

# Influence of Race and Sex on Prevalence and Recurrence of Colon Polyps

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**Background:** African Americans (AAs) have a higher incidence of colorectal cancer (CRC) and present with more advanced disease compared with whites. An increased prevalence of polyps has also been noted in men regardless of race. We sought to validate these observations and assess whether the increase in CRC in AAs is owing to polyp prevalence or incidence differences vs other factors.

**Methods:** A detailed endoscopy database was used to identify patients undergoing their first outpatient colonoscopy for screening or minimal symptoms from January 26, 1996, through September 19, 2006. Multivariate models were constructed to predict prevalence and incidence of polyps.

**Results:** Of individuals undergoing colonoscopies, 3732 met our study criteria (41.3% male and 29.2% AA); 761 (20.4%) had polyps. Male sex (odds ratio, 1.67; 95% confidence interval [CI], 1.39-2.02) independently pre-

dicted polyps but race did not. A random 100-patient sample showed no significant racial difference in the proportion of adenomatous polyps among those with polyps (68.0% white vs 60.0% AA,  $P = .60$ ). Of 57 patients who had a follow-up colonoscopy a median of 3.6 years after their index procedure, 18 (31.6%) were male, 7 (12.3%) were AA, and 19 (33.3%) were older than 65 years. Thirty-five (61.4%) had a polyp recurrence. Adjusting for time to subsequent colonoscopy and other confounders, neither male sex (adjusted hazard ratio, 0.98; 95% CI, 0.43-2.21) nor race (1.89; 0.68-5.24) significantly predicted incidence of recurrent polyps.

**Conclusions:** In this series, male sex but not race predicted prevalence of polyps. Incidence of recurrent polyps was higher in neither male patients nor AAs, but the power of this analysis is limited.

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**E**ACH YEAR APPROXIMATELY 150 000 Americans are diagnosed as having colorectal cancer (CRC) and more than 50 000 will die of it, ranking CRC second only to lung cancer in causing US cancer deaths.<sup>1</sup> Screening of average-risk populations has been shown to reduce the incidence and mortality of CRC,

## See Invited Commentary at end of article

but access and participation in screening have been problematic.<sup>2-4</sup> Although significantly improved from previous years, only 60% of Americans older than 50 years received an accepted form of CRC screening in 2006, which is significantly less than for breast, cervical, or prostate cancers.<sup>5-7</sup>

Although overall CRC mortality rates have improved, the improvement for African Americans (AAs) has been more modest.<sup>8</sup> African Americans appear to still have a 19% higher incidence and 39% higher mortality compared with other racial groups in the United States.<sup>9</sup> This disparity may be ow-

ing to unequal participation in screening programs<sup>10</sup>; however, some recent data suggest that this may not be true,<sup>5-7,11,12</sup> and receipt of cancer care after diagnosis may also have racial differences.<sup>13</sup> Other factors, such as differences in age at onset,<sup>14,15</sup> tumor locations,<sup>16-18</sup> and even molecular and genetic differences,<sup>19,20</sup> may exist and may play a role. However, it is not clear where along the adenoma-carcinoma sequence AAs' excess cancer risk lies: adenoma prevalence at a given age, adenoma incidence or recurrence, or adenoma progression to cancer. The polyp differences have been studied much less than the cancer differences, and the former is the primary target of clearing colonoscopies. Polyp (age-corrected) prevalence and incidence (or recurrence) after polypectomy are the main data points needed for making changes to screening or surveillance in AAs; screening earlier and more often simply because cancer or cancer-related death is more common might not be the best response.

Male sex also has been reported as a significant risk factor for polyps,<sup>21-24</sup> and age-related CRC risk and mortality are higher in men.<sup>1,8</sup> Current screening guidelines are not sex specific.<sup>17,25-27</sup> The aim of this study was

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to determine whether race and sex independently influenced colon polyp prevalence, location, or rates of polyp recurrence (incidence), using a detailed endoscopy database spanning more than a decade.

