Review of studies on metabolic genes and cancer in populations of African descent

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Abstract: Genetic polymorphisms described for a number of enzymes involved in the metabolism of tobacco carcinogens and alcohol have been linked to increase cancer risk. Racial disparities in cancer between whites and populations of African descent are well documented. In addition to differences in access to health care, both environment and genetic factors and their interaction may contribute to the increased cancer risk in minority populations. We reviewed the literature to identify case-control studies that included subjects of African descent. Meta-analyses investigating the association of genetic polymorphisms in tobacco metabolic genes and cancer were performed. Although several genes and cancers have been studied, only one or two studies per gene for each cancer site have been published, with the exception of breast (*CYP1A1* and *CYP1B1*), lung (*GSTM1, CYP1A1,* and *NQO1*), and prostate (*CYP3A4 A293G* and *CYP17*). Marginal statistically significant associations were observed for *CYP3A4 A293G* and *CYP17 5′UTR* polymorphisms and prostate cancer. Our findings support the need for additional genetic association studies of breast, prostate, and lung cancers that include a larger number of minority participants. Because incidence and mortality rates for these cancers rank highest among populations of African descent, concentrated research in these areas are warranted. ***Genet Med* 2010:12(1):12–18.**

Key Words: *cancer, Africans, African-Americans, genetic susceptibility*

Phase I and Phase II metabolic genes encode important enzymes in the metabolism of tobacco carcinogens. Phase I enzymes are responsible for converting chemicals into compounds that bind mainly with DNA, thus being genotoxic. An example of Phase I enzymes is the Cytochrome P-450(CYP) family, which play a major role in tobacco carcinogen activation. Phase II enzymes are involved in the cellular detoxification of many carcinogens. The glutathione *S*-transferase (*GSTM1, GSTP*, and *GSTT1*) is an example of a Phase II enzyme. Substrates for GSTs include acetaldehyde, an alcohol metabolite, and several intermediate metabolites of polyaromatic hydrocarbons found in tobacco smoke. Genetic polymorphisms have been described for a number of enzymes involved in the metabolism of tobacco carcinogens and alcohol, and many of these polymorphisms have been linked to phenotypic differences in enzyme activity or expression.[1,2] Differences in the metabolic activation and detoxification pathways of these metabolic genes are likely to be a major source of interindividual variation in cancer susceptibility. However, in the absence of the main exposure (such as tobacco smoke), the contribution of these genetic factors is likely relevant. Genetic polymorphisms modulate the association observed between exposure (such as tobacco smoke) and cancer. Therefore, gene-environment interactions must be considered when evaluating the associations between exposures and diseases.

Racial disparities in cancer risk between whites and populations of African descent have been well documented in the United States. Between 1975 and 2006, the age-adjusted incidence rates for all cancer sites combined were 466.6/100,000 for whites and 505.9/100,000 for African-Americans.[3] In addition to differences in access to health care, it is likely that both environment and genetic factors and their interaction contribute to the increased cancer risk observed in minority populations. However, few studies addressing gene-environment interactions have been conducted. For a number of cancer types, case-control studies have reported that polymorphisms in tobacco metabolic genes are associated with cancer risk,[4–6] but investigations of these associations according to ethnic background are limited. Some case-control studies include smaller numbers of African-American subjects compared with whites, therefore are unable to report meaningful results for African-Americans because of lack of statistical power. For example, a previous pooled analysis of case-control studies evaluating the association of *GSTM1* and *CYP1A1* polymorphisms in oral and pharyngeal cancer reported no overall association, although the odds ratio (OR) in 294 African-Americas and Africans cases combined was almost 2.0.[7] We have systematically reviewed the literature to identify all case-control studies that have included subjects of African ancestry and provided a summary of these existing studies. We have also performed meta-analyses investigating the association of genetic polymorphisms in tobacco metabolic genes and cancer risk in populations of African descent.

