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Polymorphisms in *CYP17* and *CYP3A4* and Prostate Cancer in Men of African Descent

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Abstract

BACKGROUND—A meta and pooled analysis of published and unpublished case-control studies was peNorrformed to evaluate the association of *CYP17* (rs743572) and *CYP3A4* (rs2740574) polymorphisms and prostate cancer in men from the USA, Caribbean and Africa.

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The authors have no conflicts of interest to report.

METHODS—Eight publications (7 studies) and two unpublished studies for *CYP17* included 1,580 subjects (559 cases and 1,021 controls) and eleven publications and three unpublished studies for *CYP3A4* included 3,400 subjects (1,429 cases and 1,971 controls).

RESULTS—Overall, the *CYP17* heterozygous and homozygous variants were not associated with prostate cancer, but they confer a 60% increased risk of prostate cancer in a sub-group analysis restricted to African-American men (T/C+C/C, OR: 1.6, 95% CI: 1.1–2.4). No associations were observed for *CYP3A4*, overall and in stratified analyses for African-Americans and Africans. The pooled analysis suggests that after adjusting for study, age, PSA and family history of prostate cancer, *CYP17* was found to be associated with prostate cancer for men of African ancestry (Adjusted OR: 3.5, 95% CI: 1.2–10.0).

CONCLUSIONS—Our findings suggest that genetic factors involved in the androgen pathway play a role in prostate cancer risk among men of African ancestry.

Keywords

Prostate cancer; Genetics; African ancestry

INTRODUCTION

Prostate Cancer (PCa) is one of the most common causes of death in men (1). In the US the Surveillance Epidemiology and End Results (SEER) reported that the age-adjusted PCa incidence rate for all races was 151.9 per 100,000 in 2009 (2) with a higher incidence in men of African descent compared to white men (238.8 per 100,000 vs. 149.7 per 100,000 for the period 1979–2009) (2).

Established risk factors for prostate cancer include older age, genetic susceptibility, and race/ethnicity. Environmental exposure to hormone disruptors, diet, socioeconomic status, and access to health care have been studied as potential factors in prostate cancer etiology (3,4). Because of the prominent role of hormone levels in prostate cancer development, it has been hypothesized that genes involved in hormone production and metabolism could play a key role in determining an individual's susceptibility to the effects of endogenous hormones. Potential candidate genes include *CYP3A4* and *CYP17*. These Phase I metabolic genes are involved in drug metabolism; *CYP3A4* encodes an enzyme involved in several pathways including drug metabolism, and the oxidation of both testosterone and estrogen (5). The *CYP17* gene encodes an enzyme that is a key step in the steroidogenic pathway that produces progestins, androgens, estrogens and glucocorticoids (6). Among the *CYP17* gene polymorphisms, one (rs743572) has been more extensively studied because its variant allele (conventionally called A2; a T→C transition in the 5'UTR) may affect the binding characteristics of the promoter region thus modifying the gene's function (7). This could have consequences on androgen levels and prostate cancer risk.

CYP3A4 is a highly polymorphic gene; the polymorphism located in the 5' regulatory region of the gene (rs2740574) has been reported to be associated with prostate cancer both in Black and White populations. Even though there are published case-control studies evaluating the relationship between *CYP3A4* and *CYP17* polymorphisms and prostate cancer, very few include populations of African descent. A recent meta-analysis conducted by Wang et al. reported that a polymorphism in *CYP17* (rs743572) is associated with an increased risk of prostate cancer in men of African descent (8). There is no summary relative risk estimate for *CYP3A4* polymorphisms and prostate cancer in men of African descent. The present study was made possible through a partnership of the Genetic Susceptibility to Environmental Carcinogens study (GSEC, www.gsec.net) and the African-Caribbean Cancer Consortium (AC3, www.ac-ca-consortium.org) (9), which constituted the GSEC-

AC3 consortia. In addition, other research groups with relevant information for men of African ancestry have shared data for this project. We herein report the relationship between selected *CYP3A4* and *CYP17* polymorphisms and prostate cancer risk in men of African descent by analyzing existing published studies and presenting unpublished data from two studies conducted in Nigeria and Jamaica.

