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Increased Frequency of *KRAS* Mutations in African Americans Compared with Caucasians in Sporadic Colorectal Cancer

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OBJECTIVES: The basis for over-representation of colorectal cancer (CRC) in African-American (AA) populations compared with Caucasians are multifactorial and complex. Understanding the mechanisms for this racial disparity is critical for delivery of better care. Several studies have investigated sporadic CRC for differences in somatic mutations between AAs and Caucasians, but owing to small study sizes and conflicting results to date, no definitive conclusions have been reached.
METHODS: Here, we present the first systematic literature review and meta-analysis investigating the mutational differences in sporadic CRC between AAs and Caucasians focused on frequent driver mutations (*APC*, *TP53*, *KRAS*, *PI3CA*, *FBXW7*, *SMAD4*, and *BRAF*). Publication inclusion criteria comprised sporadic CRC, human subjects, English language, information on ethnicity (AA, Caucasian, or both), total subject number >20, and information on mutation frequencies.
RESULTS: We identified 6,234 publications. Meta-analysis for *APC*, *TP54*, *FBXW7*, or *SMAD4* was not possible owing to paucity of data. *KRAS* mutations were statistically less frequent in non-Hispanic Whites when compared with AAs (odds ratio, 0.640; 95% confidence interval (CI): 0.5342–0.7666; $P=0.0001$), while the mutational differences observed in *BRAF* and *PI3CA* did not reach statistical significance.
CONCLUSIONS: Here, we report the mutational patterns for *KRAS*, *BRAF*, and *PI3CA* in sporadic CRC of AAs and Caucasians in a systematic meta-analysis of previously published data. We identified an increase in *KRAS* mutations in sporadic CRC in AAs, which may contribute to worse prognosis and increased mortality of CRC in AAs. Future studies investigating health-care disparities in CRC in AAs should control for *KRAS* mutational frequency.
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INTRODUCTION

Colorectal cancer (CRC) is the third most common cause of cancer-related death in the United States and is expected to result in ~49 000 deaths in 2016.[1] African Americans (AAs) have higher incidence of CRC and increased CRC mortality rates compared with Caucasians.[1] In addition, AAs have more right-sided cancers,[2] are diagnosed with CRC at earlier ages,[3] and have a higher percentage of late-stage disease compared with Caucasians at the time of diagnosis.[4] The basis for this are most likely multifactorial and complex. Possible underlying factors include differences in diet,[5] gut microbiome,[6] and inflammatory conditions such as obesity,[7] as well as variances in disease-specific gene mutations that may be playing important roles in sporadic CRC development. In addition to genetics and environmental factors, reduced health-care literacy and lower socioeconomic status are also thought to contribute to health-care disparities with regards to CRC.

Lower socioeconomic status was repeatedly shown to have an impact on CRC prognosis;[8,9] however, certain minorities that are as strongly connected to a lower socioeconomic status as AAs, such as Indigenous populations on Hawaii or Hispanics, have equal or even lower CRC incidence and mortality when compared with Caucasians.[10,11] This strongly suggests that there are other specific causes for the health-care disparities seen in AAs with regards to CRC. One of the reasons why overall CRC incidence declined over the last decades is most certainly due to increased screening efforts.[12] A decline in CRC incidence and mortality was also noted in AAs, however, especially older AAs who had less education and income had lower screening compared with Caucasians. This significantly contributed to persistent disparities among these groups,[13] but is unlikely to be the only cause.

