polyps (n= 105) or as polyp-free controls (n=615) through an index colonoscopy and completed a structured interview to collect reproductive history information. Multivariable polytomous logistic regression was used to compare case groups to controls and to each other; odds ratios (OR) and 95% confidence intervals were estimated.

Results—There was no association between OC use, duration of use, or recency of use and the risk of either adenomas or serrated polyps [adjusted OR for OC ever use (95% CI) =0.85(0.58–1.23) and 0.96(0.66–1.40), respectively], and associations did not differ by lesion severity within the adenoma or serrated pathways. Further, no associations were observed between other reproductive factors and risk of colorectal polyp subtypes.

Conclusions—Our results suggest that reproductive factors, including OC use, are not associated with early colorectal cancer precursor lesions.

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INTRODUCTION

While most studies, including a meta-analysis of twelve cohort and seventeen case-control studies, suggest an inverse association between oral contraceptives (OC) use and risk of colorectal cancer (CRC);¹ a more recent large prospective study reported no association.² Observational studies have consistently reported an inverse association between postmenopausal hormone replacement therapy (HRT) and CRC risk.³ Other reproductive factors such as parity and premenopausal status have also been associated with reduced CRC risk.⁴

As most CRCs arise from polyp precursor lesions, including advanced adenomas and a subset of serrated polyps, termed sessile serrated polyps,⁵ these reproductive factors may also be inversely associated with colorectal polyps, particularly specific polyp subtypes. Paradoxically, a recent study suggested an increased risk of small/early-stage adenomas with OC use.⁶ We investigated the relationship between reproductive factors and the risk of colorectal polyps, particularly subtypes, in a colonoscopy-based study in western Washington State.

MATERIALS & METHODS

Study population

Details of the study population have been described previously.⁵ Briefly, 24–79 year-old women enrollees at Group Health, an integrated health care system in western Washington, underwent a colonoscopy for any indication from 1998–2007. Lesions identified at colonoscopy received a standardized pathology review; tubular, tubulovillous, and villous adenomas were classified as adenomas while hyperplastic polyps, traditional serrated adenomas, and sessile serrated polyps were grouped together into the serrated polyps group. Thus, the study population comprised of adenomas (n=299), serrated polyps (n=337), synchronous adenomas and serrated polyps (n=105), and polyp-free controls (n=615). Adenomas were further classified based on lesion severity as advanced (≥ 10mm diameter, ≥ 20% villous components, or with high-grade dysplasia) or non-advanced. Serrated polyps were further classified as being either hyperplastic or sessile serrated (considered as advanced lesions). Institutional review boards at Fred Hutchinson Cancer Research Center and Group Health approved the study.

Exposure assessment

Participants completed a structured self-administered questionnaire to collect detailed reproductive history. OC use was categorized according to ever use, duration and recency of use. Due to small numbers of current OC users in this study population (<5%), we did not evaluate associations with current OC use. We also collected information on other reproductive factors, such as age at menarche, age at first birth, number of pregnancies, menopausal status, age at menopause, and use (and type) of HRT.

Statistical analysis

Multivariable polytomous logistic regression was used to compare case groups with controls as well as with other case groups. Odds ratios (OR) and 95% confidence intervals (CI) were estimated adjusted for the following covariates, selected *a priori* based on prior studies reporting that these factors were associated with OC use (and other reproductive factors under study) or with colorectal polyps: age, race, education, body mass index, smoking, alcohol, anti-inflammatory drug use, and previous endoscopy. Additionally, every model was mutually adjusted for OC use and other reproductive factors, based on the exposure being evaluated. We evaluated multiple aspects of OC use, including duration and recency of use, using the method described by McKnight *et.al.*⁷ For lesion severity-specific analyses, we excluded persons with synchronous adenomas and serrated polyps (n= 105) to avoid any mixing of associations. All analyses were conducted using Stata v14.0.

Statistical Power

Power calculations were conducted using PS v3.1.2. Given our sample size and $\alpha=0.05$, this study had 80% power to detect an OR of 0.6–1.6 for OC use; minimum detectable ORs for other exposures were also in the 0.5–1.8 range for various case groups.