METHODS

Selection criteria

A Medline literature search for case-control and nested case-control studies published between 1966 and October 5, 2009, on the association of metabolic gene polymorphisms and any cancer in populations of African descent was conducted using the search term: (*African-American or African*) and (*gene or polymorphism*) and *cancer*. Only studies published in English, French, Spanish, or Italian and reporting genotypes for incident cases and controls using polymerase chain reaction methods were included in this review. Genes included were both Phase I and Phase II metabolic genes. The search yielded 80 original

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articles. Studies that did not provide race-specific genotype data by cases and controls were excluded from the analysis. Overlap of study subjects was evaluated by comparing sources of data described in the published methods and through crossreferencing using the Genetic Susceptibility to Environmental Carcinogens database (www.gsec.net).[8] In the case of multiple publications reporting overlapping data, the more inclusive study was retained. An additional search was performed with each gene polymorphism identified from the first search along with alternative names and (variant or polymorphism) and cancer. This search yielded 19 additional studies.

Of the 99 publications, three were excluded because data on subjects of African descent was combined with those of mixed ancestry[9–11]; three publications presented data that overlapped with more inclusive publications from the same authors[12–14]; seven did not provide race-specific genotype data[15–21]; three provided allele frequencies only[22–24]; one did not report genotype data for the controls[25]; two studies reported only on haplotypes[26,27]; and one was a methylation study and did not report on gene polymorphisms.[28] After exclusions, 79 studies remained for consideration in this review and meta-analysis (see Table, Supplemental Digital Content 1, http://links.lww.com/GIM/A91, which describes the publications included in this study).

Statistical analysis

Study-specific crude ORs and 95% confidence intervals (CIs) were recalculated to assess the association of each metabolic gene polymorphism and cancer, based on the reported genotype data by cases and controls. Meta-analytical techniques were applied for all metabolic gene polymorphisms reported in three or more studies using inverse-variance weighting to calculate the fixed and DerSimonian and Laird weighting to calculate random effects summary estimates.[29] Random effects summary estimates were reported only when between-study heterogeneity was observed. Heterogeneity was evaluated using a Q-statistic, with significance considered at $P < 0.10$,[30] and I^2 metric and 95% CI to measure the percent variation in the OR because of heterogeneity.[31,32] I^2 values that are 50% or higher indicate large between-study heterogeneity, whereas values of 25–50% indicate moderate between-study heterogeneity. In the absence of statistical heterogeneity, the summary or meta-OR and corresponding 95% CI were reported based on the fixed effects model; when heterogeneity was observed, the results from the random effects model were reported. Corresponding forest plots were generated for a visual representation of all meta-analyses. The overall estimate and CI reported in the figures represent the meta-OR and CI. The Harbord test[33] was used to test for small-study effects, with significance considered at $P < 0.10$. The definition of race was self-reported in the studies included in this analysis, and African-American populations have various degrees of admixture. In an attempt to create homogeneous groups for analysis, differences in genotype frequencies between African-Americans and other African control populations were tested for the genes, which were included in the meta-analysis. Tests on the equality of proportions were performed for each group, and summary ORs were reported separately. In addition, stratified analyses according to geographic areas were performed where possible. All statistical analyses were carried out using STATA SE, version 10, software (StataCorp LP, College Station, TX).

RESULTS

We have summarized the studies that have reported data for various polymorphisms in populations of African descent and grouped according to cancer type (see Table, Supplemental Digital Content 1, http://links.lww.com/GIM/A91, which describes the publications included in this study). For breast cancer, 20 polymorphisms have been studied, but for 16 of the polymorphisms (79%) only one or two studies were conducted. There were three studies on *CYP1A1 Ile/Val,* four studies on *CYP1B1 V432L,* and five studies each on *CYP1A1 Msp1* and *CYP1A1* African-American-specific (AA specific) polymorphisms. For lung cancer, 18 polymorphisms have been studied, but for 14 of the polymorphisms (78%), only one or two studies were published. There were seven studies on *CYP1A1 Msp1,* four studies each on *GSTM1* deletion and *NQO1* (*C609T*), and three studies on *CYP1A1* (AA specific) polymorphisms. For prostate cancer, 27 polymorphisms have been studied, but for 25 of them (95%), only one or two studies have reported data. There were four studies on *CYP3A4* (*A293G*) and five studies on *CYP17* (*5′UTR*). For all other cancers (bladder, pancreas, kidney, head and neck, colon, brain, ovarian, esophagus, and leukemia), there was one or two publications for each polymorphism.