Even though the development of CRC is widely accepted to be driven by the sequential acquisition of somatic mutations,[14]

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it is not yet understood whether the acquisition process is different in AAs and Caucasians. A difference in the frequency of sporadic somatic mutations in AAs and Caucasian CRC patients has been proposed before.[15] However, most studies have limited study sizes or only partly controlled for additional confounders. While some investigations in this matter did not yield definitive results,[16] other studies reported on differences that have not yet[17] been reproduced. A recent report by Yoon *et al.*[18] demonstrated different mutational frequencies in AAs, Caucasians, and Asians, but was limited to UICC stage III CRCs. These discrepancies in study results could be due to variations in study sizes, differences in study populations, and perhaps due to the substantial heterogeneity in the genetics and lifestyles of individuals self-identifying as AAs or Caucasians. Recently, a meta-analysis investigating the frequency of microsatellite instability, a characteristic of less aggressive and hypermutated CRCs, found no statistically significant difference between AAs and non-Hispanic Whites (NHWs), albeit microsatellite instability frequency trended to be lower in AAs.[19] Even though statistical significance was not reached, this study hints toward biologically different CRC in AAs and Caucasians.

To better characterize the differences in high-frequency mutations in AA and Caucasian CRCs, we performed the first systematic literature review and meta-analysis to obtain a larger data set to overcome above limitations. An improved understanding of the underlying causes of CRC health-care disparities would benefit both AA communities through more effective prevention and treatment options, and all CRC patients through a deeper understanding of the complex pathophysiology of CRC development.

METHODS

Identification of high-frequency driver mutations. The algorithm published by Lopez-Bigas *et al.*[20] was used to identify the seven most common driver mutations in The Cancer Genome Atlas colorectal data set.[21] To increase the likelihood of reaching statistical significance, we focused on high-frequency mutations.

Literature search. The search query that was used to identify studies was ("Colorectal Neoplasms"[Mesh] OR "Rectal Neoplasms"[Mesh] OR "Colonic Neoplasms"[Mesh] OR colorectal cancer OR colon cancer OR rectal cancer) AND ("Mutation"[Mesh] OR mutation OR mutated) AND (APC OR "Genes, APC"[Mesh] OR "Adenomatous Polyposis Coli Protein"[Mesh] OR PI3CA OR "Phosphatidylinositol 3-

