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The association of age and race and the risk of large bowel polyps

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Abstract

Background—Blacks have a higher incidence of colorectal cancer (CRC) and a younger age at diagnosis compared to Whites. Few studies have investigated racial differences in risk of metachronous adenomas and serrated polyps whether this risk differs by polyp characteristics or age of patient.

Methods—We analyzed data pooled from three placebo-controlled adenoma chemoprevention trials to explore racial differences in the risk of large bowel polyps in patients 50 and > 50 years of age. Using generalized linear regression, we estimated risk ratios (RR) and 95% confidence intervals (CI) as measures of the association between race and risk of one or more adenomas or serrated polyps after randomization.

Results—Among the 2605 subjects who completed at least one follow-up exam, blacks 50 years of age had a higher risk of any conventional adenoma (RR 1.70, 95% CI 0.99–2.92) and advanced neoplasms (RR 4.05, 95% CI 1.43–11.46) and a non-significantly lower risk of serrated polyps (RR 0.75 (95% CI 0.34–1.62) compared to whites. Among patients > 50 years there was no racial difference in risk of adenomas (RR 1.08, 95% CI 0.92–1.27) or advanced neoplasms (RR

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1.05, 95% CI 0.71–1.56)). However, blacks had a significantly lower risk of serrated polyps (RR 0.65, 95% CI 0.49–0.87) than whites.

Conclusions—Our results demonstrate a higher risk of metachronous adenomas in blacks compared to whites at younger ages.

Impact—Our results suggest that the racial disparity in CRC incidence may be due to an excess of neoplasia in younger blacks.

Keywords

colorectal; adenoma; serrated polyps; race; early-onset

Introduction

Colorectal cancer (CRC) is the second most common malignancy in the US among both men and women (1). The CRC incidence rate is 20% higher in blacks compared to whites, a disparity that has increased over the last twenty years (1–3). Invasive CRC most often develops from conventional adenomas or serrated polyps yet whether racial factors impact the incidence of CRC precursor lesions is not clear.

Several investigations have compared the prevalence of colorectal polyps by race at screening colonoscopy (4–8) and, most studies, but not all (9), have reported a higher risk among blacks compared to whites, especially for advanced or proximal lesions (5, 8, 10). Only a few studies have compared the risk of metachronous polyps by race and none has reported a significant difference in adenomas(11–13) but one observed a lower risk of serrated polyps in blacks compared to whites (14). The lack of a significant association in metachronous adenomas by race may be due to low statistical power, as there were few blacks undergoing follow-up exams in two (12, 13) of the three studies. Alternatively, because CRC is diagnosed at earlier ages and tends to be more aggressive in younger blacks compared to younger whites (15, 16), racial differences in recurrence at younger ages may be present in a subset of patients but the effect could be masked if all ages are combined in analysis. To disentangle the impact of race and age on risk of metachronous large bowel polyps, we pooled data from three large placebo-controlled adenoma chemoprevention trials. Specifically, we hypothesized that the association between black race and risk of any or advanced neoplasms would be stronger among younger than older patients undergoing follow-up colonoscopy.

Materials and Methods

This analysis was based on pooled data from three placebo-controlled, randomized colorectal adenoma chemoprevention trials: the Antioxidant Polyp Prevention Study (17); the Calcium Polyp Prevention Study (18); and the Aspirin Folate Polyp Prevention Study, (19) the details of which are reported elsewhere. Written informed consent was obtained from each participant and the Institutional Review Board of every participating institution approved the studies.

All eligible subjects had one or more histologically confirmed colorectal adenomas and underwent a complete colonoscopy at baseline with the endoscopist attesting that all polyps were removed. For the Antioxidant and Calcium studies (17, 18), adenomas were required to be removed within 3 months before recruitment. For the Aspirin Folate study, eligible patients had at least one of the following: one or more colorectal adenomas removed within 3 months before recruitment, one or more adenomas removed within 16 months before recruitment and a lifetime history of two or more confirmed adenomas, or a one or more adenoma at least 1 cm in diameter removed within 16 months before recruitment (19). Subjects were then randomized to the study agent or placebo with scheduled colonoscopic surveillance at one and four years after the qualifying examination in the Antioxidant and Calcium studies, and at three years in the Aspirin/Folate trial. Treatment ended at the year four examination in the Antioxidant and Calcium studies (risk defined as randomization to year 4) and at the year three examination (risk period defined as randomization to year 3) for aspirin in the Aspirin Folate Study (although folate treatment continued in most subjects) (20).

