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Functional variants in *CYP1A1* and *GSTM1* are associated with clearance of cervical HPV infection

Staci L. Sudenga¹, Sadeep Shrestha¹, Maurizio Macaluso², Edward E. Partridge³, Gary L. Johanning⁴, and Chandrika J. Piyathilake^{5,*}

¹Department of Epidemiology, School of Public Health, University of Alabama at Birmingham, Birmingham, AL

²Division of Biostatistics and Epidemiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

³Department of Obstetrics and Gynecology, School of Medicine, University of Alabama at Birmingham, Birmingham, AL

⁴Biosciences Division, Center for Cancer & Metabolism, SRI International

⁵Department of Nutrition Sciences, School of Nutrition, University of Alabama at Birmingham, Birmingham, AL

Abstract

Objective—We evaluated time to clearance of high risk (HR) HPV infection in relation to functional variants in three genes (*CYP1A1*, *GSTT1*, and *GSTM1*).

Methods—The study group consisted of 450 HR-HPV infected women from the Atypical squamous cells of undetermined significance-low-grade squamous intraepithelial Lesion Triage Study (ALTS) cohort followed up at the clinical center at Birmingham, Alabama. The Cox proportional hazard model with the Wei-Lin-Weisfeld (WLW) approach was used, controlling for relevant covariates.

Results—Women who were polymorphic for *CYP1A1* experienced a HR-HPV clearance rate that was 20% (HR=0.80, p=0.04) lower than women without the polymorphism for *CYP1A1*, adjusting for all other cofactors. The *GSTM1* null genotype was associated with higher HR-HPV clearance rate (HR= 1.39, p=0.006). The polymorphism in *GSTT1* was not significantly associated with time to clearance of HR-HPV.

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*Chandrika Piyathilake, BDS, MPH, PhD, Professor of Nutrition Sciences, Wallace Tumor Institute 420 D, 1824 6th Avenue South, Birmingham, AL 35294-3300, Phone: 1-205-975-5398, piyathic@uab.edu.

Conflict of Interest

None of the authors have any financial relationships or conflicts of interest to declare.

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Conclusions—Xenobiotic metabolism genes may influence the natural history of HR-HPV infection and its progression to cervical cancer.

Keywords

CYP1A1; GSTT1; GSTM1; Host genetics; ALTS

Introduction

HPV infection is a necessary but not sufficient cause of cervical cancer. Whereas the vast majority of infected individuals naturally clear their infection(s), further research is warranted to distinguish risk factors that lead a subset of individuals infected with high risk HPV (HR-HPV) types to have persistent infection and later develop cervical lesions [1]. Functional variants of three xenobiotic metabolism genes: cytochrome P450, family 1, subfamily A, polypeptide 1 (*CYP1A1*), glutathione S-transferase mu 1 (*GSTM1*), and glutathione S-transferase theta 1 (*GSTT1*) have been associated with several cancers including cervical cancer but the results have been inconsistent [2–6]. Previous research has also found increased risk of cervical disease associated with combinations of these three polymorphisms, suggesting that interaction between these polymorphisms may be important [3]. Inconsistent findings on the association of these polymorphisms with cervical cancer also suggest that studying this association at an early endpoint, HPV infection, may help elucidate the carcinogenic process [7].

It is unknown how polymorphisms in the three genes interact with HPV infection. We hypothesized that the three genetic variant among these genes may influence HPV clearance. In this study we examined the association of the three host gene polymorphisms with HR-HPV infection outcomes taking into account other risk factors, multiple HPV co-infections, and repeated HPV infections.

Methods

Study Population

The parent study, the Atypical squamous cells of undetermined significance-low-grade squamous intraepithelial Lesion Triage Study (ALTS) was designed to determine the optimal clinical management for low-grade cervical cytological abnormalities [8, 9]. Between October 1996 and December 1998, 1549 women were recruited from clinical centers located in Birmingham, Alabama, Oklahoma City, Oklahoma, Pittsburgh, Pennsylvania, and Seattle, Washington. The women in this study were enrolled based on having cytology diagnoses of atypical squamous cells of undetermined significance (ASC-US) and low grade squamous intraepithelial lesion (LSIL). Participants with cytology diagnoses of ASC-US and LSIL from referring community laboratories were followed every 6 months for 2 years [10]. This study includes a subset of the ALTS cohort, from the clinical center at Birmingham, Alabama. The administration of a risk-factor questionnaire, pelvic examinations, collection of specimens for cytology and HPV testing, and cervicography were carried out by the main ALTS personnel, and the results were made available for the ancillary study.

