American Journal of Epidemiology

Vol. 177, No. 7
DOI: 10.1093/aje/kws282
Advance Access publication:
March 3, 2013

Original Contribution

Differences in Epidemiologic Risk Factors for Colorectal Adenomas and Serrated Polyps by Lesion Severity and Anatomical Site

Andrea N. Burnett-Hartman*, Michael N. Passarelli, Scott V. Adams, Melissa P. Upton, Lee-Ching Zhu, John D. Potter, and Polly A. Newcomb

* Correspondence to Andrea N. Burnett-Hartman, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, M4-B402, Seattle, WA 98109 (e-mail: aburnett@fhcrc.org).

Initially submitted February 8, 2012; accepted for publication May 31, 2012.

Using a case-control design, we evaluated differences in risk factors for colorectal polyps according to histological type, anatomical site, and severity. Participants were enrollees in the Group Health Cooperative aged 20–79 years who underwent colonoscopy in Seattle, Washington, between 1998 and 2007 and comprised 628 adenoma cases, 594 serrated polyp cases, 247 cases with both types of polyps, and 1,037 polyp-free controls. Participants completed a structured interview, and polyps were evaluated via standardized pathology review. We used multivariable polytomous logistic regression to compare case groups with controls and with the other case groups. Factors for which the strength of the association varied significantly between adenomas and serrated polyps were sex ($P < 0.001$), use of estrogen-only postmenopausal hormone therapy ($P = 0.01$), and smoking status ($P < 0.001$). For lesion severity, prior endoscopy ($P < 0.001$) and age ($P = 0.05$) had significantly stronger associations with advanced adenomas than with nonadvanced adenomas; and higher education was positively correlated with sessile serrated polyps but not with other serrated polyps ($P = 0.02$). Statistically significant, site-specific associations were observed for current cigarette smoking ($P = 0.05$ among adenomas and $P < 0.001$ among serrated polyps), postmenopausal estrogen-only therapy ($P = 0.01$ among adenomas), and obesity ($P = 0.01$ among serrated polyps). These findings further illustrate the epidemiologic heterogeneity of colorectal neoplasia and may help elucidate carcinogenic mechanisms for distinct pathways.

adenoma; colorectal polyps; risk factors; serrated polyps

Abbreviations: BMI, body mass index; CI, confidence interval; CIMP, CpG island methylator phenotype; ICD-9, *International Classification of Diseases, Ninth Revision*; MSI, microsatellite instability; NSAID, nonsteroidal antiinflammatory drug; OR, odds ratio; SSP, sessile serrated polyp.

Colorectal cancer is a heterogeneous disease resulting from several pathways which have distinct precursor lesions (broadly termed polyps) and probably varying risk factors (1). Current polyp classification schemes group polyps by the colorectal cancer pathway with which they are associated (2). The most common pathway, termed the adenoma-carcinoma pathway, accounts for approximately 75% of colorectal cancer cases (3), and polyps in this pathway include tubular adenomas, tubulovillous adenomas, and villous adenomas. Adenomas are established precursor lesions for colorectal cancer (4), although few adenomas will progress to cancer (5). Adenomas ≥10 mm in diameter, with villous components, or with high-grade dysplasia are more likely to become malignant and are termed "advanced adenomas" (4, 6).

A separate pathway, termed the "serrated pathway," has been characterized over the last decade (7). Serrated polyps give rise to a subset of cancers that are generally characterized by CpG island methylator phenotype (CIMP) and often exhibit proto-oncogene B-Raf (*BRAF*) mutation and microsatellite instability (MSI) (8–11). Serrated polyps include hyperplastic polyps, sessile serrated polyps (SSPs), and traditional serrated adenomas (2). Traditional serrated adenomas exhibit marked dysplasia and have been recognized

as potential precursors for colorectal cancer (12–14). In contrast, other serrated polyps, like hyperplastic polyps, are not dysplastic and previously were considered to have no malignant potential (15). However, recently, a subset of hyperplastic polyps has been reclassified as SSPs. SSPs have a saw-toothed appearance at the surface and are characterized by a proliferation zone that has moved upwards away from the base of the colonic crypt, basal crypt distortion, altered crypt polarity, and dysmaturational features (16, 17). Now, consensus is emerging that SSPs may be an "advanced" lesion in the serrated pathway (18, 19). Because of the potential clinical importance of SSPs, some argue that these newly classified polyps should be referred to as sessile serrated adenomas (18, 19). However, to avoid confusion and reinforce the fact that these polyps are histologically distinct from conventional adenomas, we use the term SSP.

Previous studies have evaluated risk factors for serrated and adenomatous polyps; although these distinct entities share many risk factors, certain risk factors differ between polyp groups or appear to have stronger associations with one group than with the other (15, 20–24). In addition, anatomical subsites within the colon are associated with different cancer risk factors (25). These differences may provide insight into the unique mechanisms by which cancer initiation occurs at each anatomical site and in each pathway. Despite this, few studies of adenomas and serrated polyps have evaluated risk factors for each polyp group according to anatomical subsite, and only 1 small study of 90 SSPs specifically evaluated risk factors for SSPs (26). Therefore, we conducted a large case-control study of adenomas, serrated polyps, and polyp-free controls to evaluate differences in risk factors for distinct polyp subtypes.

MATERIALS AND METHODS

Study population

Participants were enrollees in the Group Health Cooperative, an integrated health-care provider in Washington State, aged 20–79 years who underwent an index colonoscopy for any indication between 1998 and 2007 and were diagnosed on the basis of clinical pathology with adenomas (*International Classification of Diseases, Ninth Revision* (ICD-9), code 211.3) and/or hyperplastic polyps (ICD-9 code 211.4) or who were polyp-free (controls). Eligible persons had been enrolled in the Group Health Cooperative for at least 3 years and had not undergone a prior colonoscopy within 1 year of the index colonoscopy. Participants with poor bowel preparation at the index colonoscopy and those with a prior or new diagnosis of colorectal cancer, familial colorectal cancer syndromes (such as familial adenomatous polyposis), or other colorectal disease were ineligible. A systematic sample of eligible colonoscopy patients was recruited, and approximately 75% agreed to participate and provided written informed consent. Based on medical records, persons who agreed to participate and those who refused study participation were similar with respect to age, sex, and colorectal polyp status. Study protocols were approved by the institutional review boards of the Group Health Cooperative and the Fred Hutchinson Cancer Research Center (Seattle, Washington). Additional details on the study population have been previously reported (24, 27–30).

Study questionnaire

Participants completed a structured questionnaire that elicited information on personal and family medical history, colorectal screening, height, weight, use of nonsteroidal antiinflammatory drugs (NSAIDs), hormone therapy, cigarette smoking, alcohol consumption, and physical activity. Attention was limited to experiences that had occurred at least 1 year before the index colonoscopy. Data collection took place in 2 phases, and similar questionnaires were used in both phases. During phase I, potential participants were identified from a listing of patients undergoing colonoscopy between September 1998 and March 2003 at the Group Health Cooperative gastroenterology clinic in Seattle, and participants were interviewed prior to colonoscopy. During phase II, which included patients receiving colonoscopy between December 2004 and September 2007, study participants were interviewed an average of 3–4 months following the index colonoscopy. Controls were participants who had no colorectal polyps identified during the index colonoscopy and were systematically sampled to reflect the age distribution (within a 5-year range) and calendar year of all polyp cases.