For the qualifying exam, clinical staff at each center abstracted data from the endoscopy and pathology reports on the total number of lifetime adenomas per subject for each of the three studies (i.e. Antioxidant, Calcium, and Aspirin Folate Polyp Prevention Studies). Information on adenoma size and histology were only available for Calcium Polyp Prevention Study (18), and the Aspirin Folate Polyp Prevention Study (19). During follow-up exam(s), the location and estimated size of each colorectal lesion found was recorded and the polyps were removed and sent for central histological review by a single study pathologist.

For the main analysis, polyps were classified as serrated polyps (including: hyperplastic polyps, traditional serrated adenoma, sessile serrated adenoma) or conventional adenomas (tubular, tubulo-villous, and villous). Our primary endpoints were any conventional adenoma or serrated polyp that occurred after randomization in younger and older persons, including: polyps removed at the year one and four exams in the Antioxidant and Calcium studies (17, 19) and at year three exam in the Aspirin/Folate trial (19, 20). Serrated polyps were classified as a single category because the criteria for these lesions had changed over the course of the three polyp prevention studies (14). Advanced histology neoplasms were defined as conventional adenomas with at least a 25% villous component. Advanced neoplasms were defined as invasive cancer or conventional adenomas with at least a 25% villous component, high-grade dysplasia, or 1 cm in diameter. Colonic location was designated as either proximal (inclusive of the cecum, ascending colon, hepatic flexure, and transverse colon) or distal (inclusive of the splenic flexure, descending colon, sigmoid colon, and rectum).

At enrollment, participants completed a questionnaire assessing basic demographic characteristics, lifestyle factors, medical history (including height and weight), and usual diet (using a validated food frequency questionnaire). Subjects were also asked about family history of polyps and/or colorectal cancer. We analyzed demographic factors, including age, sex, and self-reported race. Smoking status was categorized as "never," "former," and "current" users. Alcohol use was categorized drinker (> 0 drinks per day) or non-drinker.

Body mass index (BMI) was calculated from baseline information on height and weight and divided into three categories using the standard established by the World Health Organization: normal (<25 kg/m^2), overweight (25 to 29.9 kg/m^2), and obese (BMI 30 kg/m^2). In the first two polyp prevention trials, height and weight were assessed by study personnel (physician's initial assessment) and by self-report in the third study.

Statistical analysis

To assess the association between polyp type and race, we estimated risk ratios (and 95% confidence intervals) for one or more large bowel polyps after randomization, calculated with generalized linear regression analyses using a logarithmic linkage and a Poisson distribution. For the main analysis we examined the association between race and risk of any conventional or advanced neoplasm and any serrated polyp in patients 50 and > 50 years of age. Additionally, we examined race and risk of adenoma and serrated polyps in the proximal and distal colorectum. The decision to stratify our results by age was guided by an a priori hypothesis that the racial disparity in metachronous polyps would be more pronounced among younger patients compared to older, based on the fact that younger blacks compared to younger whites may have more aggressive CRC features and poorer outcomes (15, 21–23). We used Wald tests to assess main effects and statistical interactions. All effect estimates were adjusted for age, sex, treatment assignment, and follow-up time.

Results

Of the 2683 subjects who self-identified race as black or white, 2605 (97.1%) completed at least one follow-up exam after randomization. The mean age of the study participants was 59.8 years (SD (9.3)), 71.3% were men, and 7.5% of patients were black. The mean length of follow-up from time of randomization to final study exam was 38.6 (SD (9.8)) months.

Overall, we did not observe a significant association between black race and risk of any conventional adenoma, or advanced neoplasm. The RR for blacks compared to whites for risk of any metachronous conventional adenoma was 1.11 (0.95–1.31) and any advanced lesion was 1.18 (0.82–1.71). We observed a statistically significant increased risk of any right-sided conventional adenoma 1.25 (1.02–1.53) but no significant increased risk observed for the left colorectum, 1.13 (0.89–1.43). Overall results for serrated polyps were published previously (14). The interaction between race and age 50 years was p=0.17 for any conventional adenoma, p=0.03 for advanced histology adenoma, p=0.04 for any advanced neoplasm and p=0.67 for serrated polyps. Results stratified by patients 50 years of age are shown below.