When looking at the genes for which only one or two studies reported data, there was no significant association between the polymorphism and the corresponding cancer, except for one study of *GSTT* deletion and prostate cancer showing an OR of 0.5 (95% CI = 0.8–0.88)[34]; a single study of *CYP1B1 (R48G)* (OR: 2.22; 95% CI = 1.01–5.09), *CYP17* (*rs17115144*) (OR: 3.92; 95% CI = 1.04–14.43), *CYP19* (*rs11636639*) (OR: 2.36; 95% CI = 1.10–5.05), *CYP19* (*rs3751592*) (OR: 2.88; 95% CI = 1.39–6.03), and *CYP27B1* (OR: 0.29; 95% CI = 0.08–0.88) and prostate cancer[35]; one study of *CYP3A43 (P340A*) and prostate cancer (OR: 3.54; 95% CI = 1.36–9.94)[36]; one study of *CYP17* (*5′UTR*) and lung cancer (OR: 3.03; 95% CI = 1.19–8.17)[37]; and one study of *ADH2*3 (R370C*) and *ALDH2*2 (Q487K*) polymorphisms and esophageal cancer (OR: 2.19; 95% CI = 1.23–3.90 and OR: 9.26; 95% CI = 1.16–419.64, respectively).[38]

Meta-analysis

GSTM1 deletion

For all cancers, 17 publications reported data on populations of African descent, for a total of 1437 cancer cases and 2026 controls. A meta-estimate of cancer risk with the *GSTM1* deletion was only possible for lung cancer since four studies were conducted (497 cases and 624 controls). The source of controls was for the most part the healthy population (three of four studies), and all the subjects were African-American. The meta-OR was 1.26 (95% CI: 0.96–1.65). There was no statistical evidence of heterogeneity among the four studies on lung cancer (Q: 3.47; $P = 0.324$; $I^2 = 14\%$, 95% CI: 0–87) or small-study effect ($P = 0.548$).

CYP1A1 Msp1

For all cancers, there were 14 studies on *CYP1A1 Msp1* polymorphism and cancer in populations of African descent, for a total of 1782 cases and 2213 controls. Seven studies were conducted on lung cancer (960 cases and 1189 controls) and five on breast cancer (763 cases and 864 controls).

For lung cancer, four of the seven studies (57%) involved controls from the healthy population. Five included African-American subjects[37,39–42] and two included subjects from Brazil.[43,44] There was no significant difference in the frequency of the *CYP1A1 Msp1* polymorphism between African-Americans and Brazilians (42.5% vs. 43.7%, $P = 0.847$). The ORs for the *CYP1A1 Msp1* variant in the two Brazilian studies were both

increased but not significant, and there was no overall association between the *CYP1A1 Msp1* homozygous variant and lung cancer in African-Americans (meta-OR: 0.93; 95% CI: 0.62–1.40). There was moderate heterogeneity between the African-American studies (Q statistic: 6.19, P: 0.186; $I^2 = 35.0\%$, 95% CI: 0–76) and no evidence of small-study effect ($P = 0.943$). There was also no overall association between the *CYP1A1 Msp1* heterozygotes and lung cancer (meta-OR: 1.00; 95% CI: 0.82–1.21), with no evidence of heterogeneity between studies (Q statistic: 3.48; $P = 0.481$; $I^2 = 0.0\%$, 95% CI: 0–79), or of small-study effect ($P = 0.379$).