Standardized pathology review

Index colonoscopy biopsies were stored in formalin-fixed paraffin-embedded blocks. Sections were cut, placed onto slides, and stained with hematoxylin and eosin. Two study pathologists worked in tandem to conduct a standardized pathology review of polyp tissue slides and to reclassify a subset of polyps as SSPs using established protocols and classification criteria. Disagreements between study pathologists were reconciled through re-review by both pathologists and by referring to a standard training set of polyp slides. If a participant had at least 1 of the following types of polyps and no serrated polyps, he/she was classified as an adenoma case: tubular adenoma, tubulovillous adenoma, or villous adenoma. Cases with hyperplastic polyps, traditional serrated adenomas, or SSPs and no adenomas were classified as serrated polyp cases (31). SSPs were distinguished from other serrated polyps if they displayed exaggerated crypt serration, crypt dilatation, crypt branching, horizontal crypt extensions at the base, or other distortions of architectural organization and maturation that rendered them distinct from other serrated polyps (16).

Classification of lesion severity

Adenomas were classified as advanced if they 1) were ≥10 mm in diameter according to the endoscopic determination of polyp size or 2) had ≥20% villous components or high-grade dysplasia according to the standard pathology review. Among serrated polyps, SSPs were considered advanced lesions. Notably, traditional serrated adenomas are also a distinct type of advanced serrated polyp; however,

these were excluded from analyses of lesion severity because there were only 14 cases.

Classification of anatomical location

Anatomical location was abstracted from the electronic medical record. For site-specific analyses, proximal lesions were those proximal to the splenic flexure. Cases with one or more proximal polyps but no distal or rectal polyps were included in the proximal case group. Similarly, cases with one or more distal/rectal polyps but no proximal lesions were included in the distal/rectal case group.

Statistical analyses

Because we oversampled proximal cases to ensure adequate statistical power, all statistical analyses were weighted to reflect the distribution of polyps in the source population. Polytomous logistic regression was used to estimate adjusted odds ratios and 95% confidence intervals comparing each case group with the polyp-free control group (32). These same models were used to compare case groups with one another, and the Wald P value for the comparison between case groups was calculated for each risk factor.

Adjustment variables and variables of interest were selected a priori on the basis of prior studies that found an association between each factor and colorectal neoplasia. All regression analyses were adjusted for study phase, age, sex, education, body mass index (BMI; weight (kg)/height $(m)^2$), regular NSAID use (2 or more doses per week for 12 continuous months, with current use defined as 1 year prior to index colonoscopy), family history of colorectal cancer (1 or more first-degree relatives with colorectal cancer), previous endoscopy (sigmoidoscopy or colonoscopy 2 or more years prior to the study colonoscopy), postmenopausal hormone use, cigarette smoking status, usual alcohol consumption, and recreational physical activity. Approximately 7% ($n = 175$) of study participants were missing data on one or more of these exposure variables and were excluded from the analyses. Study participants excluded from analyses on the basis of missing data were not significantly different from other study participants with respect to colorectal polyp status or other variables of interest. Variables were categorized as shown in Table 1. All tables display weighted percentages and odds ratios but unweighted values for n. Weights were normalized to sum to the unweighted sample size. All statistical analyses were performed using SAS 9.2 (SAS Institute, Inc., Cary, North Carolina).

Exploratory analysis restricting the study population to participants without previous endoscopy was also conducted to determine whether the study results differed in this group.

RESULTS

Histological type

A total of 2,506 participants were included in analyses of risk factors by histological type, comprising 628 cases with adenomas only, 594 cases with serrated polyps only, 247 cases with synchronous adenomas and serrated polyps, and 1,037 colonoscopy-negative controls (Table 1). Compared with controls, adenoma cases were more likely to be older and obese and were less likely to be women, to use NSAIDs regularly, to participate in recreational physical activity, and to have undergone prior endoscopy. Cases with serrated polyps were more likely than controls to be older, to have higher education, and to be current smokers and, among women, less likely than controls to have used estrogen-only hormone therapy. Patients with synchronous adenomas and serrated polyps had risk factor profiles similar to those of the adenoma-only cases but were more likely than controls to report a family history of colorectal cancer. Other risk factors in Table 1 were not statistically significantly associated with any of the polyp groups.

Of all the risk factors evaluated, only the associations for sex, ever use of estrogen-only postmenopausal hormone therapy, and smoking status were statistically significantly different between adenoma cases and serrated polyp cases (for sex and smoking status, $P < 0.001$; for estrogen-only postmenopausal hormone therapy, $P = 0.01$). Women had a 40% (95% confidence interval (CI): 21, 55) decrease in the odds of adenoma compared with men, but the odds of serrated polyps were not associated with sex (odds ratio (OR) = 1.06, 95% CI: 0.80, 1.40). Among women, serrated polyps were inversely associated with estrogen-only postmenopausal hormone therapy (OR = 0.63, 95% CI: 0.44, 0.90), but adenomas were not (OR = 1.09, 95% CI: 0.77, 1.55). Current cigarette smoking had a stronger association with serrated polyps (OR = 3.0, 95% CI: 1.93, 4.66) than with adenomas (OR = 1.56, 95% CI: 0.99, 2.44).

Lesion severity

Of the 628 adenoma cases, 175 had 1 or more advanced adenomas (including 40 patients with synchronous advanced and nonadvanced adenomas), 286 had only nonadvanced adenomas, and 167 were excluded because of missing polyp-size data. For serrated polyps, SSP histology was considered a marker of an advanced lesion. Of the 594 serrated polyp cases, 149 had 1 or more SSPs (including 42 patients with synchronous SSPs and non-SSP serrated polyps), 431 had only hyperplastic polyps (i.e., nonadvanced serrated polyps), and 14 had traditional serrated adenomas and were excluded (Table 2).

For most risk factors, the strength of the association did not vary significantly by lesion severity. However, for adenomas, older age (≥70 years vs. < 50 years) was positively associated with advanced adenoma (OR = 3.78, 95% CI: 1.62, 8.80) but not with nonadvanced adenoma (OR = 1.25, 95% CI: 0.77, 2.27) (for nonadvanced vs. advanced adenomas, $P = 0.05$), and prior endoscopy was associated with decreased odds of advanced adenoma (OR = 0.39, 95% CI: 0.27, 0.56) but not with nonadvanced adenoma (OR = 0.99, 95% CI: 0.74, 1.32) (for nonadvanced vs. advanced adenomas, $P < 0.001$). Of all exposures examined, only education was differently associated with SSPs compared with nonadvanced serrated polyps ($P = 0.01$).

Table 1. Risk Factors for Adenomas, Serrated Polyps, and Both Polyp Types Concurrently (Polytomous Logistic Regression Analysis), Group Health Cooperative, Seattle, Washington, 1998–2007