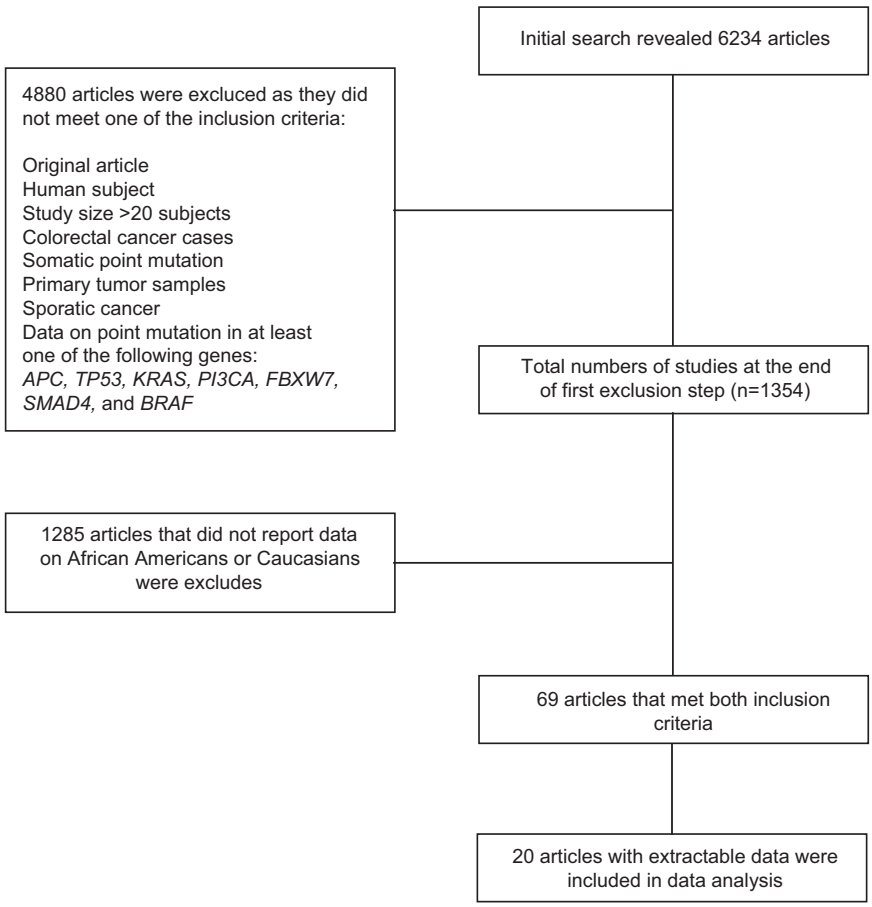

Figure 1 Flow diagram of study selection process. Initial PubMed search resulted in identification of 6,234 articles. After the application of fist exclusion step, 1,354 studies remained. Following exclusion of studies that did not report data on race or did not report data in extractable fashion, 20 studies were available for final meta-analysis.

Kinases"[Mesh] OR "PIK3CA protein, human" [Supplementary Concept] OR TP53 OR "Genes, p53"[Mesh] OR "Tumor Suppressor Protein p53"[Mesh] OR KRAS OR "Genes, ras"[Mesh] OR "KRAS protein, human" [Supplementary Concept] OR SMAD4 OR DPC4 OR MADH4 OR "Smad4 Protein"[Mesh] OR BRAF OR "BRAF protein, human" [Supplementary Concept] OR "Proto-Oncogene Proteins B-raf"[Mesh] OR FBXW7 OR "FBXW7 protein, human" [Supplementary Concept]). Both protein and gene names plus Mesh terms were used to include all studies possibly reporting on any of our target mutations in CRC.

We searched the MEDLINE database. Each hit was screened by two individual investigators, using a two-step inclusion process. In the first step, inclusion criteria were original article, English language, human subjects, subject number >20, CRC, somatic point mutations identified in primary tumor sample, sporadic cancer, and data on point mutation in at least one of the following genes: *APC*, *TP53*, *KRAS*, *PI3CA*, *FBXW7*, *SMAD4*, and *BRAF*. No time period was defined to include the maximum possible number of studies. In a second step, we included only case–control studies reporting on at least one of the target mutations and information on both AAs and Caucasians (Figure 1). For our study, White and Caucasian as well as Black and AA were used synonymously. We will use the terms Caucasian and AA for the remaining sections of this manuscript for the sake of readability, but are aware of the shortcomings of the binary racial paradigm.[22]

Data extraction. Data on first author, year of publication, sequencing method, number of AAs and Caucasians, mutational frequency of the target gene, stage, tumor location (distal vs. proximal), gender, and median age were extracted if data on these parameters was available. First authors of studies that reported data on mutational frequency and race in a non-extractable manner were contacted by email to collect the additional data set. Of the 49 authors contacted by email, 11 authors replied. Nine of the replies were negative; one author sent the data for confounders;[16] and one author sent the data set for analysis.[23]

Statistical analysis. For each mutation, the meta-analysis was conducted to estimate the effect sizes between Caucasians and AAs defined by the risk ratio, the risk difference, and the odds ratio (OR), respectively. For each reported effect sizes, both fixed and random models were used. The final chosen effect size was based on test of heterogeneity of these two races. The results were consistent either using risk ratio, risk difference or OR. The effect sizes from OR were reported in our study. The forest plots were also conducted, and presented based on OR. χ^2 power analysis were run using the observed effect sizes for *BRAF* and *PI3CA* using an α-level of 0.05.

We assessed study quality of studies reporting on *KRAS* mutations using the Newcastle–Ottowa scale.[24] Statistical analysis was repeated exclusively using excellent quality studies (scores of 8/9 or 9/9). The meta-regression analyses were also performed to adjust four covariate effects including age, gender, tumor stage. and tumor site. Finally, the residual funnel plots were conducted. All of the statistical analyses were performed using R 3.3.2 version.