METHODS

Selection Criteria

A Medline literature search was conducted for case-control studies published between 1999 and August 2011 on the association between polymorphisms in *CYP3A4* and *CYP17* and prostate cancer risk in populations of African descent. The search key terms used to extract the literature were "[African-American OR African] AND [polymorphism OR gene] AND prostate cancer AND *CYP3A4*" and "[African-American OR African] AND [polymorphism OR gene] AND prostate cancer AND *CYP17*". Several articles were identified; for this particular study only literature with original case-control studies that include men of African descent were selected, and 131 publications were identified as a result, 45 of which included data on *CYP3A4*. Among the 45 publications only 10 were case-control studies that included men of African descent, while the remaining 35 publications included reviews of other published articles, study populations other than men of African descent, and/or articles not related to prostate cancer. The *CYP17* search originally yielded 86 publications, but only 7 publications were case-control studies and included men of African descent. The full articles relative to the 17 included publications were retrieved for research analysis purposes. The authors' names and contact information was extracted from each article and an invitation to participate in an international pooled-analysis study of *CYP17* and *CYP3A4* polymorphisms and prostate cancer risk in men of African descent was extended. The protocol developed by the GSEC study for data request, data handling, confidentiality, data analysis, and publication was followed (10).

Unpublished Studies—Members of the African-Caribbean Cancer Consortium with ongoing prostate cancer studies in men of African descent contributed unpublished data from their studies.

Study in Nigeria—While the data presented in this study is unpublished the study population was recruited as part of an existing ongoing study. The description of the study population has been previously published (11). Briefly, Nigerian men ≥40 years residing in Edo, Delta, and Plateau States of Nigeria were recruited in the waiting room of surgery and urology clinics of the University of Benin Teaching Hospital and affiliated hospitals and health centers, and from door-to-door invitation in selected rural and urban communities. Study participants signed an informed consent, provided demographic and urology symptom information to a trained interviewer, allowed 30ml. of fasting venous blood draw, and underwent a digital rectal examination (DRE). Blood samples were processed and shipped to the US quarterly; PSA analysis was performed by a commercial laboratory for within the week. Men with abnormal PSA and/or DRE were followed up with a prostate biopsy.

Study in Jamaica—Following written informed consent and Ethics Committee of the University of the West Indies approval, 240 Jamaican men (114 cases, 126 controls) were recruited and consecutively enrolled between 2005 and 2007 during their first time visit to the urology clinics at the University Hospital of the West Indies, Mona Jamaica with a histologically confirmed new diagnosis of prostate cancer. Controls were selected from a pool of men visiting the clinic for treatment of urinary tract infections, urinary stones, infertility, erectile dysfunction, or decreased libido. All controls had normal DREs, total

PSA (<4.0ng/ml) or total:free PSA ratios (<0.25) and no prior cancer history. Medical records were reviewed to ensure that there was no previous history of prostate surgery or hormonal/finasteride treatment. DNA from blood was extracted, processed and shipped on dry ice to the US.

Study in Brazil—A case–control study was conducted at the Londrina State University (Paraná-Brazil) with samples collected from 172 patients (18 African descendents) from Londrina Cancer Hospital (Paraná-Brazil) and Local Urological Clinics between 2005 and 2008. The study was approved by the local Ethics Committee. The patients and control group signed a written informed consent form and answered a questionnaire about their lifestyle, ethnicity, age, occupation, and family history of cancer. Inclusion criteria were suspicious findings on a DRE and/or elevated PSA serum levels (≥2.5 ng/mL), followed by the histopathological confirmation of prostate cancer. The control group consisted of 168 (14 African descendents) cancer-free men with a negative DRE and serum PSA lower than 2 ng/ml. Controls were matched to cancer patients on the basis of age (±5 years), ethnic group (Euro and African descendents), and drinking and smoking habits. Further details are described in Rodrigues et al. (12), however, this publication only included participants of European descent.