Patients 50 years old

At study entry, blacks had a lower prevalence of family history of CRC polyp or cancer and a higher prevalence of diabetes and a greater mean number of large adenomas (Table 1). Some other baseline characteristics appeared to differ by race (black compared to white), but were not statistically significant, including: obesity (+17%), current smoker (+14%) hypertension (+13%) (Table 1).

During the follow-up period, younger blacks compared to younger whites had a higher risk of one or more conventional adenomas, advanced histology adenomas, and any advanced neoplasm (Table 2). Adjustment for number of large baseline adenomas did not appreciably affect the RR for race: conventional adenoma RR was 1.85 (95% CI 0.99–3.48), advanced histology adenoma was RR was 5.31 (95% CI 1.57–18.0), and any advanced adenoma was 3.77 (95% CI 1.16–12.3)). The percentage of serrated polyps was 24% in younger blacks and 30% in younger whites (Table 2). Associations for black race and adenoma outcomes were not appreciably different after adjusting for several other covariates (one at a time) such as smoking status, alcohol use, family history of CRC, body mass index, hypertension, high cholesterol, diabetes, or caloric intake (data not shown). RR for race and risk of adenoma or serrated polyp outcomes were similar across for each of the three polyp prevention study cohorts despite changes in the definition of serrated lesions during this time frame (data not shown).

Patients > 50 years of age

We observed that, at baseline, older blacks compared to older whites were significantly less likely to be male (−14%), have a family history of CRC (− 9%) and to report consuming alcohol (−16%). On the other hand, blacks were significantly more likely to be current smokers (+11%), hypertensive (+20%), and obese (+9%). We did not observe a difference in baseline adenomas by race (Table 1).

During the follow-up period, older blacks had a similar risk of conventional adenoma, advanced adenoma and a significantly lower risk of serrated polyps compared to whites (Table 2). Black race was associated with non-significantly higher risk of proximal conventional adenomas but no statistical difference in the distal colorectum (Table 2).

Discussion

Overall, in this pooled analysis, our primary finding, supporting our hypothesis based on CRC data, was that younger blacks had significantly more large adenomas at baseline and a higher risk of any conventional or advanced metachronous adenomas. Younger blacks tended to have a lower prevalence of family history of CRC and higher prevalence of diabetes but neither of these factors, nor several other variables we interrogated as potential confounders (e.g. smoking status, alcohol use, diabetes, high cholesterol, hypertension, number or size of baseline adenomas) appreciably changed our results. Blacks older than 50 years compared to whites had a similar risk of any conventional or advanced adenomas and a lower risk of serrated polyps. Although we observed several differences in baseline characteristics between older patients by race, these differences did not affect the association of race and the risk of metachronous lesions.

To our knowledge, our study is the first to specifically examine the relationship between race and risk of metachronous neoplasms among a set of patients below and above fifty years of age. No previous studies have reported a difference by race and metachronous adenomas. One reason for the lack of a statistical association in previous studies may be the small numbers of blacks undergoing follow-up colonoscopy (11–13). In the Penn et al. study, for example, there were only 7 black patients who had surveillance colonoscopy and

the RR was increased, but not significantly (RR 1.89 (95% CI 0.68–5.24); in the Laiyemo et al. investigation (13) recurrence risk was similar by race for any adenoma but non-significantly increased for advanced (RR 1.18 (95% CI 0.68–2.05) and advanced proximal lesions (RR 1.31 (95% CI 0.59–2.91). Another reason for finding no significant difference by race and recurrence could be due to the age structure of the population in which these associations were examined. It is well established that sporadic CRC in younger persons is known to be more aggressive histopathologically (24–28) and is found at later stages (24, 26–30). Blacks are consistently diagnosed at a younger age and later stage of disease suggesting that differences in incidence and outcome could be related to a more aggressive phenotype among a subset of patients. In support of this idea, recent reports among those with invasive CRC have found that younger blacks, compared to younger whites have more aggressive histologic features at diagnosis and poorer CRC outcomes (15, 16, 22, 23).