RESULTS

Identification of driver mutations in CRC. First, the seven most common driver mutations in CRC were searched using an *in silico* approach. *APC*, *TP53*, *KRAS*, *PI3CA*, *FBXW7*, *SMAD4*, and *BRAF* were identified as most commonly mutated driver genes in CRC in the The Cancer Genome Atlas data set[21] and where used for the literature search.

Inclusion of studies. Following initial PubMed search, 6,234 studies were identified. Using the inclusion criteria

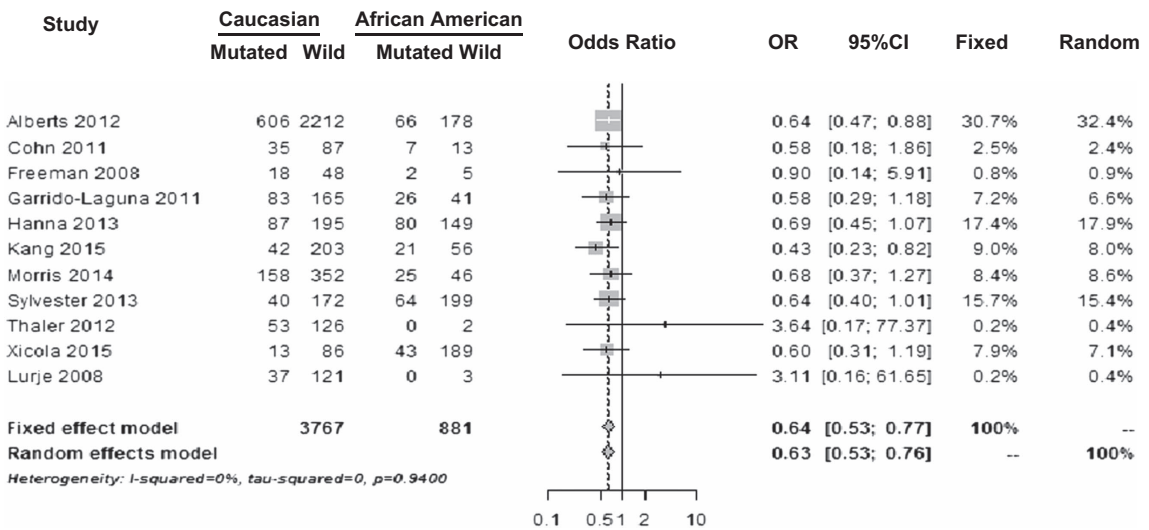

Figure 2 Forest plot showing *KRAS* mutational frequencies in studies that reported data on Caucasians and African Americans. Odds ratio (OR) for fixed-effect model shows that Caucasians were less likely to have mutations in the *KRAS* gene when compared with AAs ($P<0.0001$).

mentioned above (Figure 1), studies that reported data on target mutations in both AAs and Caucasians were identified. Of these studies, 1 reported on *APC* mutations,[25] 2 on *TP53*,[25,26] 11 on *KRAS*,[15,16,23,25,27–34] 3 on *PI3CA*,[15,25,35] none on *FBXW7* or *SMAD4*, and 6 on *BRAF*.[15,16,25,31–33] Therefore, there was not enough data to complete the meta-analysis for following targets; *APC*, *TP54*, *FBXW7*, and *SMAD4*. We proceeded with statistical analysis exclusively for *KRAS*, *BRAF*, and *PI3CA* with remaining total 13 studies.[15,16,23,25,27–35]

Mutational frequencies and sequencing types. Overall, all studies included in this meta- analysis used either Sanger or Pyrosequencing. For *KRAS* mutations, all studies reported on exon 12 and exon 13 mutations, with a subset of distinguishing between the two. For our meta-analysis, a sample with either *KRAS* exon 12 or *KRAS* exon 13 mutation was considered *KRAS* mutated. No study reported on other point mutations in the *KRAS* gene. A total of 4,648 subjects (881 AAs and 3,767 NHWs) were included for our analysis of *KRAS* mutations. All studies investigating *BRAF* mutations reported on the *BRAF* V600E mutation, and had a combined 2,063 subjects (924 AAs and 1,139 NHWs). In the case of *PI3CA*, all studies reported on mutations in exons 9 and 20, without distinguishing between the two, with a total of 662 subjects (205 AAs and 457 NHWs) included in the analysis.