## METHODS

### PATIENTS AND DATA COLLECTED

Institutional review board approval was obtained. We analyzed data contained in GI Trac (Akron Systems, Charleston, South Carolina), an endoscopy database containing prospectively entered demographic characteristics, and clinical and procedural details for study participants undergoing endoscopic procedures at the Medical University of South Carolina beginning on February 8, 1994. We included data from January 26, 1996, through September 19, 2006, on patients with minimal or no symptoms who presented for initial outpatient colonoscopy for screening or for a colonoscopy because of a positive fecal occult blood test (FOBT) result, with or without minimal symptoms. Exclusion criteria included the presence of significant symptoms (such as diarrhea, abdominal pain, and nonminor bleeding), defined as anything other than "minor red bleeding" or "altered bowel habit"; known anemia; prior colonoscopy and/or polypectomy; known current or prior CRC or polyps; inflammatory bowel disease; and prior colonic surgery. Age, race, sex, indications and symptoms, disease risk factors (such as family history), American Society of Anesthesiologists comorbidity index, procedure times, colonic preparation quality (rated as poor, incomplete, good, or excellent endoscopic views), procedure toleration, findings (including polyp number, location, and method and success in removal), and success in reaching the cecum were analyzed in the data set.

Data from the database were merged with race and pathology report results from the Oacis (Emergis Inc, Ottawa, Ontario, Canada) electronic medical record application. Pathology reports were then manually reviewed on a random selection of patients; patients with polyps were coded as having at least 1 adenoma or having no adenomas (ie, all hyperplastic).

### DATA ANALYSIS

#### Polyp Prevalence and the Effect of Race and Sex

After univariate analyses, a multivariate logistic regression model was created (SAS statistical software, version 9.1.3; SAS Institute Inc, Cary, North Carolina) by stepwise model building to obtain the age-adjusted odds ratios (ORs) of having colorectal polyps on colonoscopy for AA race and male sex, adjusted for other potential confounders, including American Society of Anesthesiologists class, positive FOBT listed as the procedure's indication, family history of CRC listed as the procedure's indication, quality of bowel preparation (dichotomized as poor or incomplete vs good or excellent), procedure time, procedure toleration (poor vs well or very well), and depth of endoscope insertion (cecum or terminal ileum vs other).

#### Polyp Incidence After Polypectomy and the Effect of Race and Sex

After univariate analyses and testing for the constant hazard assumption, a Cox proportional hazards model was constructed to assess the adjusted hazard ratios of race and sex (corrected for selected potential confounders) on polyp-free survival in the subgroup that had a polyp found on their initial colonoscopy (a small proportion of patients with polyps were eligible for subsequent [surveillance] colonoscopy within the

span of the 10-year database), adjusting for different times to subsequent colonoscopy and other potential confounders. The constant hazards assumption was tested.

### Polyp Histologic Analysis

To be able to better generalize the conclusions for our models regarding predictors of polyps to predicting adenomas, we sought to confirm the assumption that the proportion of patients with polyps that had adenomas was similar among races. Sample size calculations revealed that for a reasonable precision (95% confidence interval [CI] width of 30% [ie, ranging from 15% higher to 15% lower than the point estimate]) for the proportion of patients with adenomas (assumed to be approximately 65%),<sup>28-31</sup> we needed to manually review 100 (50 from each racial group) pathology reports.

## RESULTS

### POLYP PREVALENCE AND THE EFFECT OF RACE AND SEX

More than 17 000 colonoscopies were listed in the database, and 3732 individuals undergoing colonoscopies met our study criteria for this period; 2910 (78.0%) had no symptoms. Colonoscopy was complete to the cecum in 3680 (98.6%). The average patient age was 61.8 years, 1541 (41.3%) of the patients were men, and 1090 (29.2%) were AA; 403 (10.8%) had a positive family history of CRC listed as the procedure's indication, and 224 (6.0%) were referred because of a positive FOBT result (**Table 1**).