	% of Controls (n = 1,037)	Colorectal Polyp Cases Compared With Controls									P Value[b] for Comparison Between Case Groups		
		Adenomas Only (n = 628)			Serrated Polyps Only (n = 594)			Adenomas + Serrated Polyps (n = 247)					
		%	OR[a]	95% CI	%	OR[a]	95% CI	%	OR[a]	95% CI	$P_{AD\ vs.\ SP}$	$P_{AD\ vs.\ AD+SP}$	$P_{SP\ vs.\ AD+SP}$
Age, years													
<50	10	6	1.00		6	1.00		5	1.00				
50–59	40	37	1.27	0.84, 1.93	48	1.87	1.20, 2.91	37	1.89	0.99, 3.63			
60–69	34	38	1.64	1.05, 2.56	32	1.65	1.02, 2.67	39	2.71	1.37, 5.34			
≥70	16	19	2.08	1.29, 3.37	14	2.02	1.20, 3.40	19	3.07	1.49, 6.34	0.08	0.50	0.04
Female sex	60	48	0.60	0.45, 0.79	56	1.06	0.80, 1.40	43	0.62	0.42, 0.90	<0.001	0.88	0.01
Race													
White/Caucasian	85	83	1.00		88	1.00		85	1.00				
Black/African-American	4	3	0.81	0.44, 1.50	2	0.49	0.23, 1.02	3	0.79	0.35, 1.76			
Asian/Pacific Islander	4	6	1.52	0.94, 2.48	3	0.75	0.41, 1.35	4	1.02	0.49, 2.14			
Other	7	8	1.16	0.77, 1.75	7	0.96	0.61, 1.49	8	0.80	0.43, 1.47	0.07	0.49	0.59
Education													
High school or less	15	16	1.00		12	1.00		17	1.00				
Some college	25	24	1.11	0.79, 1.58	27	1.55	1.06, 2.26	29	1.35	0.85, 2.15			
College graduation	25	26	1.25	0.88, 1.77	28	1.66	1.14, 2.43	22	1.07	0.65, 1.75			
Graduate or professional degree	35	34	1.25	0.89, 1.76	33	1.46	1.00, 2.12	32	1.15	0.72, 1.84	0.92	0.35	0.32
Body mass index[c]													
<25	41	33	1.00		38	1.00		28	1.00				
25–29	39	39	1.08	0.84, 1.39	37	0.97	0.75, 1.26	42	1.30	0.91, 1.86			
≥30	21	27	1.65	1.23, 2.20	25	1.26	0.93, 1.71	31	2.17	1.46, 3.22	0.10	0.18	0.01
Regular use of NSAIDs													
Never use	46	48	1.00		48	1.00		53	1.00				
Former use	9	8	0.80	0.54, 1.19	9	0.89	0.59, 1.33	8	0.65	0.38, 1.14			
Current use	45	44	0.75	0.60, 0.95	43	0.81	0.64, 1.03	40	0.58	0.42, 0.80	0.59	0.13	0.06
Family history of colorectal cancer	23	18	0.94	0.72, 1.23	24	1.21	0.93, 1.58	25	1.48	1.06, 2.08	0.10	0.01	0.27
Estrogen-only therapy[d]	26	23	1.09	0.77, 1.55	20	0.63	0.44, 0.90	18	0.82	0.50, 1.37	0.01	0.31	0.34
Estrogen-progestin therapy[d]	21	18	1.03	0.72, 1.47	18	1.09	0.76, 1.57	13	0.85	0.50, 1.44	0.79	0.50	0.39
Prior endoscopy[e]	54	50	0.73	0.58, 0.91	52	0.91	0.72, 1.15	54	0.82	0.60, 1.12	0.09	0.47	0.54

Table continues

Anatomical site

Analyses of risk factors by anatomical site included 212 cases with ≥1 proximal adenomas, 323 cases with ≥1 distal adenomas, 199 cases with ≥1 proximal serrated polyps, and 322 cases with ≥1 distal/rectal serrated polyps. Cases with both proximal and distal/rectal lesions and those missing information on polyp site were excluded from the site-specific analyses (n = 93 adenomas and n = 73 hyperplastic polyps) (Table 3).

For adenomas, only ever use of estrogen-only postmenopausal hormone therapy and smoking status had statistically significantly different associations between anatomical sites. Among women, ever use of estrogen-only postmenopausal hormone therapy was associated with an increased prevalence of adenomas in the proximal colon (OR = 1.68, 95% CI: 1.05, 2.71) but a statistically nonsignificant decrease in the prevalence of adenomas in the distal colon/rectum (OR = 0.78, 95% CI: 0.48, 1.27). Current smoking status was associated with increased odds of adenoma in the distal colon and rectum (OR = 2.19, 95% CI: 1.26, 3.78) but not in the proximal colon (OR = 0.83, 95% CI: 0.40, 1.73).

For serrated polyps, only BMI and smoking status had statistically significantly different associations between anatomical

Table 1. Continued

	% of Controls (*n* = 1,037)	Colorectal Polyp Cases Compared With Controls									*P* Value[b] for Comparison Between Case Groups		
		Adenomas Only (*n* = 628)			Serrated Polyps Only (*n* = 594)			Adenomas + Serrated Polyps (*n* = 247)					
		%	OR[a]	95% CI	%	OR[a]	95% CI	%	OR[a]	95% CI	$P_{AD\ vs.\ SP}$	$P_{AD\ vs.\ AD+SP}$	$P_{SP\ vs.\ AD+SP}$
Smoking status													
Never smoker	56	51	1.00		44	1.00		46	1.00				
Former smoker	39	41	1.16	0.92, 1.46	46	1.70	1.34, 2.16	42	1.26	0.92, 1.73			
Current smoker	5	7	1.56	0.99, 2.44	10	3.00	1.93, 4.66	12	2.82	1.65, 4.81	<0.001	0.07	0.33
Alcohol consumption, drinks/week													
<1	43	46	1.00		42	1.00		46	1.00				
1–<7	36	27	0.77	0.60, 1.00	34	0.92	0.71, 1.19	25	0.74	0.52, 1.06			
7–<14	11	13	1.24	0.88, 1.74	13	1.06	0.74, 1.53	14	1.22	0.77, 1.95			
≥14	9	14	1.30	0.91, 1.85	11	0.99	0.68, 1.47	16	1.34	0.85, 2.12	0.18	0.92	0.25
Recreational physical activity, hours/week													
0	9	13	1.00		10	1.00		12	1.00				
>0–<1	16	17	0.85	0.56, 1.29	20	1.30	0.83, 2.04	18	1.11	0.63, 1.94			
1–<2	27	31	0.87	0.59, 1.27	26	0.91	0.59, 1.39	29	0.92	0.54, 1.56			
2–<6	19	16	0.63	0.41, 0.95	20	1.06	0.68, 1.66	17	0.78	0.44, 1.39			
≥6	29	24	0.60	0.41, 0.89	24	0.83	0.54, 1.27	24	0.72	0.42, 1.23	0.23	0.69	0.58

Abbreviations: AD, adenomas; CI, confidence interval; NSAID, nonsteroidal antiinflammatory drug; OR, odds ratio; SP, serrated polyps.
[a] Results were mutually adjusted for study phase and all other factors in the table.
[b] Wald-test *P* value from polytomous logistic regression models comparing polyp case subtypes with one another.
[c] Weight (kg)/height $(m)^2$.
[d] Postmenopausal use among women only.
[e] Sigmoidoscopy or colonoscopy at least 2 years before index colonoscopy.

sites (for proximal tumors vs. distal/rectal tumors, $P = 0.01$ and $P < 0.001$, respectively). BMI ≥30 was associated with an increase in the odds of distal colon and rectal serrated polyps (OR = 1.48, 95% CI: 1.04, 2.11), but there was no association with proximal serrated polyps (OR = 0.71, 95% CI: 0.41, 1.22). Similarly, current smoking was associated with increased odds of distal and rectal serrated polyps (OR = 4.08, 95% CI: 2.51, 6.65) but not proximal serrated polyps (OR = 0.88, 95% CI: 0.32, 2.39).

Exploratory analyses

Exploratory analyses restricted to persons without prior endoscopy produced point estimates similar to those of the unrestricted analyses (data not shown). However, the association between advanced adenoma and increasing age was stronger in the analyses restricted to participants without prior endoscopy.

DISCUSSION

Our results suggest that although adenomas and serrated polyps share many risk factors, there are some clear differences in the factors associated with these distinct groups. In addition, differences according to anatomical site and lesion severity were apparent. Factors for which the strength of the association varied statistically significantly between adenomas and serrated polyps were sex, use of estrogen-only postmenopausal hormone therapy, and smoking status. For adenomas, associations with age and with prior endoscopy varied by lesion severity, and associations with use of estrogen-only postmenopausal hormone therapy and with smoking status varied by anatomical site. For serrated polyps, the association with education varied by lesion severity, and the associations with BMI and with smoking status varied by anatomical site. Each risk factor for which differences between polyp subtypes were observed is discussed briefly below.