Figure 2 shows the forest plot of studies that reported *KRAS* mutational frequencies in Caucasians and AAs. For *KRAS* mutation, OR for fixed-effect model was 0.640 with 95% confidence interval (CI) (0.5342–0.7666; $P<0.0001$) and for random-effect model OR was 0.635 with 95% CI (0.5296–0.7608; $P<0.0001$). This result showed that Caucasians were 36% less likely to have mutations in the *KRAS* gene when compared with AAs. When repeating analysis exclusively including studies with excellent study quality as scored by the Ottowa–Newcastle scale[15,16,27,28,30,32] effect size did not substantially change the results, which remained statistically significant. Eight of 11 studies that reported *KRAS* mutational differences also had data available on age, gender, stage, and cancer site. Meta-regression analysis that adjusted for these covariates revealed similar distribution of these possible confounders. Mutational differences between Caucasians and AAs remained significantly different after covariate adjustment.

The forest plot of studies that reported mutational frequencies in *BRAF* in Caucasians and AAs are shown in Figure 3. For *BRAF* mutation, OR for fixed-effect model was 1.35 with 95% CI (0.9442–1.9177; $P=0.1005$) and for random-effect model OR was 1.24 with 95% CI (0.6889–2.2488; $P=0.4683$).

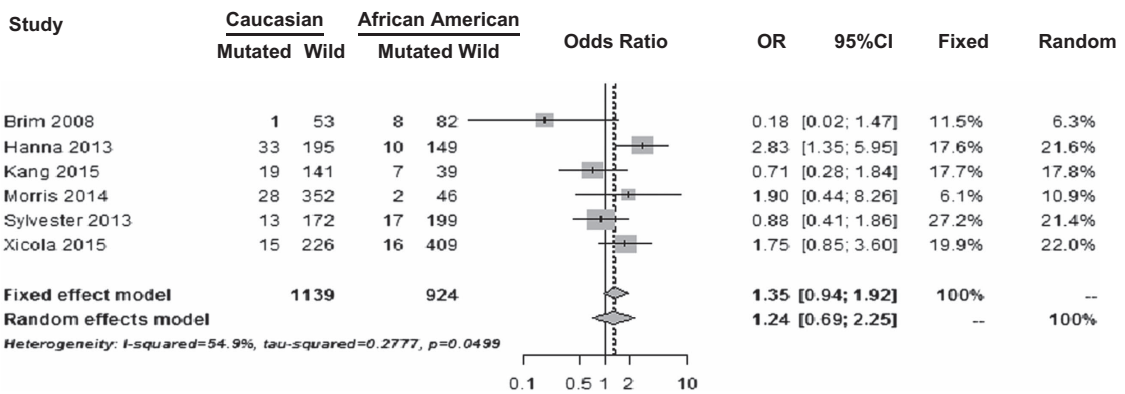

Figure 3 Forest plot showing *BRAF* mutational frequencies in studies that reported data on Caucasians and African Americans (AAs). Odds ratio (OR) for fixed-effect model shows that Caucasians were more likely to have mutations in the *BRAF* gene when compared with AAs. However, this difference did not reach statistical significance ($P=0.4683$).