Polyps were found and removed in 761 patients (20.4%). Logistic regression modeling showed that polyp prevalence was predicted by an age older than 65 years (OR, 1.35; 95% CI, 1.12-1.63) and male sex (1.67; 1.39-2.02) but not race (1.04; 0.85-1.28). Nearly identical point estimates and CIs resulted when age was modeled as a continuous variable (eg, OR of 1.64 for male sex). Male sex (OR, 1.78; 95% CI, 1.37-2.31) but not race was also found to be independently predictive of right-sided polyps. The presence of 3 polyps or more was independently predicted by male sex (OR, 2.82; 95% CI, 1.83-4.33) and a positive FOBT result (1.99; 1.001-3.96) but not race.

### POLYP INCIDENCE AFTER POLYPECTOMY AND THE EFFECT OF RACE AND SEX

Approximately 60% of the 761 patients with polyps had adenomas (approximately 450), and nearly half of these (approximately 225) would have been recruited in the first half of the decade-spanning database and would therefore have been eligible for a 5-year follow-up colonoscopy within the span of the 10-year database; two-thirds (approximately 150) of these would have still been young and healthy enough at the time of surveillance to continue with the screening program 5 years later. Fifty-seven patients (approximately 40% of those anticipated to have been eligible) had a follow-up colonoscopy at the Medical University of South Carolina a median of 3.6 years after their index procedure: 18 (31.6%) were male, 7 (12.3%) were AA, and 19 (33.3%) were older than 65

**Table 1. Characteristics of Adults Undergoing Screening Colonoscopy**

Characteristic	All, No. (%) (N=3732)	No. (%) by Race			No. (%) by Sex		
		Black (n=1090)	White (n=2575)	P Value	Male (n=1541)	Female (n=2191)	P Value
Sex							
Male	1541 (41.3)	339 (31.1)	1074 (41.7)	<.001	...	...	...
Female	2191 (58.7)	751 (68.9)	1501 (58.3)		...	...	...
Age >65 y	1340 (35.9)	399 (36.6)	919 (35.7)	.60	629 (40.8)	730 (33.3)	<.001
Race							
White	2575 (69.0)	...	...	...	1148 (74.5)	1450 (66.2)	<.001
African American	1090 (29.2)	...	...	...	354 (23.0)	710 (32.4)	
Other	67 (1.8)	...	...	...	39 (2.5)	31 (1.4)	
Family history of colorectal cancer	403 (10.8)	59 (5.4)	340 (13.2)	<.001	120 (7.8)	278 (12.7)	<.001
Fecal occult blood test result positive	224 (6.0)	65 (6.0)	152 (5.9)	>.99	99 (6.4)	127 (5.8)	.50
Poor or incomplete endoscopy view	176 (4.7)	58 (5.3)	116 (4.5)	.30	62 (4.0)	114 (5.2)	.10
Poor tolerance	22 (0.6)	4 (0.3)	21 (0.8)	.10	3 (0.2)	22 (1.0)	>.99
Cecal intubation	3680 (98.6)	1067 (97.9)	2544 (98.8)	>.99	1521 (98.7)	2156 (98.4)	.50
Polyps found	761 (20.4)	213 (19.5)	533 (20.7)	.40	416 (27.0)	368 (16.8)	<.001
Right-sided polyps	343 (9.2)	101 (9.2)	232 (9.0)	.80	204 (13.2)	151 (6.9)	<.001
≥3 Polyps	134 (3.6)	36 (3.3)	93 (3.6)	.70	88 (5.7)	46 (2.1)	<.001

years. Thirty-five (61.4%) had a polyp recurrence (71.4% of AAs and 60.0% of whites). Using the Cox proportional hazards model, neither male sex (adjusted hazard ratio, 0.98; 95% CI, 0.43-2.21) nor race (1.89; 0.68-5.24) significantly predicted incidence of polyps after polypectomy (**Table 2**).

**POLYP HISTOLOGIC REVIEW**

A manual review of a random sample of pathology reports (n=100) from the patients with polyps in this cohort was performed. It revealed no significant racial difference in the proportion of patients with polyps who had at least 1 adenomatous polyp (68.0% of whites vs 60.0% of AAs; difference, 8.0%; 95% CI, -10.7% to 26.7%; P=.60).