Sex

Prior study results vary with respect to sex differences between cases with adenomas and cases with serrated polyps. Some studies evaluating both polyp types found that, compared with women, men had higher risks of adenomas and of serrated polyps (15, 21, 33); other studies observed higher risks of adenomas in men than in women

Table 2. Risk Factors for Adenomas or Serrated Polyps by Lesion Severity[a] (Polytomous Logistic Regression Analysis), Group Health Cooperative, Seattle, Washington, 1998–2007

	% of Controls (n = 1,037)	Adenomas						*P* Value[d] (Nonadvanced vs. Advanced)	Serrated Polyps						*P* Value[d] (Hyperplastic Polyps vs. SSPs)
		Nonadvanced (n = 286)			Advanced[b] (n = 175)				Hyperplastic Polyps (n = 431)			SSPs (n = 149)			
		%	OR[c]	95% CI	%	OR[c]	95% CI		%	OR[c]	95% CI	%	OR[c]	95% CI	
Age, years															
<50	10	9	1.00		5	1.00			6	1.00		7	1.00		
50–59	40	35	0.80	0.48, 1.33	37	1.91	0.88, 4.11		48	1.85	1.14, 3.02	44	1.63	0.72, 3.67	
60–69	34	38	0.99	0.57, 1.71	37	2.82	1.26, 6.29		31	1.47	0.87, 2.49	36	2.09	0.87, 5.00	
≥70	16	18	1.25	0.77, 2.27	21	3.78	1.62, 8.80	0.05	14	1.89	1.07, 3.35	13	2.19	0.83, 5.76	0.28
Female sex	60	51	0.62	0.43, 0.90	44	0.50	0.32, 0.79	0.44	53	0.96	0.70, 1.30	63	1.37	0.82, 2.28	0.20
Race															
White/Caucasian	85	84	1.00		83	1.00			89	1.00		86	1.00		
Black/African-American	4	2	0.57	0.22, 1.47	5	1.01	0.41, 2.49		3	0.59	0.28, 1.27	1	0.21	0.02, 2.14	
Asian/Pacific Islander	4	5	1.46	0.77, 2.75	7	1.80	0.87, 3.71		3	0.62	0.31, 1.25	5	1.33	0.54, 3.27	
Other	7	9	1.32	0.80, 2.19	6	0.90	0.44, 1.82	0.53	6	0.82	0.50, 1.35	8	1.14	0.54, 2.44	0.28
Education															
High school or less	15	15	1.00		18	1.00			13	1.00		6	1.00		
Some college	25	23	1.08	0.68, 1.72	27	1.02	0.60, 1.75		28	1.52	1.02, 2.28	25	2.60	1.08, 6.24	
College graduation	25	27	1.30	0.82, 2.05	22	0.90	0.51, 1.57		28	1.59	1.05, 2.40	30	3.35	1.41, 7.99	
Graduate or professional degree	35	34	1.22	0.78, 1.91	34	1.08	0.63, 1.84	0.59	31	1.26	0.84, 1.90	39	3.63	1.55, 8.54	0.01
Body mass index[e]															
<25	41	34	1.00		33	1.00			36	1.00		46	1.00		
25–29	39	41	1.18	0.85, 1.63	38	0.96	0.63, 1.44		38	1.02	0.77, 1.36	32	0.77	0.48, 1.23	
≥30	21	25	1.55	1.06, 2.27	29	1.74	1.11, 2.73	0.71	26	1.35	0.97, 1.88	21	1.13	0.66, 1.94	0.43
Regular use of NSAIDs															
Never use	46	51	1.00		51	1.00			47	1.00		51	1.00		
Former use	9	6	0.60	0.34, 1.04	10	0.95	0.53, 1.72		7	0.76	0.48, 1.20	14	1.39	0.75, 2.56	
Current use	45	43	0.71	0.52, 0.95	39	0.65	0.45, 0.94	0.71	46	0.90	0.69, 1.16	35	0.64	0.41, 1.01	0.19
Family history of colorectal cancer	23	18	0.87	0.61, 1.24	15	0.86	0.54, 1.36	0.96	23	1.14	0.85, 1.53	28	1.54	0.97, 2.43	0.23
Estrogen-only therapy[f]	26	25	1.23	0.77, 1.96	19	0.86	0.47, 1.56	0.31	19	0.69	0.46, 1.03	23	0.55	0.30, 1.04	0.52
Estrogen-progestin therapy[f]	21	21	1.14	0.72, 1.81	15	1.12	0.61, 2.05	0.95	16	0.92	0.61, 1.38	24	1.45	0.78, 2.69	0.19
Prior endoscopy[g]	54	56	0.99	0.74, 1.32	36	0.39	0.27, 0.56	<0.001	52	0.91	0.70, 1.17	55	1.01	0.66, 1.56	0.61
Smoking status															
Never smoker	56	50	1.00		49	1.00			42	1.00		52	1.00		
Former smoker	39	44	1.23	0.91, 1.65	44	1.25	0.87, 1.81		48	1.87	1.44, 2.42	38	1.34	0.87, 2.07	
Current smoker	5	6	1.39	0.76, 2.54	8	1.41	0.70, 2.86	0.96	10	3.08	1.91, 4.96	11	2.91	1.36, 6.21	0.40

Table continues

Table 2. Continued

	% of Controls ($n = 1,037$)	Adenomas						*P* Value[d] (Nonadvanced vs. Advanced)	Serrated Polyps						*P* Value[d] (Hyperplastic Polyps vs. SSPs)
		Nonadvanced ($n = 286$)			Advanced[b] ($n = 175$)				Hyperplastic Polyps ($n = 431$)			SSPs ($n = 149$)			
		%	OR[c]	95% CI	%	OR[c]	95% CI		%	OR[c]	95% CI	%	OR[c]	95% CI	
Alcohol consumption, drinks/week															
<1	43	45	1.00		45	1.00			43	1.00		39	1.00		
1–<7	36	28	0.82	0.59, 1.15	29	0.81	0.54, 1.23		32	0.90	0.68, 1.20	38	1.05	0.66, 1.67	
7–<14	11	13	1.14	0.73, 1.78	15	1.46	0.87, 2.46		13	1.09	0.73, 1.62	12	1.11	0.57, 2.15	
≥14	9	14	1.33	0.84, 2.08	12	1.00	0.56, 1.79	0.72	12	0.96	0.63, 1.46	10	1.09	0.54, 2.20	0.74
Recreational physical activity, hours/week															
0	9	10	1.00		15	1.00			10	1.00		9	1.00		
>0–<1	16	16	1.02	0.57, 1.81	16	0.60	0.32, 1.14		19	1.34	0.82, 2.19	18	1.04	0.45, 2.39	
1–<2	27	32	1.12	0.66, 1.87	29	0.64	0.36, 1.12		27	0.97	0.61, 1.54	24	0.79	0.36, 1.73	
2–<6	19	19	0.98	0.56, 1.71	11	0.35	0.18, 0.68		20	1.09	0.67, 1.78	19	0.97	0.43, 2.21	
≥6	29	23	0.75	0.44, 1.27	29	0.52	0.29, 0.91	0.36	23	0.82	0.51, 1.31	30	0.86	0.39, 1.87	0.56

Abbreviations: CI, confidence interval; NSAID, nonsteroidal antiinflammatory drug; OR, odds ratio; SSP, sessile serrated polyp.

[a] Analyses by lesion severity excluded cases with synchronous adenomas and serrated polyps ($n = 247$), tubular adenoma cases with missing information on polyp size ($n = 167$), and cases with traditional serrated adenoma ($n = 14$).

[b] Defined as tubular adenoma ≥10 mm in diameter or adenoma of any size with villous components or high-grade dysplasia.

[c] Mutually adjusted for study phase and all other factors in the table.

[d] Wald-test *P* value from polytomous logistic regression models comparing subtypes of polyp cases with one another.

[e] Weight (kg)/height $(m)^2$.

[f] Postmenopausal use among women only.