***CYP3A4* and *CYP17* Genotyping—**Genotyping of the samples from the unpublished studies in Nigeria and Jamaica was performed in the same laboratory. Briefly, *CYP3A4* and *CYP17* polymorphisms were detected by PCR and restriction reaction. PCR was carried out in a 25-μL mixture containing 100 ng of genomic DNA, and Amplitaq Gold PCR Master Mix (Applied Biosystems, Carlsbad, California). The following primers were used: forward (5'-GGACAGCCATAGAGACAAGGG GA-3') and reverse primer (5'-CACTCACTGACCTCCTTTGAGTTA-3') for *CYP3A4*, which produced a 190-bp fragment and CYP17214F (TCCTGAGCCCAGATACCAT) and CYP823R (CCGCCCAGAGAAGTCCT) for *CYP17*, which produced a 629 bp. *CYP3A4* and *CYP17* PCR products were digested with 10 U of *MboII* (New England Biolabs, Ipswich, MA) and *MsPAI* (New England Biolabs, Ipswich, MA), respectively and digested PCR products were ran on 3% Nusieve 3:1 agarose gel (Lonza, Rockland, ME). For *CYP3A4*, A/A homozygous wild type, A/G heterozygous, and G/G homozygous variant resulted in 156 and 34bp; 190, 156 and 34bp; and 190bp digestion products, respectively. For *CYP17*, T/T, T/C, and C/C genotypes resulted in 577; 577, 305, and 272; and 305 and 272 digestion products, respectively. Genotyping of samples from the published studies included in our pooled analysis have been previously described (13–27).

Statistical Analysis—All statistical analyses were carried out using STATA SE (version 10.0) software (StataCorp LP, College Station, TX).

Meta-Analysis—Summary odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each gene variant, overall and stratified by ethnicity. Statistical heterogeneity between and within groups was tested using the Q statistic (28), to determine whether to use the fixed- or random-effects model for calculating the summary ORs. Fixed-effects methods were used if the result of the Q-test was not significant. Otherwise, we calculated pooled OR estimates and CIs assuming a random-effects model with inverse-variance weighting, using the DerSimonian and Laird method (28). The proportion of total variability attributed to between-study heterogeneity, the I^2 statistic, and its corresponding 95% CI were also calculated (29). The possibility of publication bias was assessed using Begg funnel plots and Egger's bias test (30).

Pooled Analysis—For each gene variant, crude odds ratios (ORs) for the association with prostate cancer were calculated. Summary ORs were adjusted for study site, age (continuous), PSA (continuous), using multivariable logistic regression models. The crude and adjusted ORs were also calculated for each gene polymorphism. The Q-test and I^2 statistic were calculated as described above.

RESULTS

CYP17

There were 9 studies on *CYP17* rs743572 and prostate cancer in men of African descent (Table I), five of them conducted in African American men, two in populations of African descent from Canada and Brazil, one conducted in Africa and one in the Caribbean, for a total of 559 prostate cancer cases and 1,021 controls. The source of controls was the healthy population in five studies, blood donors in one and patients hospitalized for reasons other than prostate cancer in three studies. PSA values and digital rectal examination were used to confirm the controls health status in six studies.

Overall, there was no association between the *CYP17* variant and prostate cancer. The OR of prostate cancer for the T/C versus T/T (homozygous wild-type) genotype was 1.26 (95% CI: 0.95–1.67), and for C/C versus T/T was 1.43 (95% CI: 0.94–2.2), with no heterogeneity observed among studies. The analysis of the studies including only African-American subjects however, showed a significant association between the *CYP17* polymorphism and prostate cancer. The OR of prostate cancer for the T/C versus T/T genotype was 1.51 (95% CI: 1.01–2.26), and for C/C versus T/T was 2.02 (95% CI: 1.14–3.58), with no heterogeneity observed among studies.

The authors of four studies agreed to contribute individual data for pooled analysis, for a total of 649 subjects (339 cases, 310 controls). The results (Table III) indicate a borderline association between *CYP17* and prostate cancer; after adjustment for possible confounders, the OR of prostate cancer in subjects carrying the heterozygous or homozygous variant genotype was 3.5 (95% CI: 1.2–10.0). The data were further stratified by family history for prostate cancer and by the mean PSA value (2ng/ml) among controls, but no differences in the association between *CYP17* and prostate cancer were observed across these subgroups (data not shown).

CYP3A4

There are 14 studies reporting the association between *CYP3A4* rs2740574 and prostate cancer in men of African descent (Table II). Three studies were conducted in African men, eight in African-American men, two in men of African descent and one in Caribbean men. The number of cases included is 1429, while controls are 1971; in nine studies the controls were healthy volunteers, in four studies subjects were hospitalized for reasons other than prostate cancer, in one study controls were enrolled through prostate cancer screening. In 11 studies control status was confirmed by testing PSA measurement and digital rectal examination.

