Published in final edited form as:
J Infect Dis. 2009 January 1; 199(1): 20–30. doi:10.1086/595563.

Common Variants in Immune and DNA Repair Genes and Risk for Human Papillomavirus Persistence and Progression to Cervical Cancer

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Abstract

Background—We examined host genetic factors to identify those more common in individuals whose human papillomavirus (HPV) infections were most likely to persist and progress to cervical intraepithelial neoplasia grade 3 (CIN3) and cancer.

Methods—We genotyped 92 single-nucleotide polymorphisms (SNPs) from 49 candidate immune response and DNA repair genes obtained from 469 women with CIN3 or cancer, 390 women with persistent HPV infections (median duration, 25 months), and 452 random control subjects from the 10,049-woman Guanacaste Costa Rica Natural History Study. We calculated odds ratios and 95% confidence intervals (CIs) for the association of SNP and haplotypes in women with CIN3 or cancer and HPV persistence, compared with random control subjects.

Results—A SNP in the Fanconi anemia complementation group A gene *(FANCA)* (G501S) was associated with increased risk of CIN3 or cancer. The AG and GG genotypes had a 1.3-fold (95% CI, 0.95–1.8-fold) and 1.7-fold (95% CI, 1.1–2.6-fold) increased risk for CIN3 or cancer, respectively (P_{trend} = .008; referent, AA). The *FANCA* haplotype that included G501S also conferred increased risk of CIN3 or cancer, as did a different haplotype that included 2 other *FANCA* SNPs (G809A and T266A). A SNP in the innate immune gene *IRF3* (S427T) was associated with increased risk for HPV persistence (P_{trend} = .009).

Conclusions—Our results require replication but support the role of *FANCA* variants in cervical cancer susceptibility and of *IRF3* in HPV persistence.

Human papillomavirus (HPV) infections are very common, sexually transmitted infections that infrequently persist. It is now understood that persistent infection with 1 of ~15 HPV types is required for the development of cervical cancer and its immediate precursor,

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Potential conflicts of interest: none reported.

Presented in part: 24th International Papillomavirus Conference and Clinical Workshop, Beijing, China, 3–9 November 2007 (abstract 340).

cervical intraepithelial neoplasia grade 3 (CIN3) [1, 2]. However, the factors that lead a subset of individuals infected with these oncogenic viruses to have persistent infection and to develop CIN3 or cervical cancer, whereas the vast majority of infected individuals naturally clear their infection(s), are poorly understood.

Host genetic factors are hypothesized to play a role in the pathogenesis of cervical cancer. Efforts to date in cervical cancer etiological research have focused on understanding the role of HPV, but much remains unknown about the role of host genetic factors. Current evidence for the role of host genetics in cervical cancer derives from studies such as those conducted in Scandinavian countries with well-established population registries, where evidence for familial aggregation in cervical cancer incidence has been demonstrated. The risk associations reported were strongest for full relatives, intermediate for half siblings, and lowest for nonbiological relatives, suggesting a genetic effect [3].

More direct evidence that inherited genetic factors play a role in cervical cancer pathogenesis comes from studies that have shown associations between specific human leukocyte antigens *(HLA)* and cervical cancer [4, 5]. In brief, *HLA* is essential for the presentation of viral antigens, and polymorphisms within *HLA* have been hypothesized to be involved in the pathogenesis of cervical neoplasia via their role in the immunological control of HPV. Most notably, a consistent protective effect has now been demonstrated for the *HLA DRB**1301-*DQB*1*0603 haplotype [5]. A positive association between *HLA* B7/*DQB*1*0302 and cervical disease has also been demonstrated in several populations, including the cohort in Costa Rica studied in this analysis [5]. Other than *HLA*, no other gene polymorphisms have consistently demonstrated an association with cervical cancer. Results from numerous reports on the codon 72 polymorphism in TP53 remain equivocal [6–8], and reports of associations between interleukin (IL)–10 and other candidate genes require further replication [9–15]. To date, a systematic evaluation of multiple gene polymorphisms postulated to play a role in cervical cancer has not been performed.