RESULTS

The mean age of the cohort was 59.6 years; age distribution was similar between controls and the various case groups. Consistent with the literature, cases were more likely to be obese, current smokers and non-users of NSAIDs as compared to controls; women with serrated polyps were more likely to be smokers than those with adenomas. Ever use of OCs was not associated with risk for adenomas or serrated polyps [adjusted OR (95% CI) =0.85 (0.58–1.23) and 0.96 (0.66–1.40), respectively] (Table 1). The magnitude of the association did not vary statistically significantly between adenomas and serrated polyps for ever use ($p_{\text{heterogeneity}}=0.36$), or duration and recency of use ($p_{\text{heterogeneity}}=0.38$). For associations between other reproductive factors and risk of colorectal polyp subtypes, OR estimates were all in expected direction, but there were no statistically significant associations (Table 1). Also, the strength of these associations did not vary between adenomas and serrated polyps for any reproductive factors.

When we evaluated differences in the association between OC use and reproductive factors and colorectal polyps by lesion severity, we observed no statistically significant differences between advanced and non-advanced adenomas, or between sessile serrated and hyperplastic polyps (Table 2). Although statistically non-significant, we observed a suggestive trend ($p_{\text{trend}}=0.05$) for increasing risk of sessile serrated polyps with longer duration of OC use.

Finally, we conducted sub-group analyses among those study participants that reported having undergone a screening endoscopy (32.5% of all endoscopies) and found that the results were similar in magnitude and in the same direction as the overall results.

DISCUSSION

In this case-control study evaluating the association between reproductive factors among women and the risk of colorectal polyp subtypes, we observed no association between OC use and risk of colorectal polyps, regardless of the polyp subtype or lesion severity. This is in contrast to a recently published study by Charlton et. al. that reported a slightly increased risk of non-advanced adenomas associated with OC use [OR (95% CI) = 1.11(1.02–1.21)].⁶ The authors suggested that the previously reported protective effect of OC use on adenomas may be more pronounced in more recent and younger users, while stopping OC use several years before the development of non-advanced adenomas may possibly promote colorectal adenoma development. We did not observe such a differential association with recency of OC use despite a comparable mean age in our study population. Our results are concordant with two previous case-control studies that did not report an association between OC use and risk for colorectal adenomas.^{8,9} Both these reports were comparable in terms of mean age of the study population and time since use of OC, when available. However, the previously published studies were able to make comparisons for the risk of only colorectal adenomas. Here, we were also able to report on these associations within the serrated pathway.

Although the inverse association between HRT use and CRC is well-established, a recent study reported a null association with OC pills.² In our study, we were also unable to demonstrate any association between HRT use and development of colorectal polyps. Our null results are also consistent with a previous study that compared hyperplastic polyps with adenomas, and observed no association with OC use, parity, and age at first birth.¹⁰ Here, in addition to reporting on adenomas, we were also able to examine the risk for sessile serrated polyps with these reproductive factors.

Other factors may also contribute to the inverse association between reproductive factors and CRC. For example, changes in the formulation and use patterns of OC and HRT use may have played a role in the development of colorectal polyps. However, we were unable to evaluate this in the current manuscript. In conclusion, our results along with the results of prior studies of CRC should be reassuring about any risk for the great majority of US women who have used these common contraceptives.

Acknowledgments

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Associations between oral contraceptive use and other reproductive factors and risk of colorectal polyps, Group Health Cooperative, Seattle, Washington, 1998–2007^a