HPV detection and classification

Cervical brush samples were collected every 6 months for two years. The viral DNA from cervical lavage were identified through L1 consensus primer PGMY09/11 polymerase chain reaction amplification and reverse line blot hybridization to detect 38 HPV genotypes: HR-HPV subtypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68), low risk HPV(LR-HPV) subtypes (6, 11, 26, 40, 42, 53, 54, 55, 57, 61, 62, 64, 66, 67, 69, 70, 71, 72, 81, 85, 91, 73 [PAP238A], 82 [W13B], 83 [PAP291], and 84 [PAP155]), and a β -globin internal control [9, 11]. The results were classified as negative or positive for each of the 38 HPV types at each visit and β -globin negatives were excluded from the analyses. Two consecutive HPV-negative tests were required to confirm clearance to minimize the influence of false-negative test results. HPV-infected women whose test became negative at the last study visit were censored at that time. Type-specific HPV status was assumed to remain unchanged across single missing visits. Infections spanning more than two consecutive missing visits were excluded because of the increased uncertainty regarding HPV status.

We chose to focus our analysis on clearance of HR-HPVs because persistence of these types cause cervical pre-cancer and cancer. We did not assess the influence of the target gene polymorphism on the clearance of LR-HPV. Of the 709 women sampled, 317 were excluded from the longitudinal analysis in this study for the following reasons: HPV infection status known only at baseline (N=96), pregnancy during follow-up (N=1), HPV-negative for all 38 types throughout the study period (N=61), only infected with LR-HPV during follow up (N=58), and inadequate follow up (2 consecutive missing visits, N=101). Among the 392 HR-HPV-positive women included in this study, 149 of them were able to clear their HR-HPV infection(s) during follow up, 86 had persistent HR-HPV infection(s), and 157 had mixed outcomes, i.e., cleared an HPV 52 infection but had a persistent HPV16 infection.

Laboratory methods

Genotyping CYP1A1—The DNA sample from PBMCs was amplified in a 25- μ l volume containing genomic DNA, 2 μ M primers [5'-CAGTGAAGAGGTGTAGCCGC-3' (forward) and 5'-TAGGAGTCTTGTCTCATGCC-3' (reverse)], 0.2 mM of each deoxynucleotide triphosphate, 1 X PCR buffer G (Epicentre, Madison, WI), and 2.5 units of Taq polymerase (Promega, Madison, WI) [12]. Amplification was performed by initial denaturation at 94°C for 5 min, followed by 30 cycles at 94°C for 1 min, 61°C for 1 min, 72°C for 1 min, and a final extension at 72°C for 10 min.

An *MspI* restriction fragment length polymorphism in the 3' noncoding region of the *CYP1A1* gene was detected by PCR amplification as described by Hayashi, *et al* [12]. An aliquot of the amplified mixture was digested with *MspI* (New England Biolabs, Beverly, MA). The 340-bp PCR product from individuals with the wild-type allele is not digested by *MspI*. The 340-bp PCR product is digested by *MspI* when the variant allele is present, to yield two fragments of 140- and 200-bp. Heterozygous individuals have all three bands (340-, 140- and 200-bp) after PCR and *MspI* digestion. Individuals were categorized as either homozygous for the wild-type allele or heterozygous/homozygous for the variant allele.

Genotyping *GSTM1* and *GSTT1*—A multiplex PCR assay described by Xiong *et al.*, was used to genotype both the *GSTT1* and *GSTM1* polymorphism [13]. The *DHFR* gene was amplified as an internal control to ensure that DNA degradation was not responsible for lack of amplification of *GSTM1* and *GSTT1*. *GSTM1*, *GSTT1*, and *DHFR* were coamplified in a 25- μ l reaction mixture containing 100 ng of genomic DNA as the template, 3.5 pmol of each *GSTM1* primer, 2.9 pmol of each *GSTT1* primer, 6.2 pmol of each *DHFR* primer, 0.2 mM of each deoxynucleotide triphosphate, 1 X PCR buffer G (Epicentre, Madison, WI), and 2.5 units of Taq polymerase (Promega, Madison, WI). The conditions for PCR amplification were as follows: an initial melting step at 95°C for 5 min followed by 30 cycles of 95°C for 30 s, 56°C for 45 s, and 72°C for 45 s, with a final step of 72°C for 10 min for elongation. The PCR products were separated on 1.2% agarose gels, and the gels were stained with ethidium bromide and photographed with a photodocumentation camera (Fisher Scientific, Pittsburgh, PA).