For breast cancer, four of the five studies involved African-American subjects and controls from the healthy population (543 cases and 646 controls).[45–48] The fifth study involved a Nigerian population with hospital controls (220 cases and 218 controls).[49] There was no significant difference in the frequency of the *CYP1A1 Msp1* polymorphism between African-Americans and Africans from Nigeria (41.8% vs. 40.37%, $P = 0.711$). The meta-OR for the *CYP1A1 Msp1* homozygous variant in African-Americans (meta-OR: 1.19; 95% CI: 0.71–1.99) was compared with the OR for the single African study (OR: 0.91; 95% CI: 0.41–2.00), and neither was statistically significant. There was also no association between the *CYP1A1 Msp1* heterozygous variant with breast cancer in African-Americans (meta-OR: 0.95; 95% CI: 0.74–1.22) or in the single African study (meta-OR: 0.94; 95% CI: 0.61–1.44). For African-Americans, there was evidence of large between-study heterogeneity for both the homozygous (Q statistic: 7.42; $P = 0.060$; $I^2 = 60\%$, 95% CI: 0–87) and heterozygous (Q statistic: 5.02; $P = 0.170$; $I^2 = 40\%$, 95% CI: 0–80) variants but no evidence of small-study effect for either ($P = 0.626$; $P = 0.884$).

CYP1A1 Ile/Val

For all cancers combined, nine studies included separate results on populations of African descent, for a total of 1022 cases and 1692 controls. A meta-estimate of cancer risk with the *CYP1A1 Ile/Val* was only possible for breast cancer since three studies reported data for a total of 528 cases and 791 controls. The other cancers studied included ovarian, lung, pancreas, and head and neck cancers. All four breast cancer studies included African-Americans, and the source of controls was the healthy population. No significant association was reported in any individual study. A meta-estimate was only possible for the association of *CYP1A1* variant (*Ile/Val* and *Val/Val* allele carriers combined) and breast cancer (meta-OR: 0.77; 95% CI: 0.46–1.30). There was no evidence of between-study heterogeneity (Q statistic: 2.50; $P = 0.286$; $I^2 = 20\%$, 95% CI: 0–92) or small-study effect ($P = 0.366$).

CYP1A1 African-American specific

There were nine studies on the African-specific polymorphism (1123 cases and 1624 controls), for lung, breast, and ovarian cancer. Four studies reported data for breast cancer, and three studies reported data for lung cancer.

For breast cancer, four of the five studies included African-American populations (542 cases and 645 controls)[45–48] and the fourth included a Nigerian population (229 cases and 227 controls).[49] The source of controls was the healthy population for all except for the Nigerian study. There was a significant difference in the frequency of this polymorphism between African-Americans and Africans from Nigeria (15.8% vs. 24.2%, $P = 0.005$). The summary estimate was calculated for the association of *CYP1A1* (AA specific) variant (*wt/var* and *var/var* allele carriers combined) for African-Americans (meta-OR: 1.14; 95% CI: 0.83–1.57) and was similar compared with the OR reported for Nigerians (OR: 0.94; 95% CI = 0.60–1.48).

For lung cancer, the three studies included African-American populations (319 cases and 626 controls),[41,50,51] and all the controls were from healthy populations. The summary estimate was also calculated for the association of *CYP1A1* (AA specific) variant (*wt/var* and *var/var* allele carriers combined) (meta-OR: 1.00; 95% CI: 0.70–1.45). There was no evidence of heterogeneity among studies for lung (Q statistic: 1.65; $P = 0.438$; $I^2 = 0.0\%$, 95% CI: 0–90), and there was moderate heterogeneity between the African-American breast cancer studies (Q statistic: 5.61; $P = 0.132$; $I^2 = 47\%$, 95% CI: 0–82). There was no evidence of small-study effect for neither lung ($P = 0.294$) nor breast ($P = 0.985$).