[g] Sigmoidoscopy or colonoscopy at least 2 years before index colonoscopy.

Table 3. Risk Factors for Adenomas or Serrated Polyps by Anatomical Location[a] (Polytomous Logistic Regression Analysis), Group Health Cooperative, Seattle, Washington, 1998–2007

	% of Controls (n = 1,037)	Adenomas						*P* Value[c] (Proximal vs. Distal/Rectal)	Serrated Polyps						*P* Value[c] (Proximal vs. Distal/Rectal)
		Proximal (n = 212)			Distal/Rectal (n = 323)				Proximal (n = 199)			Distal/Rectal (n = 322)			
		%	OR[b]	95% CI	%	OR[b]	95% CI		%	OR[b]	95% CI	%	OR[b]	95% CI	
Age, years															
<50	10	6	1.00		7	1.00			7	1.00		7	1.00		
50–59	40	38	1.25	0.69, 2.30	42	1.43	0.82, 2.50		47	1.49	0.70, 3.14	49	1.96	1.16, 3.32	
60–69	34	39	1.46	0.77, 2.79	34	1.52	0.84, 2.76		36	1.72	0.77, 3.85	29	1.46	0.83, 2.60	
≥70	16	16	1.68	0.83, 3.39	17	2.01	1.06, 3.83	0.86	10	1.51	0.60, 3.81	16	2.19	1.19, 4.03	0.95
Female sex	60	57	0.71	0.48, 1.05	47	0.59	0.41, 0.85	0.45	60	1.05	0.66, 1.67	55	1.09	0.79, 1.52	0.87
Race															
White/Caucasian	85	84	1.00		84	1.00			89	1.00		87	1.00		
Black/African-American	4	3	1.13	0.52, 2.50	3	0.55	0.21, 1.42		1	0.17	0.02, 1.71	3	0.63	0.29, 1.39	
Asian/Pacific Islander	4	3	0.96	0.44, 2.06	8	1.88	1.05, 3.36		4	0.88	0.35, 2.13	3	0.71	0.34, 1.48	
Other	7	10	1.34	0.79, 2.27	6	0.85	0.47, 1.57	0.11	6	0.91	0.43, 1.94	7	1.05	0.63, 1.75	0.88
Education															
High school or less	15	18	1.00		13	1.00			8	1.00		14	1.00		
Some college	25	20	0.86	0.53, 1.40	25	1.44	0.88, 2.36		24	1.82	0.89, 3.71	29	1.53	1.00, 2.35	
College graduation	25	26	1.23	0.77, 1.99	29	1.66	1.01, 2.72		32	2.22	1.10, 4.47	27	1.55	1.00, 2.41	
Graduate or professional degree	35	36	1.34	0.85, 2.13	34	1.44	0.88, 2.35	0.56	37	1.83	0.91, 3.67	30	1.30	0.84, 2.01	0.41
Body mass index[d]															
<25	41	32	1.00		36	1.00			49	1.00		34	1.00		
25–29	39	38	1.14	0.80, 1.63	42	1.04	0.75, 1.45		35	0.79	0.53, 1.20	39	1.10	0.81, 1.51	
≥30	21	30	1.92	1.30, 2.85	22	1.23	0.83, 1.82	0.07	16	0.71	0.41, 1.22	27	1.48	1.04, 2.11	0.01
Regular use of NSAIDs															
Never use	46	45	1.00		51	1.00			51	1.00		48	1.00		
Former use	9	8	0.75	0.42, 1.32	9	0.92	0.56, 1.53		12	1.21	0.67, 2.19	6	0.62	0.37, 1.06	
Current use	45	47	0.83	0.61, 1.15	40	0.70	0.51, 0.96	0.39	37	0.68	0.46, 1.03	46	0.90	0.68, 1.19	0.25
Family history of colorectal cancer	23	20	1.13	0.79, 1.62	18	0.92	0.64, 1.33	0.39	23	1.13	0.72, 1.78	25	1.23	0.90, 1.68	0.74
Estrogen-only therapy[e]	26	31	1.68	1.05, 2.71	19	0.78	0.48, 1.27	0.01	24	0.79	0.44, 1.43	17	0.51	0.33, 0.78	0.20
Estrogen-progestin therapy[e]	21	23	0.98	0.61, 1.57	17	1.24	0.76, 2.03	0.45	22	1.11	0.61, 2.02	16	1.13	0.73, 1.74	0.96
Prior endoscopy[f]	54	50	0.73	0.53, 1.00	46	0.70	0.52, 0.94	0.83	49	0.76	0.52, 1.12	53	0.97	0.74, 1.27	0.28
Smoking status															
Never smoker	56	56	1.00		51	1.00			58	1.00		38	1.00		
Former smoker	39	40	1.05	0.76, 1.43	40	1.19	0.87, 1.62		38	1.16	0.79, 1.71	49	2.07	1.56, 2.75	
Current smoker	5	4	0.83	0.40, 1.73	9	2.19	1.26, 3.78	0.05	4	0.88	0.32, 2.39	12	4.08	2.51, 6.65	<0.001

Table continues

Table 3. Continued

	% of Controls ($n = 1,037$)	Adenomas						P Value[c] (Proximal vs. Distal/Rectal)	Serrated Polyps						P Value[c] (Proximal vs. Distal/Rectal)
		Proximal ($n = 212$)			Distal/Rectal ($n = 323$)				Proximal ($n = 199$)			Distal/Rectal ($n = 322$)			
		%	OR[b]	95% CI	%	OR[b]	95% CI		%	OR[b]	95% CI	%	OR[b]	95% CI	
Alcohol consumption, drinks/week															
<1	43	50	1.00		44	1.00			38	1.00		45	1.00		
1–<7	36	24	0.63	0.44, 0.90	29	0.84	0.60, 1.18		40	1.10	0.72, 1.67	30	0.80	0.59, 1.09	
7–<14	11	13	1.20	0.76, 1.90	14	1.26	0.80, 1.98		13	1.12	0.62, 2.03	12	0.95	0.61, 1.46	
≥14	9	12	1.19	0.73, 1.94	13	1.16	0.72, 1.86	0.95	9	1.06	0.55, 2.05	13	0.98	0.63, 1.52	0.65
Recreational physical activity, hours/week															
0	9	11	1.00		13	1.00			7	1.00		11	1.00		
>0–<1	16	16	0.94	0.52, 1.70	17	0.82	0.48, 1.42		15	1.10	0.47, 2.56	23	1.41	0.85, 2.36	
1–<2	27	32	1.04	0.61, 1.79	30	0.76	0.46, 1.25		29	1.22	0.56, 2.64	26	0.83	0.51, 1.35	
2–<6	19	16	0.75	0.42, 1.36	15	0.55	0.32, 0.97		21	1.21	0.54, 2.72	19	1.02	0.61, 1.70	
≥6	29	24	0.74	0.42, 1.28	25	0.58	0.35, 0.96	0.49	28	1.00	0.46, 2.19	22	0.72	0.44, 1.18	0.20

Abbreviations: BMI, body mass index; CI, confidence interval; NSAID, nonsteroidal antiinflammatory drug; OR, odds ratio.

[a] Analyses by anatomical site excluded cases with synchronous adenomas and serrated polyps ($n = 247$), cases with both proximal and distal/rectal lesions, and cases with missing information on anatomical subsite ($n = 93$ adenomas and $n = 73$ hyperplastic polyps).

[b] Mutually adjusted for study phase and all other factors in the table.

[c] Wald-test P value from polytomous logistic regression models comparing subtypes of polyp cases with one another.

[d] Weight (kg)/height $(m)^2$.

[e] Postmenopausal use among women only.