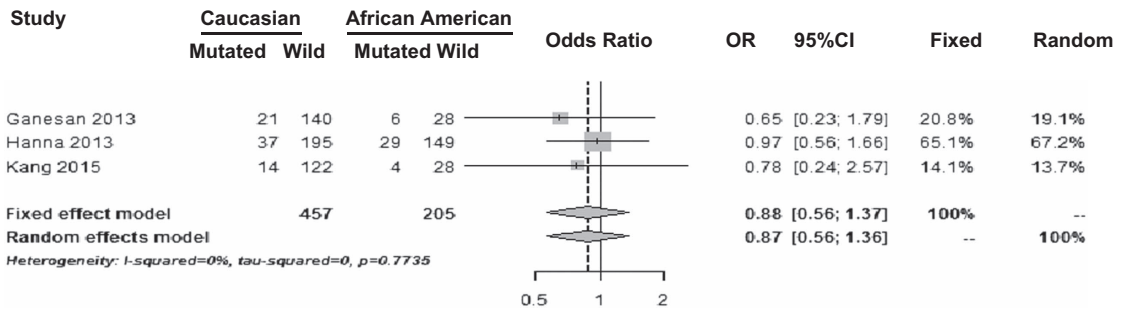

Figure 4 Forest plot showing *PI3CA* mutational frequencies in studies that reported data on Caucasians and African Americans (AAs). Odds ratio (OR) for fixed-effect model shows that Caucasians were less likely to have mutations in the *PI3CA* gene compared with AAs. However, this difference was not statistically significant ($P=0.5574$).