CYP1B1 V432L

For all cancers, combined six studies reported data separately for populations of African descent. Four were breast cancer studies, and three of the four studies involved hospital controls. There were three breast cancer studies that included African-Americans (293 cases and 325 controls)[48,52,53] and the fourth included a Nigerian population (228 cases and 226 controls).[54] There was a significant difference in the frequency of this polymorphism between African-Americans and Africans from Nigeria (47.1% vs. 19.5%, $P < 0.0001$). Neither the African-American studies nor the African study reported an association between the homozygote or heterozygote polymorphisms and breast cancer (data not shown). There was moderate heterogeneity between the African-American studies and no evidence of small-study effect (data not shown).

NQO1 (C609T)

Four studies on lung cancer and the *NQO1* polymorphism in African populations were published and three of the four included healthy controls as comparison group (358 cases and 375 controls). All the studies included African-Americans. No association with lung cancer was reported for the *NQO1* (*C609T*) variant (*CT + TT*), (meta-OR: 0.91; 95% CI = 0.67–1.23), and there was no evidence of heterogeneity among the studies (Q statistic: 0.68; $P = 0.878$; $I^2 = 0.0\%$, 95% CI: 0–85) or small-study effect ($P = 0.762$).

CYP3A4 (A293G)

Four of the six studies involving the *A293G* polymorphism of the *CYP3A4* gene were conducted on prostate cancer, for a total of 608 prostate cases and 776 controls. The other two studies were on breast cancer. There is a consensus among studies on the association between the polymorphism and prostate cancer in populations of African descent. Three of the four prostate cancer studies included African-American[55–57] populations only, whereas one included both African-American and Nigerian populations.[58] There were 531 African-American cases and 694 controls, and there were 77 Nigerian cases and 82 controls. There was a significant difference in the frequency of the *CYP3A4* (*A293G*) polymorphism (GG) between African-Americans and Africans from Nigeria (41.2% vs. 74.4%, $P < 0.0001$). Although there was no association of *CYP3A4 A293G* homozygote variant and prostate cancer in Nigerians (OR: 0.3; 95% CI = 0.01–3.63) or in African-Americans, the meta-OR was almost twofold (meta-OR: 1.55; 95% CI = 0.81–2.95) for African-Americans (Fig. 1), but there was large between-study heterogeneity (Q statistic: 8.24; $P = 0.041$; $I^2 = 64.0\%$, 95% CI: 0–88) and no small-study effect ($P = 0.231$). Similarly, there was no association between *A293G* heterozygous variants and prostate cancer for the Nigerian (OR: 0.38; 95% CI =