The *GSTT1*, *GSTM1* and *DHFR* primers generate 480-base pair (bp), 215-bp and 280-bp fragments, respectively. In this assay, the absence of a 480-bp band or a 215-bp band indicates the *GSTT1* null or *GSTM1* null genotypes, respectively, provided that the 280-bp fragment of the *DHFR* internal control is amplified.

Statistical Analysis

CYP1A1 did not deviate from Hardy-Weinberg Equilibrium (HWE) in all participants and also in a sub-population of African-American. HWE was not evaluated for *GSTM1* and *GSTT1* polymorphism because the PCR technique used in this study only recognizes the presence (wild-type or heterozygous genotype) or the absence (null genotype) of the genes, but does not distinguish between heterozygous and homozygous wild-type.

The unit of analysis is time to HR-HPV clearance and therefore each woman can contribute multiple types of HR-HPV infection to the analysis (ie a woman could be co-infected with HPV16 and HPV52 so each of these types would be followed to determine time to clearance which allows the woman to contribute two HPV types to the analysis). The Cox proportional hazard model was used to assess all type specific HR-HPV clearance with functional variants in *CYP1A1*, *GSTM1*, and *GSTT1*. Due to the possible correlation between co-infected HPV types, the Wei-Lin-Weisfeld (WLW) extension was used with the Cox models. The WLW approach can simultaneously analyze time to HPV clearance of several types of HPV either at the same or different visits [14]. This method produces a population-averaged interpretation and allows different baseline hazards functions for each HPV type. LR-HPV infections were adjusted for as time-varying covariate in the model.

The multivariable model was adjusted for cofactors that have been associated with cervical cancer development: age, education, smoking, parity, highest cervical Bethesda classification diagnosis during follow-up, age at first sexual intercourse, number of lifetime sexual partners and use of oral contraceptives [15]. All analyses were adjusted for self-reported race to account for confounding by population stratification. Stratified analysis by each race was also performed to examine if there were variations. Regression coefficients of the interaction between any two of the three genotypes were tested to examine the joint association of the polymorphisms with the HPV outcomes. Stratified analyses by smoking

were also done since previous studies have shown associations with smoking and the genetic variants.

Results

Among the 392 HR-HPV infected women, the majority was black/non-Hispanic (65%), and did not smoke (67%) (Table 1). There were 908 different HR-HPV infections/co-infections (512 prevalent infections and 396 incident infections) among the 392 women and 545 (390 prevalent infections and 155 incident infections) of these cleared during follow-up (Table 2). The top five most common HR-HPV infections by type were: HPV-16 (N=138), HPV-52 (N=111), HPV-35 (N=73), HPV-58 (N=70), and HPV-18 (N=65). Of the 545 HR-HPV infections that cleared during follow up, the average time to clearance was 108 days (range 197 days, min 46 days, max 243 days).

In the analysis of HR-HPV infections, clearance of HR-HPV infection using the Cox proportional hazard WLW model, women who were homozygous/heterozygous for the *CYP1A1* variant allele had a HR-HPV clearance rate that was 21% (HR=0.79, p=0.04) lower than women that were homozygous for the wild-type allele, adjusting for known cofactors and LR-HPV co-infection (Table 1). The *GSTM1* null genotype was associated with higher HR-HPV clearance rate (HR= 1.39, p=0.006) adjusting for known cofactors and LR-HPV co-infection (Table 1). The *GSTT1* null genotype was not significantly associated with time to HR-HPV clearance. The interaction between the three polymorphisms was not statistically associated with time to HR-HPV clearance.

There were significant differences between African American and white women in the frequencies of the *CYP1A1* variant allele (45% vs. 19%, p-value <0.001) and of the *GSTM1* null genotype (26% vs. 55%, p-value <0.001). Cox proportional hazard models stratified by race yielded similar hazard ratios for the three polymorphisms. Although race was not a significant factor in the univariate analysis, all analyses were adjusted for race to avoid any confounding by population stratification. An additional analysis stratified by smoking status showed no significant differences in HR-HPV clearance or in the prevalence of genetic variants between smokers and nonsmokers; however we did adjust for smoking in the multivariable model. There was no interaction between smoking and the genetic variants in the association with HR-HPV (data not shown).