Additionally, there is significant data to suggest a higher prevalence of aggressive neoplasia in blacks undergoing screening exams. In one of the earliest reports to examine polyp prevalence by race, Lieberman and colleagues (10) found that blacks had a higher risk of larger polyps (> 9mm) compared to whites, especially African-American women. Lebwohl and colleagues (5) found an increased risk among blacks compared to whites of proximal and advanced neoplasm but also reported an association with any adenoma (OR 1.76 (95% CI 1.52–2.04)) findings which were recently corroborated by Sanchez et al. (RR 3.0 (95% CI 1.1–8.3))(7). Others(8, 9), however, have observed a similar risk of prevalent and advanced adenomas by race, but a higher risk of proximal adenomas in blacks compared to whites – proximal location is associated with poorer survival among patients with invasive cancer (31–33). Because these studies include prevalent adenomas detected at screening exams (typically after the age of 50), the age at which these adenomas form is not known, yet higher rates of advanced polyps at first screening exam suggests that a subset of blacks either have more aggressive adenoma growth rates and/or develop adenomas at an earlier age.

The present investigation demonstrates a higher recurrence of any conventional and advanced neoplasms among younger but not older blacks compared to whites. The reason for this is unclear, but suggests that there may be differences in the rate of carcinogenesis in a subset of younger patients or proclivity to develop polyps within a more aggressive pathway. Increasingly, CRC is a recognized as heterogeneous disease, which can evolve through distinct pathways at varying rates (34–40). CRC can be broadly separated into three pathways evolving through (1) the chromosomal instability pathway (CIN) which tend to arise from conventional adenomas and (2 &3) CpG island methylated pathway(s) (CIMP I & CIMP II) (34–40) which appear to arise from serrated lesions (sessile serrated polyps and traditional serrated adenomas). Our results suggest that younger black patients may be more likely to develop metachronous adenomas through the CIN pathway. Older blacks had a reduced risk of serrated polyps compared to whites but our data did not allow us to make a conclusive judgment regarding risk of serrated polyps in younger blacks because of the small sample size. Previously, we observed a reduced risk in serrated polyps among all ages combined (14) which was similar to what others (41–43) have also reported. These results speak against a methylated milieu, but future studies will be needed to determine if this is true by measuring whether the pathologic and molecular features differ by race. Future

studies should also aim to include patients with conventional adenomas and/or serrated polyps at the qualifying exam in order to adequately assess the risk of different types of metachronous lesions by race.

Our study had several limitations. First, all of our patients had to have at least one adenoma at to be eligible for the study, these patients may differ from average risk patients. Second, patients participating in a chemoprevention trial are likely a select group and also likely differ from the general population. We also had a very small number of younger black patients, especially among those less than 50 years of age. All of these factors may limit the generalizability of our findings. We also lacked information on potential important confounders, such as, physical activity level. Further, we did not have detailed pathologic information on the histology of the serrated lesions and all of our patients had a documented conventional adenoma at baseline -- whether the risk of metachronous serrated polyps would have differed in patients with a serrated adenoma at baseline is not known and requires further study. Additionally we used self-identified race which may increase the possibility of misclassification bias. Strengths of the study include a large population of white patients, central pathological review, and standard follow-up by protocol. To date, this is the largest study, despite the limitations cited above, that has looked at the risk of metachronous adenomas by race in younger and older age groups.

The American College of Gastroenterology recommends that average risk blacks incept CRC screening at age 45 years rather than age 50 years because of the earlier age of onset of CRC, higher stage at diagnosis and increased stage adjusted mortality compared to whites (44). Our data showing a greater number of large baseline adenomas and advanced adenomas in blacks ages 50 years compared to whites of the same age would support that recommendation. Overall, the results of our study provide some evidence that the racial disparity in CRC incidence may be due, in part, to an excess of neoplasia in younger blacks. Much larger studies will be needed to confirm these findings.

Acknowledgments

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Table 1

Baseline Characteristics of patients in the pooled data from three polyp prevention studies (n=2683)