**COMMENT**

Colon cancer-related mortality does not necessarily correlate with polyp prevalence and incidence because there are other major factors that determine age and location of cancers at time of diagnosis and their related survival. Knowledge of polyp prevalence and race, stratified by race and sex, is needed to make sound decisions regarding sex or race stratifications (if any) in colon cancer or polyp screening guidelines regarding starting age or frequency of surveillance, especially in average-risk individuals. In 2005, the American College of Gastroenterology recommended that AAs begin screening 5 years earlier than whites, at the age of 45 years, and that sigmoidoscopy be abandoned for screening in AAs,<sup>25</sup> with no sex-stratified guidelines proposed by any of the societies; the other gastroenterology and cancer societies have not included race-based stratifications in their guidelines. However, in this study, males had a higher age-corrected prevalence (a nearly 3-fold increase in likelihood of having multiple polyps) although not a higher incidence of recurrent polyps. African American race was predictive of neither polyp prevalence nor incidence. There are inherent obstacles to getting larger num-

**Table 2. Summary of Cox Proportional Hazards Model Examining the Influence of Race and Sex on Polyp-Free Survival**

Characteristic	aHR (95% CI)
Sex	0.98 (0.43-2.21)
Race	1.89 (0.68-5.24)
Age less than 65 years	0.84 (0.36-1.95)
Family history of colorectal cancer	1.34 (0.39-4.59)
Endoscopy view	1.28 (0.37-4.46)

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval.

bers for the incidence analysis (only a proportion of patients who have undergone polypectomy have adenomas, and only some of these patients are eligible for surveillance within the follow-up period, are still within the recommended age limits at surveillance, and comply with surveillance). These limit the power of the incidence analysis and raise the possibility of type II error in this regard (ie, true predictors of recurrent polyps being labeled “nonsignificant”).

This study adds to the body of evidence that men are at higher risk for colonic dysplasia and neoplasia. Age-related cancer risk varies markedly by sex. Analysis of Surveillance Epidemiology and End Results data reveals that women ages 50 to 59 years have a 2.9% absolute risk compared with 4.7% for men.<sup>32</sup> A large Polish study<sup>21</sup> in 2006 noted consistently lower numbers needed to screen to detect advanced neoplasia in men compared with similarly aged women in 3 consecutive age brackets. In fact, the numbers needed to screen for men aged 50 to 54 years was similar to those for women aged 60 to 66 years. Imperiale et al<sup>33</sup> showed that among patients in Indiana *without* an adenoma at baseline, the adenoma incidence could be higher in men (OR, 1.88), but there were no adjustments made in that analysis for the variable time delay until their follow-up colonoscopy (which may have been longer in men);

patients with polyps at baseline were excluded and the influence of race was not explored. The large surveillance study of VA patients by Lieberman et al<sup>34</sup> was predominantly male, so it did not allow sex-stratified conclusions, and race was not analyzed. On the basis of these and similar studies, Lieberman et al<sup>32</sup> and others<sup>35</sup> have proposed that sex be included among the risk factors already in use for CRC risk stratification.

Men in our study were also more likely than women to have right-sided polyps. Two previous studies<sup>23,24</sup> have reported that women were more likely to have proximal lesions, but others have found that, when correcting for age and distal findings, men may even have a greater risk of right-sided advanced neoplasia.<sup>22</sup>

For cancer, the literature suggests that there may be a rightward or proximal shift of colon cancer in AAs.<sup>16-18</sup> For polyps, a few uncontrolled studies<sup>36,37</sup> in AAs have suggested that polyps were more common and more likely right-sided. However, factors such as differences in indication or different rates of unreported symptoms could potentially account for this apparent shift in polyp location or frequency, when a control group is not studied and when one does not correct for other confounders. A Clinical Outcomes Research Initiative (CORI) database study<sup>38</sup> seemed to confirm the tendency of AAs to have more right-sided polyps (OR, 1.3), without any pathology report data; however, as in our study, they found no difference in overall prevalence or total polyp number between the races. A second CORI study<sup>39</sup> found an increase in polyps larger than 9 mm in AAs, but the magnitude of increased risk was small (OR, 1.1). In our data set, an exact polyp size was too inconsistently recorded to be used in multivariate models. However, of those recorded, the proportion with polyps larger than 9 mm was slightly higher in AAs compared with whites. This difference did not reach significance (29.3% vs 23.4%;  $P = .068$ ), but the power of this analysis was limited. The CORI study<sup>39</sup> also reported a more clinically important OR (1.6) for AA women specifically; but in our data set, there was no statistically significant interaction between sex and race, and the absolute difference in the proportion of patients with polyps larger than 9 mm in AA men vs AA women was less than 1%. Last, another potential explanation for higher polyp prevalence in AA patients in some studies is that the AAs screened in these studies may have been more “selected” than the whites because of variable access to colonoscopy; however, in our study, this is likely less of a factor because the proportion of AAs in our prevalence cohort closely mirrors that of South Carolina (29.5% AAs) and Charleston County (34.5% AAs).<sup>40</sup>