When we stratified the analysis by highest cervical Bethesda classification diagnosis during follow-up without adjusting for the other relevant covariates, the clearance of HR-HPVs was faster among women with LSIL/HSIL compared to women with normal/ASCUS in women with *GSTM1* null genotype (HR=1.39, p=0.03) suggesting a possible modifying effect of cytology/histology diagnoses on the clearance of HR-HPVs in this group of women. There were 44 women with 112 HPV infections in our analysis that were treated for CIN2/3 during follow-up and these women were included in the analyses (Table 1 and 2). When we removed these women from the analyses to determine if treatment had an effect on time to HPV clearance, the results were similar to the full analysis (data not shown).

Discussion

We assessed the effect of functional variants in the three xenobiotic metabolism genes on HR-HPV type specific clearance rates among women with a baseline cytology diagnosis of ASC-US or LSIL. We found that the variant allele homozygous/heterozygous for *CYP1A1* was associated with a decreased clearance rate HR-HPV, controlling for known HPV risk factors in women with ASC-US or LSIL. Similarly this variant allele homozygous/heterozygous for *CYP1A1* was shown to be significantly associated with HPV16 infection in a hospital based case-control study in India [2]. While the majority of previous research has focused on this variant and its association with cervical cancer risk, in which two studies found an increased risk for development of cervical cancer [2, 3] and a third found a null association [4], we found it to be significantly associated with longer time to clearance of HR-HPV infection. The effect of the polymorphism in *CYP1A1* results in increased enzyme activity, although the results have not been consistent [16–18]. The increased *CYP1A1* enzyme activity over time could result in oxidative stress, which could lead to DNA damage, potentially facilitating HR-HPV integration and reducing the lower likelihood of its clearance [2].

A cross-sectional study in India compared the frequency of the genotypes between HPV16 positive and negative women and found that the null genotypes for *GSTT1* and *GSTM1* were associated with HPV16 positivity [2]. The null genotypes for *GSTT1* and *GSTM1* are associated with the presence of HPV16 and our objective was to determine if clearance of HR-HPV was also associated with the absence of these two genes. We found that the *GSTM1* null genotype was significantly associated with increased clearance of HR-HPV while *GSTT1* was not. We also assessed HPV16 clearance and *CYP1A1*, *GSTT1* and *GSTM1* variants (data not shown) and found that there were not significant associations, although interpretations of these findings are difficult because of the small sample size (a total of 138 infections, of which 84 cleared during the observation period).

Evidence about the association between cervical cancer risk and polymorphism in *GSTM1* and *GSTT1* is mixed. Two meta-analyses have recently attempted to address this issue [5, 6], and both found that the null genotype of *GSTM1* polymorphism was associated with a significantly increased risk of cervical neoplasia. The association between *GSTT1* polymorphism and cervical neoplasia was inconsistent between the two meta-analyses (Gao, *et al* found a significant increased risk, while Economopoulos, *et al* found a null association) [5, 6]. The *GSTM1* null genotype is associated with faster clearance of HR-HPV in our population, but is associated with an increased risk of cervical cancer in several other populations.

The limitations of our study need to be considered. First, our genotyping methods for *GSTT1* and *GSTM1* can only distinguish between individuals with the null genotype versus those with a functional copy [19, 20]. While new methods can assess gene copy number (0, 1 or 2 copies of the gene), our genotyping method is still commonly used and is similar to the methods employed in studies included in recent meta-analyses [5, 6]. We found that having no enzyme activity versus functional activity for *GSTT1* and *GSTM1* did not significantly affect the time to clearance of any HPV, but did find a significant association between the

GSTM1 null genotype and HR-HPV clearance. Second, this cohort is comprised of women with low-grade cervical abnormalities and therefore the results are not generalizable to all women who have an HR-HPV infection. It would be interesting to assess the relationship between these genetic variants and abnormal and normal cytology grade; however, we were unable to do so since all women were diagnosed with abnormal pap.

In conclusion, in this study a functional variant in *CYP1A1* and *GSTM1* null genotypes were associated with clearance rates of HR-HPV infection, while the variant in *GSTT1* was not significantly associated with HPV clearance. While further research is warranted, our findings suggest that xenobiotic metabolism genes influence the natural history of HR-HPV infection and its progression to cervical cancer.