We evaluated the association of 92 candidate single-nucleotide polymorphisms (SNPs) in 49 immune response and DNA repair genes—selected on the basis of previous evidence of functional consequence or reported association with cervical cancer, HPV infection, or other infections—with risk of HPV persistence and progression to CIN3 or cervical cancer in the population-based Guanacaste cohort in Costa Rica (table 1). We hypothesized that immune response gene polymorphisms would affect risk for HPV persistence and progression to cancer by modulating the immune response. We also hypothesized that DNA repair genes would play a role in progression through their function in identifying and repairing DNA damage caused by HPV or HPV cofactors. We evaluated selected genetic variants on the basis of prior laboratory evidence that suggested functional consequences for an allele or associations with cervical cancer or viral infection in previous studies.

METHODS

Study Population

The present study was nested within a population-based cohort study of 10,049 women in Guanacaste, Costa Rica. In brief, the Guanacaste Study involved a population-based cohort of 10,049 women recruited over an 18-month period in 1993–19944 and followed for 7 years. For cohort participants, cervical cells were available for HPV testing, as described elsewhere [16, 17], and buffy coat specimens were available for host-gene polymorphism testing.

For the present analysis, we selected the following women from the cohort study: (1) all women histologically confirmed to have prevalent or incident CIN3 or cancer (n = 184;

median age, 36 years [range, 18–86 years]); (2) all women with evidence of HPV persistence, defined as women who tested positive for the same HPV type at 2 consecutive visits (n = 432; median duration of persistence, 25 months [range, 5–93 months]); and (3) a random selection of control subjects from the population-based cohort (n = 492). We note that 403 (82%) of the random control subjects were HPV negative at study enrollment, 54 (11%) were positive for a single type, and 34 (7%) were positive for >1 HPV type. We also identified additional individuals with CIN3 or cancer from Guanacaste who received a diagnosis of CIN3 or cancer during the period in which our cohort study was conducted (hereafter referred to as "supplemental case patients"). These supplemental case patients were initially identified from review of the Costa Rican National Tumor Registry and review of cytology listings from the National Cytology Laboratory in Costa Rica, followed by review of hospital and/or pathology records to verify that they had had CIN3 histologically confirmed. Of 448 women identified as eligible, 56 (13%) were deceased, 18 refused (4%), 39 (8%) could not be found, and 4 (1%) were sick or pregnant, with the result that 331 (74%) of the women were included as supplemental case patients (median age, 42 years; range, 20–89 years). We note that although a third of the case patients in the cohort study had cancer, half of the supplemental case patients had cancer, resulting in a slightly higher median age. Twenty milliliters of peripheral blood were collected from the enrolled supplemental case patients, and DNA was extracted from one 10-mL tube. The study was approved by both the National Cancer Institute and Costa Rican institutional review boards, and all subjects provided signed informed consent in accordance with US Department of Health and Human Services guidelines.

Laboratory Methods

DNA extraction—DNA was extracted from buffy coats with PureGene purification kits (Autopure; Gentra Systems) at Sera-Care (Frederick, Maryland). For the supplemental case patients, DNA extraction was done at the University of Costa Rica.

HPV testing—For specimens from the cohort study, cervical cells collected with cervix brushes and stored in standard transport medium were used for polymerase chain reaction–based HPV DNA testing with L1 MY09/MY11 consensus primer methods [16, 18, 19]. Supplemental case patients did not have cervical cells collected for HPV testing.

Host genotyping—Of the 1439 women selected, 454 random control subjects, 390 women with HPV persistence, 149 women with CIN3 or cervical cancer from the cohort study, and 322 supplemental case patients with CIN3 or cervical cancer had sufficient buffy coat DNA for genotyping. We selected SNPs with ≥5% prevalence in the control group and evidence of functional consequence or hypothesized association with cervical cancer, HPV infection, or other viral infections. Genotyping was conducted at the National Cancer Institute Core Genotyping Facility (Gaithersburg, Maryland) by use of Taqman (Applied Biosciences) or Epoch Biosciences platforms. Sequence data and assay conditions are provided online (Cancer Genome Anatomy Project SNP500Cancer Database, http://snp500cancer.nci.nih.gov) [20]. For quality control (QC), we included duplicate samples from 100 participants, which were interspersed for all assays and to which the laboratory was blinded. Agreement for QC duplicates was 99% for all assays except *IRF3* (rs2304204), which was excluded from further analysis because of a 9.6% discordance among QC specimens. For each plate of 368 samples, the following 4 genotype-specific QC samples were also included: homozygote wild-type (WT), heterozygote, homozygote variant, and DNA-negative controls.