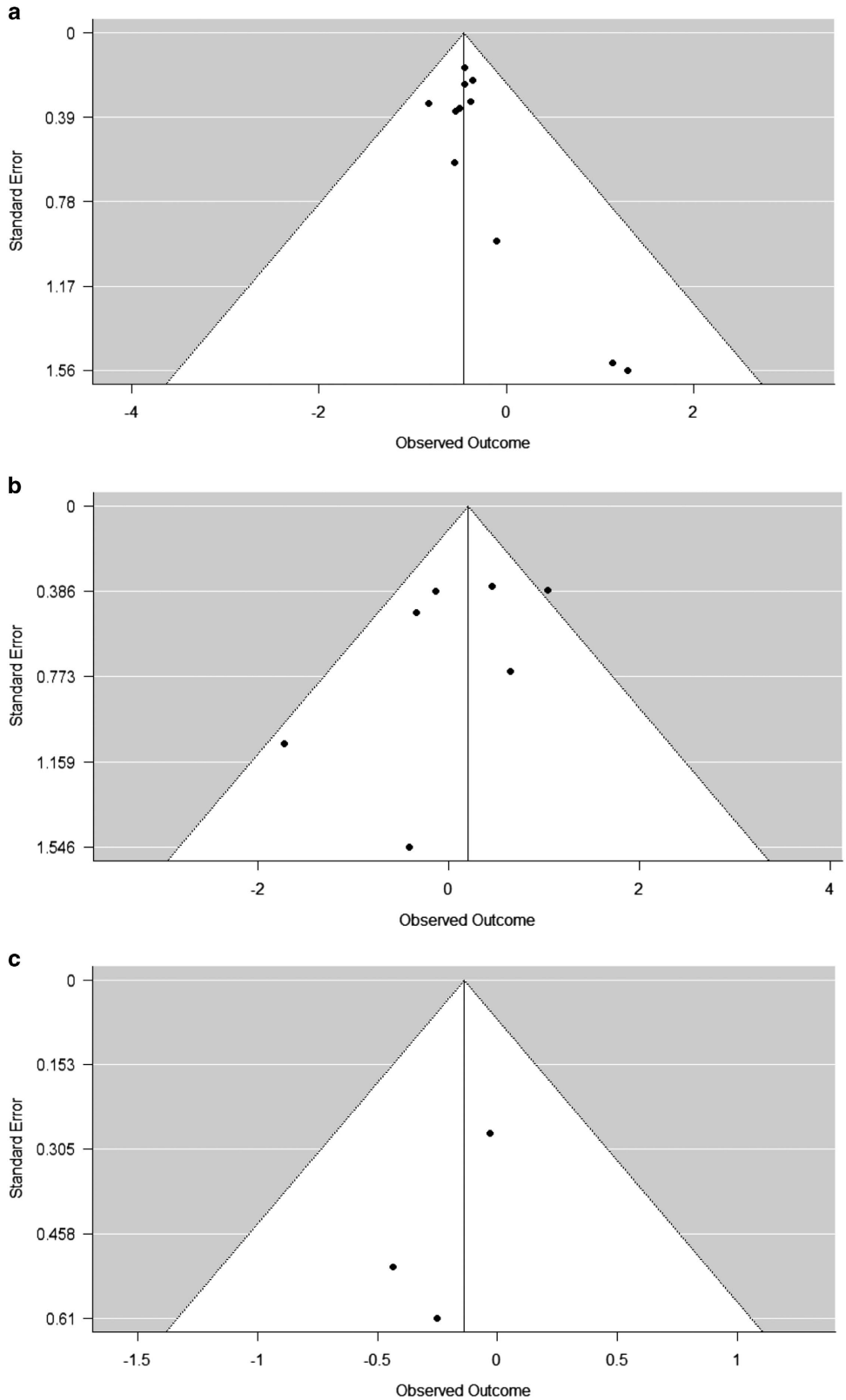

Figure 5 Funnel plots of studies that reported data on mutational frequencies in (**a**) *KRAS*, (**b**) *BRAF*, and (**c**) *PI3CA*. There were no significant differences with respect to publication bias among studies that reported mutational differences on *KRAS* ($P = 0.94$) and *PI3CA* ($P = 0.77$) at $\alpha = 0.05$ significance level. However, Funnel plot for *BRAF* revealed significant differences between studies ($P = 0.049$).

Although Caucasians were 35% more likely to have *BRAF* mutation compared with AAs this did not reach statistical significance.

Figure 4 shows the forest plot of studies that reported *PI3CA* mutational frequencies in Caucasians and AAs. For *PI3CA* mutation, OR for fixed-effect model was 0.875 with 95% CI (0.5606–1.3662; $P = 0.5574$) and for random-effect model OR was 0.870 with 95% CI (0.5587–1.3561; $P = 0.7735$). Results indicated that Caucasians were 12.5% less likely to have *PI3CA* mutation compared with AAs. However, this difference was not statistically significant.

To discern whether our results with regards to *PI3CA* and *BRAF* mutations were true negatives, we performed power analysis using the observed effect sizes and an α-level of 0.05. Power to identify in mutational frequencies for *PI3CA* and *BRAF* was 55% and 29%, respectively.

To investigate the possibility of publication bias, test of heterogeneity was run and funnel plots were created for studies that reported data on mutational differences in *KRAS*, *BRAF*, and *PI3CA* (Figure 5). No significant differences in regards to publication bias were found among studies that reported mutational differences on *KRAS* and *PI3CA* at $\alpha = 0.05$ significance level (Figure 5a,c, *P*-values 0.94 and 0.77, respectively). Funnel plot for *BRAF* revealed significant differences between studies (Figure 5b, *P*-values 0.049) at $\alpha = 0.05$ significance level.

DISCUSSION

This is the first systematic literature review and meta-analysis of high-frequency somatic driver mutations in sporadic CRC in AAs and Caucasians. Our results revealed higher frequencies of *KRAS* mutations in AAs compared with Caucasians, with no statistically significant differences in *BRAF* and *PI3CA* mutations. As our study was underpowered with regards to *BRAF* and *PI3CA* mutations, our results do not exclude the possibility of differences in the mutational frequency of these genes between AAs and Caucasians, but underline the importance of further studies.

As activating *KRAS* mutations are strongly correlated with worse prognosis in sporadic CRC,[36] the increased frequency of *KRAS* mutations in AAs may contribute to the higher mortality observed in AA CRC patients. Importantly, our results remained significant after controlling for possible confounders such as age, gender, stage, or cancer site. Therefore, the difference in *KRAS* mutation status is most likely a contributory factor to health-care disparities in CRC at least in AAs. *KRAS* mutation status should be considered as an important variable to include in future studies, especially for those studying the health-care disparities between AAs and Caucasians in CRC. Controlling for *KRAS* mutational status in study cohorts can perhaps improve the accuracy of final conclusion, especially if investigations focus on CRC racial health-care disparities.