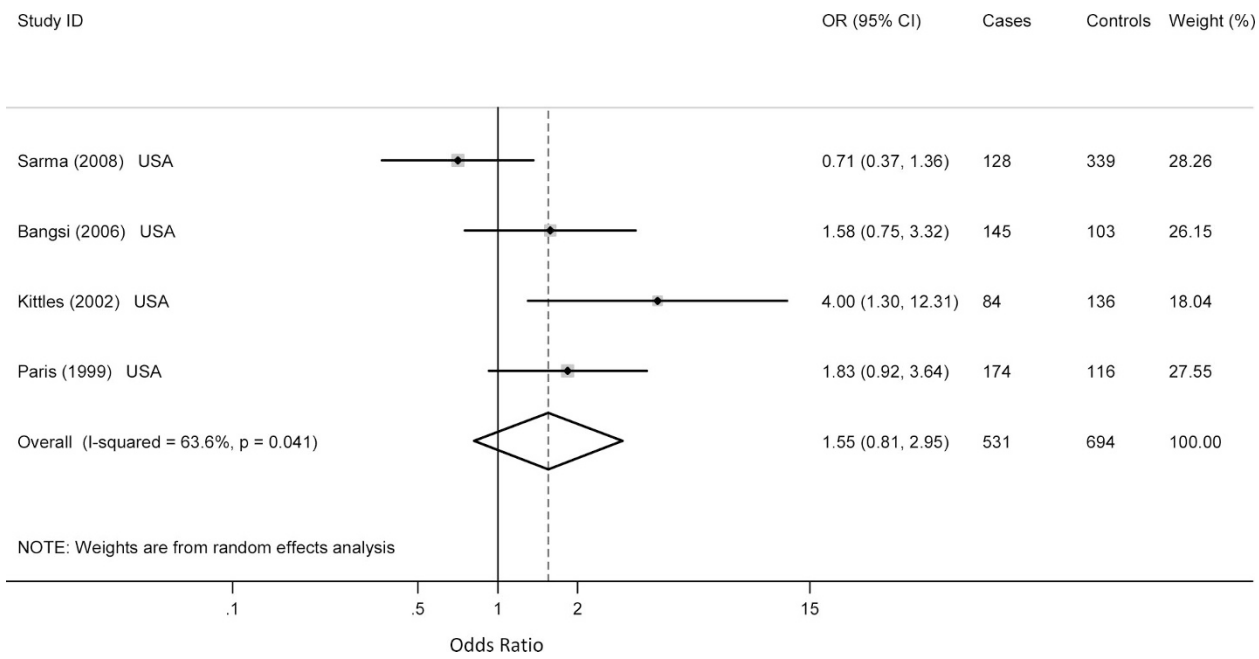

Fig. 1. Published case-control studies show a significant association of the *CYP3A4 (A293G)* homozygous variant and prostate cancer in African-Americans. The shaded boxes represent the study-specific odds ratios, and horizontal lines represent the confidence intervals; the size of the rectangles depict how each study is weighted in the analysis, and the diamond represents the meta-OR and its width represents the CI for the meta-OR.

0.01–5.32) or the African-American (meta-OR: 1.26; 95% CI: 0.72–2.20) studies. There was large heterogeneity between the African-American studies (Q statistic: 6.63; $P = 0.085$; $I^2 = 55\%$, 95% CI: 0–85) and evidence of small-study effect ($P = 0.05$).

CYP17 (5′UTR)

For all cancers combined, eight studies reported data for the *CYP17 5′UTR* polymorphism (595 cases and 839 controls). Five studies were conducted on prostate cancer, for a total of 277 cases and 494 controls.[55,59–62] Two studies were on breast cancer[48,63] and one study on lung cancer.[37]

All the prostate cancer studies included African-American populations. The homozygous variant polymorphism was marginally associated with prostate cancer (meta-OR: 1.56; 95% CI: 0.97–2.51), without evidence of heterogeneity among studies (Q statistics: 2.31; $P = 0.679$; $I^2 = 0.0\%$, 95% CI: 0–79), or small-study effect ($P = 0.759$) (Fig. 2). There was no statistically significant association between the heterozygous variant and prostate cancer (meta-OR: 1.35; 95% CI: 0.65–2.80), although considerable between-study heterogeneity was present (Q statistics: 13.39; $P = 0.010$; $I^2 = 70\%$, 95% CI: 24–88). There was no evidence of small-study effect ($P = 0.276$).

DISCUSSION

This review of the literature indicates that although there is a wealth of studies on genetic polymorphisms and cancer risk, studies on populations of African descent are few. This observation is in contrast with the fact that for decades, underrepresented minorities have shown higher mortality rates than most other ethnic groups from cancer.[64,65] Despite the fact that studies have shown that genetic susceptibility to tobacco carcinogens increases individual cancer risk,[66] information on individual susceptibility to tobacco and gene-environment interaction are lacking in subjects of African descent, mostly because they are underrepresented in current research studies. Therefore, it is not yet possible to determine whether association exists between a given genetic polymorphism and cancer risk in populations of African descent and the degree of interaction between such polymorphisms and environmental exposure.