Table 1

	Controls (n=615) n (%)	Adenomas only (n = 299)		Serrated polyps only (n=337)		Both adenomas & serrated polyps (n=105)		P for comparison between groups ^b			
		Cases n (%)	Adjusted [†] OR(95% CI)	Cases n (%)	Adjusted [†] OR(95% CI)	Cases n (%)	Adjusted [†] OR(95% CI)	AD vs SP	AD vs AD+SP	SP vs AD+SP	
OC use											
Ever use											
	No	180 (29.3)	99 (33.2)	REF	96 (28.6)	REF	26 (24.8)	REF	0.36	0.19	0.16
	Yes	435 (70.7)	199 (66.8)	0.85 (0.58,1.23)	240 (71.4)	0.96 (0.66,1.40)	79 (75.2)	1.42 (0.78,2.58)			
Duration and Recency (years)											
0		189 (30.9)	101 (34.1)	REF	103 (30.7)	REF	26 (25.5)	REF	0.38	0.16	0.21
>0<=5											
	Recency 0–25	28 (14.6)	12 (13.8)	0.93 (0.74,1.17)	6 (6.9)	1.06 (0.85,1.33)	3 (11.1)	1.30 (0.91,1.85)			
	Recency >25	164 (85.4)	75 (86.2)	0.87 (0.58,1.30)	81 (93.1)	0.98 (0.66,1.46)	24 (88.9)	1.35 (0.72,2.55)			
>5											
	Recency 0–25	115 (54.3)	44 (44.9)	0.93 (0.61,1.43)	67 (47.5)	1.22 (0.81,1.83)	19 (44.2)	1.62 (0.86,3.06)			
	Recency >25	95 (44.8)	54 (55.1)	0.87 (0.55,1.37)	74 (52.5)	1.13 (0.72,1.76)	24 (55.8)	1.69 (0.83,3.44)			
Other reproductive factors											
Age (years) at menarche									0.68	0.21	0.10
	<13	290 (47.6)	137 (46.1)	REF	150 (44.8)	REF	51 (49.0)	REF			
	13	319 (52.4)	160 (53.9)	1.13 (0.79,1.62)	185 (55.2)	1.21 (0.85,1.71)	53 (51.0)	0.92 (0.54,1.56)			
Age (years) at first birth									0.37	0.28	0.21
	0	62 (11.0)	15 (5.6)	REF	25 (8.4)	REF	13 (13.7)	REF			
	<25	260 (46.0)	122 (45.7)	1.40 (0.71,2.73)	128 (43.1)	1.12 (0.60,2.08)	45 (47.4)	0.66 (0.29,1.48)			
	25	243 (43.0)	130 (48.7)	1.73 (0.90,3.33)	144 (48.5)	1.31 (0.72,2.40)	37 (39.0)	0.85 (0.38,1.88)			
Parity									0.36	0.19	0.16
	0	62 (11.0)	15 (5.6)	REF	25 (8.5)	REF	13 (13.7)	REF			
	1+	504 (89.1)	252 (94.4)	1.57 (0.83,2.99)	271 (91.6)	1.23 (0.68,2.21)	82 (86.3)	0.75 (0.35,1.59)			
Menopausal status									0.36	0.19	0.16
	Pre	114 (18.5)	45 (15.1)	REF	52 (15.4)	REF	17 (16.2)	REF			

	Controls (n=615) n (%)	Adenomas only (n = 299)		Serrated polyps only (n=337)		Both adenomas & serrated polyps (n=105)		P for comparison between groups ^d		
		Cases n (%)	Adjusted [†] OR(95% CI)	Cases n (%)	Adjusted [†] OR(95% CI)	Cases n (%)	Adjusted [†] OR(95% CI)	AD vs SP	AD vs AD+SP	SP vs AD+SP
Age (years) at Menopause										
	Post	501 (81.5)	253 (84.9)	1.16 (0.64,2.08)	285 (84.6)	0.87 (0.51,1.49)	88 (83.8)	1.07 (0.45,2.57)	0.53	0.10
	<50	224 (45.6)	96 (38.3)	REF	133 (47.5)	REF	34 (40.5)	REF		
	50	267 (54.4)	155 (61.8)	1.23 (0.85,1.78)	147 (52.5)	0.95 (0.67,1.35)	50 (59.5)	1.30 (0.75, 2.27)		
HRT	No	269 (44.4)	130 (44.4)	REF	167 (50.3)	REF	47 (44.8)	REF	0.36	0.19
	Yes	337 (55.6)	163 (55.6)	0.94 (0.65,1.37)	165 (49.7)	0.71 (0.50,1.02)	58 (55.2)	0.83 (0.48,1.43)		0.16
Type of HRT	No HRT	269 (44.9)	130 (45.3)	REF	167 (51.2)	REF	47 (46.1)	REF	0.38	0.14
	E only	112 (18.7)	47 (16.4)	0.80 (0.48,1.32)	45 (13.8)	0.57 (0.35,0.94)	24 (23.5)	0.98 (0.49,1.93)		
	P or E+P	208 (34.7)	104 (36.2)	1.04 (0.69,1.57)	108 (33.1)	0.76 (0.51,1.13)	30 (29.4)	0.70 (0.37,1.30)		
	T or E+T	10 (1.7)	6 (2.1)	0.76 (0.20,2.95)	6 (1.8)	0.94 (0.29,3.03)	1 (1.0)	0.45 (0.05,3.89)		0.11