[f] Sigmoidoscopy or colonoscopy at least 2 years before index colonoscopy.

and no association between sex and serrated polyps (22, 23), similar to our findings. Sex differences between polyp types could be mediated by hormones or by differences between men and women in the distribution of unknown, pathway-specific colorectal cancer risk factors.

Estrogen-only postmenopausal hormone therapy

The inverse association between postmenopausal hormone therapy and colorectal cancer is well-documented (34–37), but the link between colorectal polyps and hormone therapy is less clear. Similar to our results, results from the Polyp Prevention Trial suggested that the association between polyps and postmenopausal hormone therapy varied according to anatomical site; distal adenomas were associated with a decreased risk (OR = 0.56, 95% CI: 0.32, 1.00), and proximal adenomas were associated with a statistically nonsignificant increased risk (OR = 1.39, 95% CI: 0.85, 2.26) (38). In a separate study population, Morimoto et al. (15) evaluated adenomas and hyperplastic polyps and reported a 30% decrease in the odds of hyperplastic polyps and a 50% decrease in the odds of adenomas associated with postmenopausal hormone therapy; associations by site were not reported. Our results suggest that the association between colorectal polyps and postmenopausal hormone therapy depends on polyp type and polyp location. Furthermore, results from a recent study suggest heterogeneity in the association between postmenopausal hormone use and colorectal cancer according to molecular tumor characteristics (39). These findings warrant further investigation and may provide insight into the mechanisms by which estrogen may inhibit colorectal cancer.

Cigarette smoking

The finding that cigarette smoking has a stronger association with serrated polyps than it does with adenomatous polyps is supported by several prior studies (15, 20–22, 40) and was reinforced in the present study. Furthermore, colorectal cancer analyses suggest that the carcinomas most likely to arise from the serrated pathway—that is, cancers that are *BRAF*-mutated, CIMP-high, and MSI-high—are specifically associated with cigarette smoking (41–43). These cancers occur most often in the proximal colon (44, 45), yet our results suggest a stronger association between distal/rectal colorectal polyps and cigarette smoking. Several other studies, including a meta-analysis of the association between colorectal cancer and cigarette smoking, also suggest a specific association with distal/rectal neoplasia (33, 46, 47). However, in the Iowa Women's Health Study, a large cohort study of over 37,000 women, Limsui et al. (43) recently reported an association between proximal colon cancer and cigarette smoking. Further research is needed to determine mechanisms by which cigarette smoking plays a role in the serrated pathway and to explore site-specific associations.

Age

The risk of colorectal cancer increases with increasing age, peaking between ages 60 and 79 years (48). Therefore, it is not surprising that our results suggested that older age has a stronger association with advanced adenomas than with nonadvanced adenomas. However, the age distribution of people with adenomas was not statistically significantly different from the age distribution of those with serrated polyps. This is in contrast to prior studies suggesting that people with adenomas tend to be older than those with serrated polyps (15, 33).

Prior endoscopy

Colorectal screening endoscopy is associated with a decreased risk of colorectal cancer incidence and mortality (49–54). During endoscopy, detection and removal of adenomas, particularly advanced adenomas, can avert progression to malignant disease (55). Because most serrated polyps, including hyperplastic polyps and SSPs, were traditionally not considered targets of screening endoscopies, identification of these polyps would not have prompted changes in patient management or increased colorectal cancer surveillance. Therefore, our results indicating that prior endoscopy is associated with decreased odds of specifically advanced adenomas may be a consequence of screening guidelines that target polyps in the adenoma-carcinoma pathway (56).

Education

Our results suggest that increasing education was associated with increased odds of SSPs, but there was no association between education and other polyps. This was an unexpected finding. Prior studies of colon neoplasia and indicators of socioeconomic status are mixed. Generally, studies of European populations report a positive (57–60) or null (61) association between increasing socioeconomic status and colon cancer risk. However, recent studies of North American populations have tended to find inverse associations between colon cancer and increasing socioeconomic status, potentially mediated by differences in screening (62–64). If the positive association between SSPs and increasing education is replicated, future studies should evaluate whether there is differential detection of SSPs among persons with higher educational levels because of better compliance with bowel preparation procedures, or whether lifestyle factors associated with high socioeconomic status are important to the etiology and progression of lesions in the serrated pathway.

Body mass index

A recent meta-analysis of the association between colorectal cancer and BMI suggested an increase in the risk of colorectal cancer with increasing BMI (65). Studies of adenomas also tend to support a positive association between risk of colorectal neoplasia and increasing BMI (66–69). However, the association between serrated polyps and BMI is less clear, with some studies suggesting a positive association (26, 70) and others finding no statistically significant association between serrated polyps and BMI (71, 72). Furthermore, prior studies suggest that sex may modify the association between colorectal neoplasia and BMI (15, 65, 73).

Additionally, the association may vary by anatomical site (65). With results similar to ours, Wallace et al. (70) reported that BMI was associated with an increased risk of serrated polyps specifically in the distal colon and rectum. The association between BMI and colorectal neoplasia is complex, and further investigation is needed to determine the role of BMI in the serrated pathway.

Risk factors for synchronous adenomas and serrated polyps

Patients with synchronous adenomas and serrated polyps had stronger associations with age, obesity, NSAID use, and family history of colorectal cancer than those with only 1 type of polyp. Because these are all well-established factors associated with colorectal cancer risk (35), it may be that persons with both types of polyps represent a high-risk group for the development of colorectal cancer. This thesis is supported by prior studies (74, 75). Additional longitudinal studies are needed to determine whether persons with synchronous adenomas and serrated polyps are at high risk for the development of advanced colorectal neoplasia.

Limitations

To our knowledge, this is the largest and most comprehensive study to have evaluated differences in risk factors between distinct colorectal polyp subgroups. Although we included a large number of participants, the necessity of classifying cases according to multiple features resulted in smaller subgroups for analyses and may have reduced our power to detect associations. At the same time, the large number of comparisons made in our analysis may have resulted in some spurious associations. Despite these statistical challenges, the ability to connect risk factors to specific subsets of polyps can provide insight into mechanisms for cancer initiation and progression in different carcinogenic pathways. In addition, our study results may have been subject to differential recall bias; however, for case-case comparisons of polyp subtypes, recall-related misclassification of exposures would likely have been nondifferential (76). We also did not have detailed information on prior colorectal polyp diagnoses. If prior polyps were removed during an earlier endoscopy, odds ratio estimates may have been attenuated; however, exploratory analyses restricted to persons without prior endoscopy produced findings similar to those of the unrestricted analyses. Finally, serrated polyps, particularly SSPs, are difficult to visualize, and it is likely that serrated polyps were missed in some controls and other polyp cases (77). This would have resulted in bias towards the null, so reported associations for serrated polyps may be conservative.

Conclusions

Overall, the results of our study further illustrate the heterogeneous nature of colorectal cancer and its precursor lesions. Furthermore, our analyses of SSPs suggest that these newly characterized lesions have a strong association with smoking, similar to hyperplastic polyps, and that SSPs may also be associated with higher levels of education. By connecting risk factors with specific subgroups of polyps, our results may help identify high-risk groups for colorectal cancer surveillance and open new avenues for understanding mechanisms that are unique to different colorectal cancer pathways.

ACKNOWLEDGMENTS

Author affiliations: Department of Cancer Prevention, Fred Hutchinson Cancer Research Center, Seattle, Washington (Andrea N. Burnett-Hartman, Michael N. Passarelli, Scott V. Adams, John D. Potter, Polly A. Newcomb); Department of Epidemiology, School of Public Health, University of Washington, Seattle, Washington (Andrea N. Burnett-Hartman, Michael N. Passarelli, John D. Potter, Polly A. Newcomb); Pathology Department, School of Medicine, University of Washington, Seattle, Washington (Melissa P. Upton); and Group Health Cooperative, Seattle, Washington (Lee-Ching Zhu).