Baseline Characteristic	Age ≤ 50 years			Age > 50 years		
	Black (n=22)	White (n=403)	P ^{a}	Black (n=179)	White (n=2079)	P ^{b}
Age—yrs. (SD)	44.0 (6.1)	44.8 (5.0)	0.44	60.9 (7.1)	62.8 (6.8)	0.0006
Male—no. (%)	13 (59)	264 (65)	0.54	107 (60)	1529 (74)	0.00001
Smoker—no. (%)						
Never	9 (40)	178 (44)		71 (40)	702 (34)	
Former	5 (23)	136 (34)		58 (33)	1017 (49)	
Current	8 (36)	87 (22)	0.24	49 (28)	343 (17)	0.0001
Body Mass Index -- no. (%)						
Normal (< 25 kg/m^2)	4 (18)	141 (35)		38 (21)	634 (31)	
Overweight (25–29 kg/m^2)	10 (46)	179 (45)		86 (48)	974 (47)	
Obese (≥ 30 kg/m^2)	8 (37)	82 (20)	0.12	55 (31)	464 (22)	0.007
Alcohol >0 drinks per week						
Yes— no. (%)	14 (74)	280 (74)	0.99	87 (53)	1370 (69)	0.0001
Diabetes						
Yes— no. (%)	2 (9)	9 (2)	0.05	20 (11)	159 (8)	0.09
High Cholesterol						
Yes— no. (%)	5 (24)	99 (25)	0.94	43 (24)	572 (28)	0.31
Hypertension						
Yes— no. (%)	6 (27)	57 (14)	0.09	99 (55)	717 (35)	0.0001
Family History of Polyps						
Yes— no. (%)	3 (16)	140 (39)	0.05	10 (7)	348 (19)	0.0001
Family History of CRC						
Yes— no. (%)	3 (16)	139 (38)	0.05	27 (18)	492 (27)	0.03
Baseline Adenoma no., mean (SD)						
No. of prior adenomas^c	2.18 (2.1)	1.78 (1.6)	0.19	2.40 (1.9)	2.69 (2.9)	0.19
Large (≥ 1 cm)^c	0.53 (0.7)	0.25 (0.5)	0.01	0.31 (0.6)	0.32 (0.6)	0.99

Baseline Characteristic	Age ≤ 50 years			Age > 50 years		
	Black (n=22)	White (n=403)	P [a]	Black (n=179)	White (n=2079)	P [b]
Advanced[c]	0.52 (0.7)	0.37 (0.6)	0.28	0.44 (0.7)	0.41 (0.7)	0.59
Treatment						
Yes – no. (%)	14 (64)	302 (75)	0.24	119 (66)	1441 (69)	0.43

[a] p-value for difference between baseline characteristic and race for those ≤ 50 years of age

[b] p-value for difference between baseline characteristic and race for those > 50 years of age

[c] The lifetime total number of prior adenomas found and removed was available for all three studies (17–19). Number of large or advanced adenomas was only collected for the Calcium study and Aspirin Folate study.

Table 2

Association of race and risk of conventional adenomas and serrated polyps in people ≤50 and > 50 years of age

	≤50 years				> 50 years			
	Black (n=21)	White (n=390)		RR[a] (95% CI)	Black (n=172)	White (n=2022)		RR[a] (95% CI)
Conventional Adenoma								
Any	10	130	1.0	1.70^c (0.99–2.92)	82	958	1.0	1.08 (0.92–1.27)
Advanced Histology[b]	4	19	1.0	5.52^c (1.87–14.97)	22	228	1.0	1.25 (0.86–1.90)
Any Advanced[b]	4	26	1.0	4.05^c (1.43–11.46)	23	288	1.0	1.05 (0.71–1.56)
Proximal	7	90	1.0	1.72 (0.85–3.49)	63	649	1.0	1.24^d (1.00–1.53)
Distal	6	56	1.0	1.93 (0.89–4.24)	49	583	1.0	1.08 (0.84–1.38)
Serrated Polyp								
Any	5	118	1.0	0.75 (0.34–1.62)	35	623	1.0	0.65^d (0.49–0.87)
Proximal	2	29	1.0	1.17 (0.28–4.89)	13	206	1.0	0.67 (0.40–1.16)
Distal	4	101	1.0	0.69 (0.28–1.69)	27	518	1.0	0.61^d (0.43–0.86)

[a] RR for black race compared to white race adjusted for age, sex, study treatment assignment, and follow-up time

[b] Advanced histology adenoma includes lesions with 25% or more villous histology; any advanced adenoma includes adenomas that have advanced histology, large size, high-grade dysplasia, and/or invasive cancer.

[c] p-value for differences between younger blacks and whites for any conventional adenoma (p=0.06), advanced histology (p =0.002), and any advanced adenoma (p =0.008).

[d] p-value for difference between older blacks and whites for any proximal conventional adenoma (p=0.05), serrated polyp (p=0.004) and distal serrated polyps (p =0.004).