Abbreviations: OC Oral contraceptive; HRT Hormone replacement therapy, E Estrogen; P Progesterone; T Testosterone; AD Adenomas; SP Serrated polyps

^a All models have been adjusted for age (<50, 50–60, 60–70, 70+ years), race (White, Non-white), education (High school or less, Some college, College degree+), body mass index (<25, 25–29, ≥30 kg/m²), smoking (Never, Former, Current), alcohol (continuous), anti-inflammatory drug use (Ever/never), history of previous colorectal endoscopy, and mutually adjusted for OC use and other reproductive factors

^b P for heterogeneity (wald test P value) from polytomous logistic regression models comparing polyp case subtypes to one another

Table 2

Associations between oral contraceptive use and other reproductive factors and risk of colorectal polyps by lesion severity, Group Health Cooperative, Seattle, Washington, 1998–2007^{a,b,c}

	Controls (n=615) n (%)	Non-advanced adenomas (n = 143)			Advanced adenomas (n=76)			Hyperplastic polyps (n = 232)			Sessile serrated polyps (n=94)			<i>P</i> _{HP vs SSP^d}
		Cases n (%)	Adjusted [†] OR(95% CI)	Cases n (%)	Adjusted [†] OR(95% CI)	Cases n (%)	Adjusted [†] OR(95% CI)	Cases n (%)	Adjusted [†] OR(95% CI)	Cases n (%)	Adjusted [†] OR(95% CI)	Cases n (%)	Adjusted [†] OR(95% CI)	
Ever use														0.09
	No	180 (29.3)		45 (31.5)	REF	26 (34.2)	REF	76 (32.8)	REF	18 (19.2)	REF			
	Yes	435 (70.7)		98 (68.5)	0.88 (0.53,1.45)	50 (65.8)	1.21 (0.62,2.35)	156 (67.3)	0.77 (0.50,1.18)	76 (80.9)	1.91 (0.90,4.05)			
Duration and recency (years)														0.08
0		189 (30.9)		47 (32.9)	REF	26 (36.1)	REF	76 (33.5)	REF	18 (19.2)	REF			
>0–<=5														
	Recency 0–25	28 (14.6)		8 (17.0)	0.89 (0.66,1.21)	1 (6.3)	1.29 (0.86,1.93)	4 (7.41)	0.92 (0.71,1.19)	2 (6.7)	1.64 (1.07,2.50)			
	Recency >25	164 (85.4)		39 (83.0)	0.88 (0.51,1.51)	15 (93.7)	1.11 (0.54,2.30)	50 (92.6)	0.86 (0.55,1.35)	28 (93.3)	1.83 (0.88,3.82)			
>5														
	Recency 0–25	115 (54.3)		20 (46.5)	0.81 (0.46,1.43)	13 (43.3)	1.94 (0.93,4.04)	40 (44.4)	0.91 (0.57,1.46)	23 (50.0)	2.39 (1.17,4.92)			
	Recency >25	95 (44.8)		23 (53.5)	0.80 (0.43,1.48)	17 (56.7)	1.67 (0.75,3.74)	50 (55.6)	0.85 (0.51,1.42)	23 (50.0)	2.68 (1.14,6.29)			
Others reproductive factors														
Age (years) at menarche														0.88
	<13	290 (47.6)		73 (51.1)	REF	30 (39.0)	REF	101 (43.9)	REF	44 (46.3)	REF			
	13	319 (52.4)		70 (49.0)	0.93 (0.57,1.52)	47 (61.0)	1.48 (0.80,2.74)	129 (56.1)	1.15 (0.77,1.71)	51 (53.7)	1.15 (0.64,2.06)			
Age (years) at first birth														0.17
	<25	260 (51.7)		49 (39.5)	REF	43 (61.4)	REF	87 (46.0)	REF	37 (48.1)	REF			
	25	243 (48.3)		75 (60.5)	2.15 (1.29,3.58)	27 (38.6)	0.70 (0.37,1.32)	102 (54.0)	1.42 (0.94,2.15)	40 (51.9)	0.80 (0.46,1.41)			
Parity														0.09
	0	62 (11.0)		7(5.3)	REF	0	REF	18 (8.7)	REF	5 (6.2)	REF			
	1+	504 (89.1)		124 (94.7)	1.42 (0.59,3.41)	70 (100)	–	189 (91.3)	0.96 (0.49,1.88)	76 (93.8)	3.78 (0.84,16.98)			
Menopausal status														0.09
	Pre	114 (18.5)		26 (18.3)	REF	8 (10.4)	REF	32 (13.8)	REF	20 (21.1)	REF			
	Post	501 (81.5)		116 (81.7)	0.74 (0.34,1.60)	69 (89.6)	3.22 (0.99,10.4)	200 (86.2)	0.92 (0.49,1.72)	75 (79.0)	0.60 (0.27,1.34)			
Age (years) at Menopause														0.51