In the United States, studies have investigated reasons for the underrepresentation of African-Americans in medical research. Shavers-Hornaday and Lynch[67] reviewed the literature and reported that the reasons for underrepresentation of African-Americans in research may be due to participant barriers such as distrust; poor access; quality and utilization of health care; lack of knowledge about clinical trials; language and culture; and investigator barriers, such as failure to actively recruit participants because of preexisting beliefs regarding the ability to recruit and retain participants; small number of minority research investigators; limited relationships between minority health care providers; and fears of how research results will be interpreted. Nevertheless, the successful recruitment and participation of African-Americans have been accomplished by some investigators, although these studies are few. Efforts to increase the number of represented minority participants in research studies are warranted.

We have shown that for each gene, there are several different cancer types that were studied. The majority of these include breast, prostate, and lung cancers, which are reported to be among the top four cancers with the highest incidence and mortality rates in African-Americans.[3] Although several genes have been studied for various cancers, only one or two studies per gene for each cancer site have been published, with the exception of breast (*CYP1A1* and *CYP1B1*), lung (*GSTM1, CYP1A1,* and *NQO1*), and prostate (*CYP3A4 A293G* and

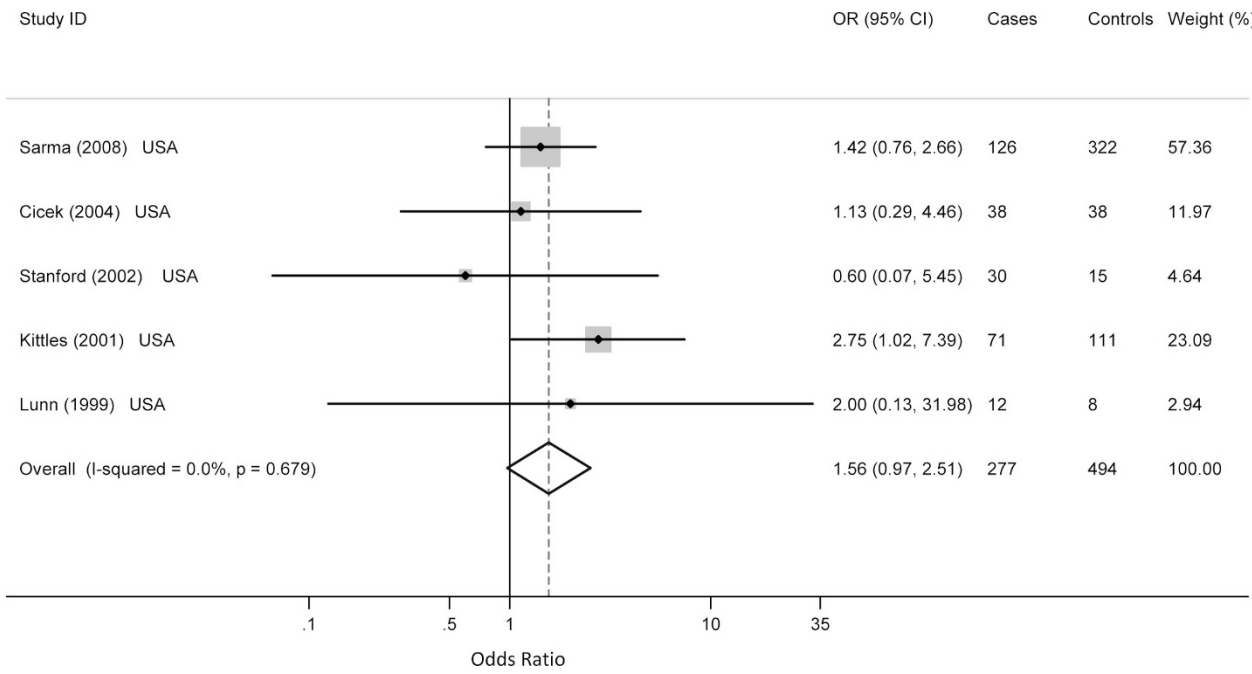

Fig. 2. Published case-control studies show a marginal significant association of the *CYP17 5′UTR* homozygous variant and prostate cancer in African-Americans. The shaded boxes represent the study-specific odds ratios, and horizontal lines represent the confidence intervals; the size of the rectangles depict how each study is weighted in the analysis, and the diamond represents the meta-OR and its width represents the CI for the meta-OR.