African Americans are presenting with slightly more advanced cancers (25% had stage IV disease at diagnosis vs 20% of whites)<sup>9,15,16,41-44</sup> and have their cancers diagnosed at a slightly younger age (mean age, 66.4 vs 69.7 years for whites).<sup>15</sup> In a large California study, 10.6% of AAs with colon cancer were younger than 50 years when their cancers were diagnosed compared with only 5.5% of whites.<sup>14</sup> It is difficult to explain this finding without there being a difference in polyp occurrence or recurrence, but a significantly higher polyp prevalence and incidence do not seem to serve as the explanation; per-

haps the rate of malignant transformation of adenomas is different (this theory has not been studied) or other advanced features are more common. However, even larger polyps (>9 mm) only appear to be marginally more common in AAs,<sup>39</sup> if at all. Differences in mortality are more complex to explain because we know that even among patients with the same stage disease (II or III), mortality rates appear higher for AAs,<sup>45</sup> and there may be other issues related to access to surgical and oncologic care and preferences for care playing a role.

Patients with minimal symptoms or positive FOBT results were included in the analyses. The main reason was that, especially 10 years ago, categorizing patients according to their minimal symptom (such as remote hemorrhoidal blood on the toilet paper) or noting a FOBT result (sometimes poorly obtained, such as a digitally derived stool sample) as the “indication” was commonplace. There was a disincentive to label these procedures as “screening,” which was not reimbursable for most patients. In fact, this practice may have been differentially applied among different races and insurance coverage plans, and excluding all these patients would have introduced other biases. Our group has shown, in a more recent data set of more than 3000 patients, that even listed indications, such as bleeding, diarrhea, and pain, did not predict a higher chance of finding a polyp.<sup>46</sup> Although FOBT did not predict polyps in this analysis, it is not surprising that a real-life FOBT does not necessarily predict polyps with the same power as did the strict-protocol FOBT in the prospective trials.

Other limitations of our study include the lack of histopathological data for every patient. However, in our pathology report subset, a significant difference in polyp histologic breakdown was not seen. This finding implies that the relationship of sex and race with polyps, given that the percentage of adenomas stays constant, should mirror that of sex and race with adenomas. However, having a pathology report on every patient would have been ideal because a small difference in the proportion of adenomas (eg, 10.0%-15.0% relative change [60.0% vs 68.0%]) could still be present. Unfortunately, because only a small proportion of patients have advanced adenomas, the random sample would not have had the power to detect small absolute differences in rates of advanced histologic features between races and sexes (advanced features were only noted in the latter half of our subsample [ $n = 50$ ] and were present in 28.0%-32.0% across the racial groups, which is comparable to the 22.1% [5.2 to 23.5] noted in the study by Barclay et al<sup>47</sup>). Also, because of the time span of the data set, more recently proposed quality metrics, such as withdrawal time, were not recorded in the data set. The overall adenoma detection rate for this database’s colonoscopies is admittedly relatively low but lands between that of the slow (>25%) and fast (<15%) withdrawal time of colonoscopies reported in the literature.<sup>47</sup>

In conclusion, the racial differences in CRC morbidity and mortality may not be due to significant differences in adenoma formation and recurrence. For the latter, additional study is required from other large longitudinal databases or large prospective studies to help clarify whether the lack of predictors in incidence are owing to type II error. Our data do not support a race-

stratified starting age for screening; more data are needed to make any recommendations about stratified surveillance intervals, but our limited data do not support stratification at this time. Important sex differences in age-adjusted polyp prevalence (and possibly location), however, do exist in our population and in others. As such, men may benefit from earlier screening. Again, data are more limited with respect to incidence or recurrence of polyps after polypectomy in men, but probably men would not benefit from a shorter surveillance interval, given their apparently similar incidence of recurrent polyps compared with women.