The meta analysis did not suggest an association between prostate cancer and the *CYP3A4* polymorphisms studied. The OR of prostate cancer with the A/G polymorphism versus the A/A (homozygous wild-type) genotype was 0.98 (95% CI: 0.73–1.35), and for G/G versus A/A was 1.18 (95% CI: 0.83–1.66). For all studies, moderate heterogeneity was observed between studies. The sensitivity analysis indicated that the Fernandez et al. study (18) influenced the meta OR - therefore that study was excluded from the meta OR calculations.

The stratified analysis by ethnicity did not suggest any association between prostate cancer and *CYP3A4* either in African-American or African men.

The pooled analysis of four studies for which individual data were received confirmed the lack of association between *CYP3A4* and prostate cancer in men of African descent, after adjusting for potential confounders. There were originally five studies with *CYP3A4* data (N = 990, 478 controls and 512 cases), but heterogeneity among studies was observed; the sensitivity analysis indicated that Fernandez et al (18) contributed to the heterogeneity, therefore the study was removed in the combined analysis. The participants of this study were not predominantly African, rather defined as “colored”, a specific mixed South African ethnic group. The association between the *CYP3A4* polymorphism and prostate cancer was further studied by stratifying the data set according to family history for prostate cancer and for PSA mean levels among controls; the results were similar to the results obtained in the main analysis (data not shown).

DISCUSSION

The current meta-analysis suggests a possible association between *CYP17* rs743572 and prostate cancer in men of African ancestry, with a significant association limited to African-American men. Only one study was available among African men and one among Caribbean men; therefore, conclusions on these ethnic groups are not possible at this time based on the small sample sizes. A previous meta-analysis (31) suggested a significant association of the same *CYP17* polymorphism with prostate cancer risk in men of African descent, but the analysis only included three studies. A focused analysis on black men (32) suggested an association between *CYP17* and prostate cancer. A subsequent meta-analysis (8) included six studies and suggested a significant association between *CYP17* rs743572 and prostate cancer, but the specific ethnic background of the men of African ancestry included was not further specified. In the present analysis we were able to confirm that the association is clearly present in African-American men, while data on African and Caribbean men are too sparse for drawing any conclusion. The analysis of individual data of a subset of the studies confirms the significant association of *CYP17* rs743572 and prostate cancer, after adjustment for possible confounding factors.

The *CYP17* gene encodes a key enzyme for steroid hormone biosynthesis and metabolism(33), thus the polymorphism may affect hormone levels; high levels of androgens have been considered as risk factors for prostate cancer, but studies of circulating androgens have failed to confirm an association (34,35). There is indirect information from the PCPT study that medications such as finasteride, which block the conversion of circulating testosterone to dihydrotesterone in the prostate, are associated with a reduction in prostate cancer incidence (36–38).

It is not clear why previous meta-analyses, while confirming the present results, did not show a similar association in White and Asian populations (8,31). It is possible that in men of African ancestry the *CYP17* rs743572 is a marker of polymorphisms in other metabolic genes involved in hormone synthesis and metabolism; alternatively, dietary factors and/or endogenous hormonal levels may vary according to race and ethnicity (39,40), and may act on the gene function thus modulating the individual's prostate cancer risk associated with the *CYP17* rs743572 polymorphism. Our study suggests that the androgen pathway and *CYP17* specifically contributes to prostate cancer incidence in men of African descent. Although other androgen pathway genes may be relevant, the review of the published literature revealed that a limited number of case-control studies have been conducted in populations of African ancestry (32). One publication was identified that evaluated the association of 116 genetic polymorphisms in 12 genes involved in the androgen pathway with prostate cancer.

The genes included were CYP17, HSD17B3, ESR1, SRD5A2, HSD3B1, HSD3B2, CYP19, CYP1A1, CYP1B1, CYP3A4, CYP27B1, and *CYP24A1* (16). The study reported an increased association of *CYP19* with prostate cancer for African-American men (Adjusted Odds Ratio: 1.90, 95% CI 1.03–3.51).

The analysis of studies on *CYP3A4* rs2740574 and prostate cancer in men of African ancestry yielded no evidence of association between the polymorphism and prostate cancer, overall or in subgroup analyses restricted to African-American and African men. There is one previous meta-analysis involving this gene variant as a risk factor for prostate and breast cancer (41), however the publication included a limited number of men of African ancestry (one study on African men, one on African-American). The present analysis is the largest conducted so far, involving over 1,400 prostate cancer cases and 1,900 controls; this large number allowed for stratification according to ethnicity, thus confirming the lack of association in African-American as well as in African men. Because CYP3A4 is involved in the oxidation of testosterone to less active forms of the hormone (2β, 6 β, or 15 β hydroxytestosterone), a polymorphism that modifies the bioavailability of testosterone may indirectly increase the activity of the alternative pathway that converts testosterone to dihydrotestosterone, a compound that mediates prostate cell growth. Despite this interesting premise, the present analysis was not able to confirm a role of *CYP3A4* rs2740574 in prostate cancer risk in men of African descent. Similarly, the analysis of individual data on a subset of the sample confirms the results.