CYP17). For the breast cancer studies that reported data for African-Americans and Africans, the frequencies of the *CYP1A1* AA-specific and *CYP1B1 V432L* variants in the controls were significantly different between the two populations. Neither of the two populations showed statistically significant associations of these genes and breast cancer. It is possible that the difference in gene variant frequencies between the two African-descent populations might be attributed to admixture among African-Americans or to linkage disequilibrium with other relevant genetic polymorphisms, suggesting that further studies in African descent populations are needed.

For prostate cancer, a marginal association was observed for *CYP3A4 A293G* and *CYP17* and prostate cancer in African-Americans, whereas an inverse relationship was reported for *CYP3A4 A293G* in the single Nigerian study. Our findings suggest that the differences in prostate cancer risk for *CYP3A4 A293G* between African-Americans and Africans and the contribution of admixture in African-Americans needs further investigation. Studies of *CYP3A4 A293G* and prostate cancer in whites report a marginally statistically significant increased OR[56,58]; two studies on *CYP17* in whites show no association[59,62]; and one study reported an increased OR.[61] Because of the small number of case-control studies in our meta-analyses, the reproducibility of the reported results for each cancer/gene association could not be evaluated, which made it difficult to interpret the reported results.

The *CYP17* gene encodes an enzyme, which functions at key points in steroid hormone biosynthesis and metabolism pathways,[68] and the polymorphism in the 5′-UTR is thought to affect hormone levels. High levels of androgens have been considered as risk factors for prostate cancer.[69] However, the relationship between the *CYP17* variant and increased hormone levels is inconclusive.[70] In 2003, a meta-analysis on the association between the *CYP17* variant and prostate cancer was published and included 10 studies conducted in Europe, Asia, and the United States (2404 prostate cancer cases and 2755 controls).[71] The report showed that the overall contribution of the *CYP17 5′UTR* polymorphism to prostate cancer risk was not evident; however, there were distinct differences based on ethnicity (European descent, OR: 1.04; 95% CI, 0.92–1.18; Asian descent OR: 1.06; 95% CI, 0.66–1.71; and African descent OR: 1.56; 95% CI, 1.07–2.28). There were three studies in this meta-analysis, 113 cases and 134 controls. Although our meta-analysis includes much larger population (5 studies, 277 cases, and 494 controls), the findings from the earlier study was consistent with our findings and suggest a need for large-scale investigation of the association of the gene variant and prostate cancer risk in males of African descent. The gene product of *CYP3A4* is involved in the oxidation of a large range of substrates including therapeutic drugs, steroids, fatty acids, and xenobiotics, and similar to *CYP17*, also plays a role in androgen metabolism.[72] It is biologically plausible that both these genetic polymorphisms may play a significant role in prostate cancer risk. Further, larger studies of the association of these gene variants and prostate cancer in populations of African descent are warranted.

Overall our findings support the need for larger studies of *CYP1A1 Msp1* and breast cancer and *CYP17* and *CYP3A4 A293G* and prostate cancer in African descent populations. The development of large-scale, population-based databases that document genetic variation in tobacco-related genes among case and control subjects that represent populations of African ancestry would serve as an important resource for cancer-control and prevention programs. Our findings support the need for additional genetic association studies of breast, prostate, and lung cancers that include larger number of minority participants and a better definition of African ancestry. Specifically, there is a need to concentrate research on these three major cancers,

because incidence and mortality rank the highest among populations of African descent. Furthermore, specific research focus is needed on genes with a sound hypothesis related to cancer risk in subjects of African descent. Our review of the literature reveals that the majority of studies have been conducted in the United States, but still very few involve African or other populations of African ancestry such as African-Caribbean. This may be due to the limited financial and infrastructural resources available to conduct these studies. Nevertheless, it is clear that efforts to increase the number of studies in African descent populations outside of the United States are warranted.

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