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**INVITED COMMENTARY**

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## Moving Toward Personalization of Colorectal Cancer Screening

Widespread use of colonoscopy has achieved a modicum of success, as evidenced by a slight decrease in CRC rates. However, a recent National Institutes of Health consensus panel noted that screening rates are still suboptimal, and thus colorectal malignant neoplasms remain the second leading cause of cancer deaths.<sup>1</sup> Moreover, performing colonoscopy on the entire average-risk population (approximately 100 million Americans 50 years or older) is remarkably inefficient, with a low yield of clinically significant neoplasia (approximately 5%-6%).<sup>2</sup> Thus, from a cancer prevention perspective, most screening colonoscopies are unproductive.

It is of paramount importance to better target patients who are likely to harbor neoplasia and thereby allow more of the population to benefit from our finite endoscopic capacity. Moreover, better targeting would avoid unnecessary cost, discomfort, and potential complications from performing colonoscopies in many patients who are neoplasia free.<sup>2</sup> Currently, age and family history are the major determinants of the CRC screening regimen. However, numerous other well-established risk factors are generally not addressed, including race, sex, body mass index, exercise level, diet, tobacco use, alcohol use, presence of diabetes, use of nonsteroidal anti-inflammatory drugs (NSAIDs) and/or aspirin, and other risk factors.<sup>3</sup>

Adding to the complexity of risk factor analysis, especially with respect to sex and race, is that CRC is made up of several distinct molecular genotypes. Women have an increased propensity to develop CRCs with high microsatellite instability (MSI-H) that exhibit diffuse genomic instability and phenotypic consequences including predilection for the proximal colon, lymphocytic infiltrate, and a stage-for-stage better prognosis.<sup>2</sup> With regard to race, the biological data are equivocal, although there is some evidence of increased MSI-H status or distinct mutational events such as *BRAF* mutations in African Americans.<sup>4</sup>

Less is known about the association between gender and adenomas or race and adenomas—relationships that are important, given that identification and removal of adenomas form the basis of the colonoscopic CRC prevention strategy. In this issue of the *Archives*, Penn and colleagues review their endoscopy database records from between 1996 and 2006 and identify 3732 patients for analysis. Their main findings suggest that age and sex are risk factors for polyps, with odds ratios of 1.35 for age older than 65 years and 1.67 for male sex. However, race was not associated with polyps (OR for African Americans, 1.04).

This important study highlights many issues related to colonoscopic database review. The use of “polyps” as an end point is imprecise, and these investigators were able to histopathologically sample only 100 of the 761 cases involving polyps to derive the estimate that 60% of polyps were actually adenomas and thus relevant to colon carcinogenesis. Moreover, adenoma size, a key determinant of neoplastic behavior, can be difficult to accurately estimate or may not be recorded at all; adenoma size was apparently not recorded in this study’s database. Thus, the relevance of these findings to CRC risk is somewhat tenuous. Finally, interpreting colonoscopic studies is inextricably linked with quality measures such as adenoma detection. Examination by colonoscopy misses approximately 20% to 25% of all adenomas (1%-2% of advanced lesions),<sup>5</sup> and the data in the study by Penn et al suggest a substantial miss rate in their series, as evidenced by an adenoma detection rate of approximately 12%, half the expected rate.

In the context of the literature, the racial data reported by Penn et al contrast with the findings of a large (n=80 061) multicenter database review, which showed that the relative risk for polyps larger than 9 mm was 1.16 for black men and 1.62 for black women.<sup>6</sup> However, recent data have demonstrated that much of the racial disparities related to CRC may be a consequence of limited health care access rather than