The present analysis has several strengths: the large number of cases and controls of African ancestry, which was gathered through a careful review of the available publications; the presence of previously unpublished data from Africa and the Caribbean; and the availability of individual-level data that allowed a more refined analysis including adjustment for possible confounders.

Despite these strengths, there are still limitations to be considered: the number of studies conducted in prostate cancer among men of African descent is still small, and especially lacking are studies conducted in men living in African and Caribbean countries. The available studies do not take into account the role of environmental factors in determining gene function in these populations that could modify an individual's cancer risk in comparison to their white counterpart. A major limitation is that data for all the genetic variants in *CYP17* and *CYP3A4* were not available for all studies; therefore our analysis was limited to a single SNP in each gene. Therefore more extensive assessment of all gene variants in both genes should be performed in future studies of these populations of African heritage.

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Table I

Studies on *CYP17* rs743572 and Prostate Cancer

				Cases			Controls			
Author, year (Country)	**ref**	**control source**	**cases/control**	**T/T**	**T/C**	**C/C**	**T/T**	**T/C**	**C/C**	**ethnicity**
Sarma, 2008 (USA)	(25)	Healthy; PSA ≤4 ng/ml, normal DRE	131/342	52	51	23	106	183	33	African American
Stanford, 2002; Kwon 2012 (USA)[#]	(2126)	Healthy	30/15	10	18	2	6	7	2	African American
Beuten, 2009 (USA)	16	Volunteers; PSA <2.5 ng/ml, normal DRE	82/209	26	40	16	79	105	25	African American
Kittles, 2001 (USA)	19	Healthy, screening; PSA ≤4 ng/ml, normal DRE	71/111	22	38	11	55	46	10	African American
Lunn, 1999 (USA)[#]	22	Hospital	12/8	4	6	2	4	3	1	African American
Nam, 2003 (Canada)	23	Hospital; normal PSA and DRE	45/45							African descent
dos Santos, 2001 (Brazil)	17	Blood donors; negative DRE and PSA < 2 ng/ml	8/72	4	3	1	33	29	10	African descent
Ukoli, 2011 (Nigeria)[#]	unp	Healthy; normal PSA and DRE	66/93	32	26	8	44	37	12	African
Jackson, 2011 (Jamaica)[#]	unp	Hospital; normal DRE, PSA <4 ng/ml	114/126	49	58	11	56	59	13	Caribbean
Total			559/1021							

	META ANALYSIS	**TT**	**T/C**	**C/C**	**T/C+C/C**
All studies	**Meta OR**	1.0 (ref)	1.26(0.95–1.67)	1.43 (0.94–2.20)	1.29(0.98–1.68)
	Q-test p-value		0.73	0.58	0.60
	I^2 p-value		0% (0–71)	0% (0–71)	0% (0–71)
	Eggers test P-value		0.77	0.55	0.93
African-American	**Meta OR**	1.0 (ref)	1.51 (1.01–2.26)	2.02(1.14–3.58)	1.62(1.10–2.37)
	Q-test p-value		0.62	0.67	0.65
	I^2 p-value		0% (0–85)	0% (0–85)	0% (0–85)
	Eggers test P-value		0.71	0.46	0.89

DRE: digital rectal examination PSA: prostate serum antigen;