	Controls (n=615) n (%)	Non-advanced adenomas (n = 143)			Advanced adenomas (n=76)			Hyperplastic polyps (n = 232)			Sessile serrated polyps (n=94)			$P_{HP \text{ vs SSP}}^d$
		Cases n (%)	Adjusted [†] OR(95% CI)	Cases n (%)	Adjusted [†] OR(95% CI)	Cases n (%)	Adjusted [†] OR(95% CI)	Cases n (%)	Adjusted [†] OR(95% CI)	Cases n (%)	Adjusted [†] OR(95% CI)	Cases n (%)	Adjusted [†] OR(95% CI)	
HRT	<50	224 (45.6)	44 (38.3)	REF	28 (41.2)	REF		94 (48.2)	REF	34 (45.3)	REF			0.09
	50	267 (54.4)	71 (61.7)	1.12 (0.68,1.84)	40 (58.8)	1.16 (0.63,2.15)		101 (51.8)	1.03 (0.69,1.54)	41 (54.7)	1.00 (0.55,1.81)			
Type of HRT	No	269 (44.4)	55 (39.9)	REF	38 (50.0)	REF		117 (50.9)	REF	45 (48.9)	REF			0.09
	Yes	337 (55.6)	83 (61.1)	1.40 (0.82,2.39)	38 (50.0)	0.81 (0.43,1.53)		113 (49.1)	0.68 (0.45,1.03)	47 (51.1)	0.74 (0.40,1.35)			
Type of HRT	No HRT	269 (44.9)	55 (40.4)	REF	38 (51.4)	REF		117 (52.0)	REF	45 (49.5)	REF			0.12
	E only	112 (18.7)	22 (16.2)	1.24 (0.62,2.46)	10 (13.5)	0.48 (0.19,1.20)		35 (15.6)	0.62 (0.36,1.08)	10 (11.0)	0.42 (0.16,1.07)			
	E + P	208 (34.7)	55 (40.4)	1.53 (0.86,2.74)	26 (35.1)	1.05 (0.52,2.09)		68 (30.2)	0.66 (0.42,1.04)	36 (39.6)	0.98 (0.52,1.84)			
	E + T	10 (1.7)	4 (2.9)	1.77 (0.43,7.38)	0	—		5 (2.2)	1.01 (0.28,3.65)	0 (0.0)	—			

Abbreviations: OC Oral contraceptive; HRT Hormone replacement therapy, E Estrogen; P Progesterone; T Testosterone; Non-adv Non-advanced adenomas; AD Advanced adenomas; HP Hyperplastic polyps; SSP Sessile serrated polyps

^aAnalyses by lesion severity excluded cases with synchronous presence of both adenomas and serrated polyps (n=105)

^bAdvanced adenomas were defined as tubular adenoma 10 mm in diameter or adenoma of any size with villous components or high-grade dysplasia

^cAll models have been adjusted for age (<50, 50–60, 60–70, 70+ years), race (White, Non-white), education (High school or less, Some college, College degree+), body mass index (<25, 25–29, >=30 kg/m²), smoking (Never, Former, Current), alcohol (continuous), anti-inflammatory drug use (Ever/never), history of previous colorectal endoscopy, and mutually adjusted for OC use and other reproductive factors

^dP for heterogeneity (wald test P value) from polytomous logistic regression models comparing polyp case subtypes to one another