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References

1. Wang SS, Bratti MC, Rodriguez AC, Herrero R, Burk RD, Porras C, et al. Common variants in immune and DNA repair genes and risk for human papillomavirus persistence and progression to cervical cancer. *J Infect Dis.* 2009; 199:20–30. [PubMed: 19012493]
2. Joseph T, Chacko P, Wesley R, Jayaprakash PG, James FV, Pillai MR. Germline genetic polymorphisms of *CYP1A1*, *GSTM1* and *GSTT1* genes in Indian cervical cancer: associations with tumor progression, age and human papillomavirus infection. *Gynecologic oncology.* 2006; 101:411–7. [PubMed: 16360200]
3. Goodman MT, McDuffie K, Hernandez B, Bertram CC, Wilkens LR, Guo C, et al. *CYP1A1*, *GSTM1*, and *GSTT1* polymorphisms and the risk of cervical squamous intraepithelial lesions in a multiethnic population. *Gynecologic oncology.* 2001; 81:263–9. [PubMed: 11330960]
4. Kim JW, Lee CG, Park YG, Kim KS, Kim IK, Sohn YW, et al. Combined analysis of germline polymorphisms of *p53*, *GSTM1*, *GSTT1*, *CYP1A1*, and *CYP2E1*: relation to the incidence rate of cervical carcinoma. *Cancer.* 2000; 88:2082–91. [PubMed: 10813720]
5. Gao LB, Pan XM, Li LJ, Liang WB, Bai P, Rao L, et al. Null genotypes of *GSTM1* and *GSTT1* contribute to risk of cervical neoplasia: an evidence-based meta-analysis. *PloS one.* 2011; 6:e20157. [PubMed: 21629772]
6. Economopoulos KP, Choussein S, Vlahos NF, Sergeantanis TN. *GSTM1* polymorphism, *GSTT1* polymorphism, and cervical cancer risk: a meta-analysis. *Int J Gynecol Cancer.* 2010; 20:1576–80. [PubMed: 21150818]
7. Sudenga SL, Shrestha S. Key considerations and current perspectives of epidemiological studies on human papillomavirus persistence, the intermediate phenotype to cervical cancer. *International journal of infectious diseases: IJID: official publication of the International Society for Infectious Diseases.* 2013
8. Piyathilake, CJ.; Henao, OL.; Macaluso, M.; Cornwell, PE.; Meleth, S.; Heimbürger, DC., et al. Cancer research. United States: 2004. Folate is associated with the natural history of high-risk human papillomaviruses; p. 8788-93.
9. Piyathilake, CJ.; Macaluso, M.; Brill, I.; Heimbürger, DC.; Partridge, EE. Nutrition. United States: 2007. Lower red blood cell folate enhances the HPV-16-associated risk of cervical intraepithelial neoplasia; p. 203-10.
10. Schiffman M, Adhizhan ME. ASCUS-LSIL Triage Study. Design, methods and characteristics of trial participants. *Acta cytologica.* 2000; 44:726–42. [PubMed: 11015972]

11. Gravitt PE, Peyton CL, Alessi TQ, Wheeler CM, Coutlee F, Hildesheim A, et al. Improved amplification of genital human papillomaviruses. *Journal of clinical microbiology*. 2000; 38:357–61. [PubMed: 10618116]
12. Hayashi S, Watanabe J, Nakachi K, Kawajiri K. Genetic linkage of lung cancer-associated MspI polymorphisms with amino acid replacement in the heme binding region of the human cytochrome P450IA1 gene. *Journal of biochemistry*. 1991; 110:407–11. [PubMed: 1722803]
13. Xiong P, Bondy ML, Li D, Shen H, Wang LE, Singletary SE, et al. Sensitivity to benzo(a)pyrene diol-epoxide associated with risk of breast cancer in young women and modulation by glutathione S-transferase polymorphisms: a case-control study. *Cancer research*. 2001; 61:8465–9. [PubMed: 11731429]
14. Xue X, Gange SJ, Zhong Y, Burk RD, Minkoff H, Massad LS, et al. Marginal and mixed-effects models in the analysis of human papillomavirus natural history data. *Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*. 2010; 19:159–69.
15. Williams VM, Filippova M, Soto U, Duerksen-Hughes PJ. HPV-DNA integration and carcinogenesis: putative roles for inflammation and oxidative stress. *Future virology*. 2011; 6:45–57. [PubMed: 21318095]
16. Bartsch H, Nair U, Risch A, Rojas M, Wikman H, Alexandrov K. Genetic polymorphism of CYP genes, alone or in combination, as a risk modifier of tobacco-related cancers. *Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*. 2000; 9:3–28.
17. Landi MT, Bertazzi PA, Shields PG, Clark G, Lucier GW, Garte SJ, et al. Association between CYP1A1 genotype, mRNA expression and enzymatic activity in humans. *Pharmacogenetics*. 1994; 4:242–6. [PubMed: 7894496]
18. Androutsopoulos VP, Tsatsakis AM, Spandidos DA. Cytochrome P450 CYP1A1: wider roles in cancer progression and prevention. *BMC cancer*. 2009; 9:187. [PubMed: 19531241]
19. Parl F. A need for true GSTM1 and GSTT1 genotyping. *Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*. 2009; 18:2793. author reply.
20. Karageorgi S, Prescott J, Wong JY, Lee IM, Buring JE, De Vivo I. GSTM1 and GSTT1 copy number variation in population-based studies of endometrial cancer risk. *Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*. 2011; 20:1447–52.