[#]studies included in the pooled analysis

Table II

. Studies on *CYP3A4* rs2740574 and Prostate Cancer

				Cases			Controls			
Author, year (Country)	**ref**	**control source**	**cases/controls**	**A/A**	**A/G**	**G/G**	**A/A**	**A/G**	**G/C**	**Ethnicity**
Ukoli 2011 (Nigeria)#	unp	Healthy; normal PSA and DRE	66/93	6	21	39	6	28	59	African
Kittles 2002 (Nigeria)	[20]	Healthy, screening; PSA ≤4 ng/ml, normal DRE	77/82	3	23	51	1	20	61	African
Fernandez 2010 (South Africa)#	[18]	Hospital; PSA ≤2.5 ng/ml, normal DRE	160/146	63	82	15	87	56	3	African
Kittles 2002 (USA)	[20]	Healthy, screening; PSA ≤4 ng/ml, normal DRE	84/136	4	32	48	23	44	69	African American
Sarma 2008 (USA)	[25]	Healthy; PSA ≤4 ng/ml, normal DRE	131/342	17	66	45	40	149	150	African American
Bangsi 2006 (USA)	[14]	Healthy	145/103	21	66	58	20	48	35	African American
Paris 1999 (USA)	[24]	Convenience sample	174/116	30	64	80	22	62	32	African American
Beuten 2009 (USA)^	[16]	Volunteers; PSA <2.5 ng/ml, normal DRE	82/209	11	39	32	23	100	86	African American
Berndt 2007 (USA)	[15]	Screening; normal PSA and DRE	103/396							African American
Zeigler-Johnson 2004 (USA)	[27]	Hospital; normal PSA and DRE	77/64	16	30	31	18	25	21	African American
Agalliu 2008 (USA)#	[13]	Healthy	145/83	30	62	53	11	48	24	African American
Nam 2003 (Canada)	[23]	Hospital; normal PSA and DRE	45/45							African descent
Rodrigues2011 (Brazil)#	unp	Volunteers; normal DRE, PSA < 2 ng/ml	18/14	12	4	2	10	3	1	African descent
Jackson 2011 (Jamaica)#	unp	Hospital; normal DRE, PSA<4 ng/ml	122/142	4	54	60	5	58	65	Caribbean
TOTAL			1429/1971							

META ANALYSIS		**A/A**	**A/G**	**G/G**	**A/G+G/G**
All Studies *	**Meta OR**	1.0 (ref)	0.98(0.73–1.35)	1.18(0.83–1.66)	1.07(0.80–1.43)
	Q-test p-value		0.27	0.18	0.26
	I^2 p-value		18% (0–58)	28% (0–64)	19% (0–59)
	Eggers test P-value		0.94	0.54	0.69
African-American **	**Meta OR**	1.0 (ref)	0.90(0.67–1.22)	1.14(0.79–1.63)	1.01 (0.76–1.33)
	Q-test p-value		0.42	0.24	0.46
	I^2 p-value		0% (0–75)	26% (0–69)	0% (0–75)
African *	**Meta OR**	1.0 (ref)	0.64(0.21–1.96)	0.55(0.19–1.59)	0.58(0.20–1.66)

META ANALYSIS	A/A	A/G	G/G	A/G+G/G
Q-test p-value		0.62	0.51	0.53

DRE: digital rectal examination;

^Numbers calculated from frequencies furnished by the Author;

*Excludes Fernandez et. al. because the sensitivity analysis revealed that Fernandez et al. influenced the heterogeneity among studies.

**Excludes Kittles et al. because the sensitivity analysis revealed that Kittles et al. influenced the heterogeneity among studies.

#studies included in the pooled analysis

Table III

Pooled Analysis of Studies on *CYP17*, *CYP3A4* and Prostate Cancer

***CYP17* rs743572**	**Controls (N)**	**Cases (N)**	**Crude OR (95 % CI)**	**Adjusted OR* (95 % CI)**
N = 649 (n of studies = 4)				
AA	143	137	1.0 (ref)	1.0 (ref)
AG	129	158	1.3(0.9–1.8)	3.6(1.2–10.5)
GG	38	44	1.2(0.7.2.0)	3.1 (0.6–18.0)
AG+GG	167	202	1.3 (0.9–1.7)†	3.5(1.2–10.1)

***CYP3A4* rs2740574**				
N = 684 (n of studies = 4)				
AA	33	52	1.0 (ref)	1.0 (ref)
AG	142	141	0.6(0.4–1.0)	1.1 (0.1–8.8)
GG	157	159	0.6(0.4.1.0)	0.5 (0.1–3.6)
AG+GG	299	300	0.6 (0.4–1.0)††	0.7(0.1–5.3)

Each study was found to be in HW equilibrium ($p<0.05$)

*Adjusted for study number, age (continuous), PSA (continuous)

†Q test (p value= 0.642); Egger test (p value = 0.633)

††Excluding Fernandez – Q-test p-value = 0.668, Eggers test p = 0.110

§Q test (p value =0.596); Eggers test (p value = 0.549