KRAS mutational status also has major implications on EGFR-inhibit-based treatment, as EGFR inhibitors have been repeatedly found to be non-beneficial in patients expressing an activating *KRAS* mutation. Our results showed increased frequency of *KRAS* mutation in sporadic CRC in AAs and this finding should encourage further testing of *KRAS* mutational status when a diagnosis of CRC is made especially in AAs. This result indicates that EGFR inhibition is less often a therapeutic option in AAs compared with Caucasians, which translates into less treatment options for AA CRC patients underscoring the need to further study tumor biology and racial disparities.

Our study has several limitations. First, the number of studies reporting on the frequency of somatic mutations in sporadic CRC in AAs and Caucasians in an extractable manner was relatively small. This is partly due to the fact that authors do not always perform subgroup analysis or report on these mutations even if data on race is theoretically available. Detailed reporting of these mutational frequencies at least in the supplementary section of articles should be strongly encouraged. Second, in this study we used AA and Black, as well as Caucasian and White synonymously to increase the detection of reported mutational differences. Even though the utilization of binary racial categories is the standard in the field, it does not accurately reflect the complexity of genetic background in individuals self-identifying as AA.[37] The haziness in the definition of racial groups may lead to the inclusion of heterogeneous groups into our analysis, thereby masking or enhancing real differences. Third, the majority of studies did not report important confounders such as age, gender, and socioeconomic status; therefore, we were not able to control for these possible confounders during *BRAF* and *PI3CA* analysis. Hopefully with adequate reporting of these covariates in future, upcoming studies can investigate the differences in somatic mutations in AAs and Caucasians while controlling for possible confounders. Fourth, we could not investigate the differences in somatic mutations in *APC*, *TP53*, *FBXW7* and *SMAD4* due to the paucity of studies which reported data on these targets.

In summary, sporadic somatic *KRAS* mutations occur more often in CRC of AAs when compared with Caucasians. This opens the field to further studies investigating what drives somatic gene mutation and how these can be distinct in frequency in different racial and ethnic groups. Large-scale clinical studies are needed to confirm this finding and also to further investigate the possibility of similar differences in other target somatic mutations.

CONFLICT OF INTEREST

Guarantor of the article: Barbara Jung, MD.
Specific author contributions: J.J.S. and B.J. conceived the study; J.J.S. created the decision tree for article inclusion, organized the data retrieval; J.J.S. and C.Y. preformed initial statistical analyses and cowrote the article; J.J.S., C.Y., V.B., J. Z., A.K., and N.K. all contributed to database search and article retrieval; Y.X. performed statistical analyses and provided figures; N.K., J.J.S., and B.J. provided editorial input.
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Potential competing interests: None.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ African Americans have higher incidence of colorectal cancer and increased morbidity and mortality from colorectal cancer compared to Caucasians.
- ✓ Underlying mechanisms of these health-care disparities are not completely understood, but somatic mutations may be contributing to observed differences.
- ✓ There are conflicting reports on differences in somatic mutations in colorectal cancer in African Americans and Caucasians.

WHAT IS NEW HERE

- ✓ This is the first meta-analysis specifically designed to compare the differences in the most commonly seen somatic mutations in colorectal cancer between African Americans and Caucasians.
- ✓ African Americans have higher incidence of *KRAS* mutations compared to Caucasians.
- ✓ No statistical differences were seen between African Americans and Caucasians in regards to *BRAF* or *PI3CA* mutations.

TRANSLATIONAL IMPACT

- ✓ Frequency of *KRAS* mutations should be compared in future studies investigating racial disparities in colorectal cancer between African Americans and Caucasians.
- ✓ Since African Americans with colorectal cancer have higher incidence of *KRAS* mutations, testing this population for *KRAS* mutation during initial work up may provide tailored treatment strategies.

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