This work was supported by the National Cancer Institute (grant P01 CA074184 to Drs. John D. Potter and Polly A. Newcomb and grant R01 CA097325 to Dr. Polly A. Newcomb) and the National Center for Advancing Translational Sciences (grant KL2 TR000421 to Dr. Andrea Burnett-Hartman).

We thank the late Dr. Jeremy Jass for his many contributions in the early stages of this research and Dr. Elena Kuo for project management.

This research was presented at the 2012 American Association for Cancer Research Annual Meeting, Chicago, Illinois, March 31–April 4, 2012.

Conflict of interest: none declared.

REFERENCES

1. Jass JR. Molecular heterogeneity of colorectal cancer: implications for cancer control. *Surg Oncol*. 2007; 16(suppl 1):S7–S9.
2. Jass JR. Classification of colorectal cancer based on correlation of clinical, morphological and molecular features. *Histopathology*. 2007;50(1):113–130.
3. Kinzler KW, Vogelstein B. Lessons from hereditary colorectal cancer. *Cell*. 1996;87(2):159–170.
4. Winawer SJ, Zauber AG, Ho MN, et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. *N Engl J Med*. 1993; 329(27):1977–1981.
5. Brenner H, Chang-Claude J, Seiler CM, et al. Case-control study supports extension of surveillance interval after colonoscopic polypectomy to at least 5 yr. *Am J Gastroenterol*. 2007;102(8):1739–1744.
6. Lieberman DA, Weiss DG, Harford WV, et al. Five-year colon surveillance after screening colonoscopy. *Gastroenterology*. 2007;133(4):1077–1085.
7. Leggett B, Whitehall V. Role of the serrated pathway in colorectal cancer pathogenesis. *Gastroenterology*. 2010; 138(6):2088–2100.

8. Jass JR. Hyperplastic polyps of the colorectum—innocent or guilty? *Dis Colon Rectum*. 2001;44(2):163–166.
9. Hawkins NJ, Ward RL. Sporadic colorectal cancers with microsatellite instability and their possible origin in hyperplastic polyps and serrated adenomas. *J Natl Cancer Inst*. 2001;93(17):1307–1313.
10. Kambara T, Simms LA, Whitehall VL, et al. *BRAF* mutation is associated with DNA methylation in serrated polyps and cancers of the colorectum. *Gut*. 2004;53(8):1137–1144.
11. Vaughn CP, Wilson AR, Samowitz WS. Quantitative evaluation of CpG island methylation in hyperplastic polyps. *Mod Pathol*. 2010;23(1):151–156.
12. Longacre TA, Fenoglio-Preiser CM. Mixed hyperplastic adenomatous polyps/serrated adenomas. A distinct form of colorectal neoplasia. *Am J Surg Pathol*. 1990;14(6): 524–537.
13. Makinen MJ, George SM, Jernvall P, et al. Colorectal carcinoma associated with serrated adenoma—prevalence, histological features, and prognosis. *J Pathol*. 2001; 193(3):286–294.
14. Jass JR. Hyperplastic-like polyps as precursors of microsatellite-unstable colorectal cancer. *Am J Clin Pathol*. 2003;119(6):773–775.
15. Morimoto LM, Newcomb PA, Ulrich CM, et al. Risk factors for hyperplastic and adenomatous polyps: evidence for malignant potential? *Cancer Epidemiol Biomarkers Prev*. 2002;11(10):1012–1018.
16. Torlakovic E, Skovlund E, Snover DC, et al. Morphologic reappraisal of serrated colorectal polyps. *Am J Surg Pathol*. 2003;27(1):65–81.
17. Higuchi T, Sugihara K, Jass JR. Demographic and pathological characteristics of serrated polyps of colorectum. *Histopathology*. 2005;47(1):32–40.
18. Huang CS, Farraye FA, Yang S, et al. The clinical significance of serrated polyps. *Am J Gastroenterol*. 2011; 106(2):229–240.
19. Snover DC. Update on the serrated pathway to colorectal carcinoma. *Hum Pathol*. 2011;42(1):1–10.
20. Ji BT, Weissfeld JL, Chow WH, et al. Tobacco smoking and colorectal hyperplastic and adenomatous polyps. *Cancer Epidemiol Biomarkers Prev*. 2006;15(5):897–901.
21. Shrubsole MJ, Wu H, Ness RM, et al. Alcohol drinking, cigarette smoking, and risk of colorectal adenomatous and hyperplastic polyps. *Am J Epidemiol*. 2008;167(9): 1050–1058.
22. Hassan C, Pickhardt PJ, Marmo R, et al. Impact of lifestyle factors on colorectal polyp detection in the screening setting. *Dis Colon Rectum*. 2010;53(9):1328–1333.
23. Hoffmeister M, Schmitz S, Karmrodt E, et al. Male sex and smoking have a larger impact on the prevalence of colorectal neoplasia than family history of colorectal cancer. *Clin Gastroenterol Hepatol*. 2010;8(10):870–876.
24. Adams SV, Newcomb PA, Burnett-Hartman AN, et al. Circulating 25-hydroxyvitamin-D and risk of colorectal adenomas and hyperplastic polyps. *Nutr Cancer*. 2011; 63(3):319–326.
25. Iacopetta B. Are there two sides to colorectal cancer? *Int J Cancer*. 2002;101(5):403–408.
26. Anderson JC, Rangasamy P, Rustagi T, et al. Risk factors for sessile serrated adenomas. *J Clin Gastroenterol*. 2011; 45(8):694–699.
27. Chia VM, Newcomb PA, Lampe JW, et al. Leptin concentrations, leptin receptor polymorphisms, and colorectal adenoma risk. *Cancer Epidemiol Biomarkers Prev*. 2007; 16(12):2697–2703.
28. Burnett-Hartman AN, Newcomb PA, Mandelson MT, et al. No evidence for human papillomavirus in the etiology of colorectal polyps. *Cancer Epidemiol Biomarkers Prev*. 2011;20(10):2288–2297.
29. Wernli KJ, Newcomb PA, Wang Y, et al. Body size, IGF and growth hormone polymorphisms, and colorectal adenomas and hyperplastic polyps. *Growth Horm IGF Res*. 2010; 20(4):305–309.
30. Burnett-Hartman AN, Newcomb PA, Mandelson MT, et al. Colorectal polyp type and the association with charred meat consumption, smoking, and microsomal epoxide hydrolase polymorphisms. *Nutr Cancer*. 2011;63(4):583–592.
31. Chung SM, Chen YT, Panczykowski A, et al. Serrated polyps with "intermediate features" of sessile serrated polyp and microvesicular hyperplastic polyp: a practical approach to the classification of nondysplastic serrated polyps. *Am J Surg Pathol*. 2008;32(3):407–412.
32. Ananth CV, Kleinbaum DG. Regression models for ordinal responses: a review of methods and applications. *Int J Epidemiol*. 1997;26(6):1323–1333.
33. Erhardt JG, Kreichgauer HP, Meisner C, et al. Alcohol, cigarette smoking, dietary factors and the risk of colorectal adenomas and hyperplastic polyps—a case control study. *Eur J Nutr*. 2002;41(1):35–43.
34. 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):574–582.
35. Potter JD. Colorectal cancer: molecules and populations. *J Natl Cancer Inst*. 1999;91(11):916–932.
36. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288(3):321–333.
37. Potter JD, Bostick RM, Grandits GA, et al. Hormone replacement therapy is associated with lower risk of adenomatous polyps of the large bowel: the Minnesota Cancer Prevention Research Unit Case-Control Study. *Cancer Epidemiol Biomarkers Prev*. 1996;5(10):779–784.
38. Woodson K, Lanza E, Tangrea JA, et al. Hormone replacement therapy and colorectal adenoma recurrence among women in the Polyp Prevention Trial. *J Natl Cancer Inst*. 2001;93(23):1799–1805.
39. Limsui D, Vierkant RA, Tillmans LS, et al. Postmenopausal hormone therapy and colorectal cancer risk by molecularly defined subtypes among older women. *Gut*. 2012;61(9): 1299–1305.
40. Potter JD, Bigler J, Fosdick L, et al. Colorectal adenomatous and hyperplastic polyps: smoking and *N*-acetyltransferase 2 polymorphisms. *Cancer Epidemiol Biomarkers Prev*. 1999; 8(1):69–75.
41. Slattery ML, Curtin K, Anderson K, et al. Associations between cigarette smoking, lifestyle factors, and microsatellite instability in colon tumors. *J Natl Cancer Inst*. 2000;92(22):1831–1836.
42. Samowitz WS, Albertsen H, Sweeney C, et al. Association of smoking, CpG island methylator phenotype, and V600E *BRAF* mutations in colon cancer. *J Natl Cancer Inst*. 2006; 98(23):1731–1738.
43. Limsui D, Vierkant RA, Tillmans LS, et al. Cigarette smoking and colorectal cancer risk by molecularly defined subtypes. *J Natl Cancer Inst*. 2010;102(14):1012–1022.
44. Barault L, Charon-Barra C, Jooste V, et al. Hypermethylator phenotype in sporadic colon cancer: study on a population-based series of 582 cases. *Cancer Res*. 2008;68(20):8541–8546.
45. Nosho K, Irahara N, Shima K, et al. Comprehensive biostatistical analysis of CpG island methylator phenotype in