Highlights

- We found that genetic variants in *CYP1A1* were significantly associated with a decreased clearance rate of HR-HPV.
- The *GSTM1* null genotype was associated with higher HR-HPV clearance rate while *GSTT1* was not significantly associated with clearance.

Demographic characteristics of the women with a HR-HPV infection and the unadjusted and adjusted Cox proportional hazard ratios for time to clearance of HPV

Table 1

		Unadjusted		Adjusted*	
	(n=392)	HR	P	HR	P
Age at Enrollment	25.3 ± 6.7	1.01	0.38	1.00	0.78
Race					
White	35.46 (139)	ref		ref	
African American	64.54 (253)	0.93	0.51	1.19	0.25
Highest Education Level					
HS Graduate or Less	59.95 (235)	ref		ref	
College	40.05 (157)	0.77	0.02	0.65	0.0007
Age at First Intercourse	16.0 ± 2.2	1.05	0.09	1.09	0.001
Total Number of Male Sexual Partners	6.6 ± 6.5	1.05	0.69	1.01	0.16
Smoking Status					
Never/Former	66.84 (262)	ref		ref	
Current	33.16 (130)	1.22	0.08	1.16	0.3
Parity					
0	20.15 (79)	ref		ref	
1+	79.85 (313)	0.94	0.64	0.97	0.84
Highest Bethesda Classification Diagnosis During Follow-up					
Normal/ASC-US	38.78 (152)	ref		ref	
LSIL/HSIL	61.22 (240)	0.94	0.55	1.01	0.92
Used Birth Control in Past 2 Years	54.08 (212)	1.2	0.11	1.27	0.06
Randomized Study Arm					
Immediate colposcopy	33.93 (133)	0.91	0.48	0.87	0.25
HPV triage	27.30 (107)	0.91	0.49	0.91	0.49
Conservative management	38.78 (152)	ref		ref	
CYP1A1					
Heterozygous (+/-)/Homozygous (-/-)	34.36 (134)	0.79	0.02	0.79	0.04
Wild Type (+/+)	65.64 (256)	ref		ref	

	Unadjusted		Adjusted*	
	HR	P	HR	P
GSTM1				
Null (-/-)	65.45 (250)	1.19	0.14	1.39
Wild Type (+/+ or +/-)	34.55 (132)	ref		0.006
GSTT1				
Null (-/-)	81.94 (313)	0.88	0.4	0.88
Wild Type (+/+ or +/-)	18.06 (69)	ref		0.41

* Adjusted for study arm, age at enrollment, education, smoking, parity, Highest Bethesda classification diagnosis during follow-up, age at first sexual intercourse, number of lifetime sexual partners, use of oral contraceptives, and co-infection with LR-HPV

Table 2

Number of study participants, HR-HPV infections and cleared infections by select gene polymorphisms, %(n)

Gene variant	N of HR-HPV infections at baseline (n=501)	N of incident HR-HPV infections (n=396)	N of infections cleared (n=545)
<i>CYP11A1</i>			
Heterozygous (+/-)/Homozygous (-/-)	33.46 (170)	32.23 (127)	31.00 (168)
Wild Type (+/+)	66.54 (338)	67.77 (267)	69.00 (374)
<i>GSTM1</i>			
Null (-/-)	62.28 (312)	65.03 (251)	61.09 (325)
Wild Type (+/+ or +/-)	37.72 (189)	34.97 (135)	38.91 (207)
<i>GSTT1</i>			
Null (-/-)	83.43 (418)	80.83 (312)	83.08 (442)
Wild Type (+/+ or +/-)	16.57 (83)	19.17 (74)	16.92 (90)