colorectal cancer using a large population-based sample. *PLoS One*. 2008;3(11):e3698.
46. Liang PS, Chen TY, Giovannucci E. Cigarette smoking and colorectal cancer incidence and mortality: systematic review and meta-analysis. *Int J Cancer*. 2009;124(10):2406–2415.
47. Poynter JN, Haile RW, Siegmund KD, et al. Associations between smoking, alcohol consumption, and colorectal cancer, overall and by tumor microsatellite instability status. *Cancer Epidemiol Biomarkers Prev*. 2009;18(10):2745–2750.
48. Murphy G, Devesa SS, Cross AJ, et al. Sex disparities in colorectal cancer incidence by anatomic subsite, race and age. *Int J Cancer*. 2011;128(7):1668–1675.
49. Kavanagh AM, Giovannucci EL, Fuchs CS, et al. Screening endoscopy and risk of colorectal cancer in United States men. *Cancer Causes Control*. 1998;9(4):455–462.
50. Newcomb PA, Norfleet RG, Storer BE, et al. Screening sigmoidoscopy and colorectal cancer mortality. *J Natl Cancer Inst*. 1992;84(20):1572–1575.
51. Selby JV. A case-control study of screening sigmoidoscopy and mortality from colorectal cancer. *New Engl J Med*. 1992;326(10):653–657.
52. Atkin WS, Edwards R, Kralj-Hans I, et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. *Lancet*. 2010; 375(9726):1624–1633.
53. Brenner H, Hoffmeister M, Arndt V, et al. Protection from right- and left-sided colorectal neoplasms after colonoscopy: population-based study. *J Natl Cancer Inst*. 2010;102(2):89–95.
54. Baxter NN, Warren JL, Barrett MJ, et al. Association between colonoscopy and colorectal cancer mortality in a U.S. cohort according to site of cancer and colonoscopist specialty. *J Clin Oncol*. 2012;30(21):2664–2669.
55. Winawer SJ, Zauber AG. The advanced adenoma as the primary target of screening. *Gastrointest Endosc Clin N Am*. 2002;12(1):1–9.
56. Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *Gastroenterology*. 2008;134(5):1570–1595.
57. Tavani A, Fioretti F, Franceschi S, et al. Education, socioeconomic status and risk of cancer of the colon and rectum. *Int J Epidemiol*. 1999;28(3):380–385.
58. van Loon AJ, van den Brandt PA, Golbohm RA. Socioeconomic status and colon cancer incidence: a prospective cohort study. *Br J Cancer*. 1995;71(4):882–887.
59. Weiderpass E, Pukkala E. Time trends in socioeconomic differences in incidence rates of cancers of gastro-intestinal tract in Finland. *BMC Gastroenterol*. 2006;6:41.
60. Leufkens AM, Van Duijnhoven FJ, Boshuizen HC, et al. Educational level and risk of colorectal cancer in EPIC with specific reference to tumor location. *Int J Cancer*. 2012; 130(3):622–630.
61. Whynes DK, Frew EJ, Manghan CM, et al. Colorectal cancer, screening and survival: the influence of socio-economic deprivation. *Public Health*. 2003;117(6):389–395.
62. Mackillop WJ, Zhang-Salomons J, Boyd CJ, et al. Associations between community income and cancer incidence in Canada and the United States. *Cancer*. 2000; 89(4):901–912.
63. Palmer RC, Schneider EC. Social disparities across the continuum of colorectal cancer: a systematic review. *Cancer Causes Control*. 2005;16(1):55–61.
64. Mouw T, Koster A, Wright ME, et al. Education and risk of cancer in a large cohort of men and women in the United States. *PLoS One*. 2008;3(11):e3639.
65. Ning Y, Wang L, Giovannucci EL. A quantitative analysis of body mass index and colorectal cancer: findings from 56 observational studies. *Obes Rev*. 2010; 11(1):19–30.
66. Neugut AI, Lee WC, Garbowski GC, et al. Obesity and colorectal adenomatous polyps. *J Natl Cancer Inst*. 1991; 83(5):359–361.
67. Bird CL, Frankl HD, Lee ER, et al. Obesity, weight gain, large weight changes, and adenomatous polyps of the left colon and rectum. *Am J Epidemiol*. 1998;147(7): 670–680.
68. Almendingen K, Hofstad B, Vatn MH. Does high body fatness increase the risk of presence and growth of colorectal adenomas followed up in situ for 3 years? *Am J Gastroenterol*. 2001;96(7):2238–2246.
69. Jacobs ET, Martinez ME, Alberts DS, et al. Association between body size and colorectal adenoma recurrence. *Clin Gastroenterol Hepatol*. 2007;5(8):982–990.
70. Wallace K, Grau MV, Ahnen D, et al. The association of lifestyle and dietary factors with the risk for serrated polyps of the colorectum. *Cancer Epidemiol Biomark Prev*. 2009; 18(8):2310–2317.
71. Lieberman DA, Prindiville S, Weiss DG, et al. Risk factors for advanced colonic neoplasia and hyperplastic polyps in asymptomatic individuals. *JAMA*. 2003;290(22): 2959–2967.
72. Omata F, Brown WR, Tokuda Y, et al. Modifiable risk factors for colorectal neoplasms and hyperplastic polyps. *Intern Med*. 2009;48(3):123–128.
73. Moghaddam AA, Woodward M, Huxley R. Obesity and risk of colorectal cancer: a meta-analysis of 31 studies with 70,000 events. *Cancer Epidemiol Biomarkers Prev*. 2007; 16(12):2533–2547.
74. Kellokumpu I, Kyllonen L. Multiple adenomas and synchronous hyperplastic polyps as predictors of metachronous colorectal adenomas. *Ann Chir Gynaecol*. 1991;80(1):30–35.
75. Costedio M, Church J. Pathways of carcinogenesis are reflected in patterns of polyp pathology in patients screened for colorectal cancer. *Dis Colon Rectum*. 2011;54(10): 1224–1228.
76. Coughlin SS. Recall bias in epidemiologic studies. *J Clin Epidemiol*. 1990;43(1):87–91.
77. Kahi CJ, Hewett DG, Norton DL, et al. Prevalence and variable detection of proximal colon serrated polyps during screening colonoscopy. *Clin Gastroenterol Hepatol*. 2011; 9(1):42–46.