No SNPs failed genotyping. Successful genotyping was achieved for 96%–100% of DNA samples for all SNPs. One SNP (*IL6* [rs1800795]) was not in Hardy Weinberg equilibrium

($P < .01$) among control subjects; genotype assignments and QC data from replicates were thus rechecked for this SNP and the accuracy of this assay was confirmed, in accordance with the sequence and assay specifications on the SNP500 Web site.

Final analytic population—We evaluated a total of 1312 women: 470 women who had received a diagnosis of CIN3 or cancer, 390 women with persistent HPV infection, and 452 random control subjects for whom genotyping results were obtained.

Statistical Analysis

Gene-disease associations—We calculated odds ratios (ORs) and 95% confidence intervals (CIs) for each genotype with respect to each disease outcome, using the homozygous WT genotype as the reference group. We first compared individuals with CIN3 or cervical cancer to random control subjects. Of the gene variants that were statistically significantly associated with CIN3 or cervical cancer ($P < .05$), we further evaluated whether their associations were consistent for HPV persistence and/or disease progression with the following respective comparisons: women with HPV persistence versus random control subjects and women with CIN3 or cervical cancer cases versus women with HPV persistence. For SNPs for which no differences in genotype frequencies were identified between women with HPV persistence and women with CIN3 or cervical cancer, we also compared the combined group of women with CIN3 or cervical cancer and women with HPV persistence ($n = 860$) to random control subjects ($n = 452$). Similarly, for those SNPs for which no difference in genotype frequencies were identified between women with HPV persistence and random control subjects, we also compared women with CIN3 or cervical cancer ($n = 470$) to the combined group of women with HPV persistence and random control subjects ($n = 842$) for increased analytic power.

We conducted both crude and analyses adjusted for age (<30 years, 30–49 years, and ≥50 years). For each outcome, we calculated the P_{trend} value on the basis of the 3-level ordinal variable (0, 1, and 2) of homozygote WT, heterozygote, and homozygote variant in a logistic regression model. For the evaluation of associations with HPV persistence, we also conducted analyses in which HPV persistence in the 390 women was restricted to the following groups: (1) women infected with any oncogenic HPV strain (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and/or 68) ($n = 180$), (2) women with persistent HPV-16 infection ($n = 41$), and (3) women who had persistent HPV infection for ≥2 years ($n = 199$; there were 82 women infected with an oncogenic strain of HPV in this group). In analyses restricted to infection with HPV-16, we also evaluated women with CIN3 or cervical cancer who tested positive for HPV-16 ($n = 25$).

In addition, we conducted analyses that restricted random control subjects to women who self-reported being sexually active; however, because the 11 virgins excluded in these analyses subsequently reported sexual activity during study follow-up and because results of analyses that excluded them were virtually identical to results of analyses that included them, we present data that includes all control subjects. All logistic regression models were unconditional and conducted using SAS software (version 8.2; SAS Institute).

Because some of our results could be false-positive findings due to chance, we calculated the probability that our findings were false-positives, using the Benjamini-Hochberg method to calculate the false discovery rate (FDR) [21], which reflects the expected ratio of false-positive findings to the total number of significant findings. We applied the FDR method to the P_{trend} values, allowing for the fewest comparisons (degrees of freedom) to assess the additive model. We considered an FDR value of <0.2 as notable. Because the FDR does not consider prior probability, we also calculated the false-positive report probabilities (FPRP) [22]. We used a criterion of 0.2, as suggested by Wacholder et al. [22]. Using this criterion,

we expected that 20% of tests with FPRP below 0.2 would have false-positive results, if our prior probabilities were correct. Prior values were determined on the basis of the weight of the scientific evidence for the outcomes of interest.

Haplotype analysis—The haplotype structure for *FANCA* (rs2239359, rs7190823, and rs7195066) was examined using Haploview (version 3.11) [23]. We estimated haplotypes by using the expectation-maximization algorithm [24]. By use of the statistical package HaploStats in R (version 2.0.1; CRAN) [25], overall differences in haplotype distribution between study groups were assessed with the global score test [26]. Risk estimates were estimated from the additive model, which fitted a logistic regression model and used posterior probabilities of the haplotypes as weights to estimate the regression coefficients in an iterative manner, adjusting for age.

RESULTS

We identified polymorphisms in 4 DNA repair genes *(FANCA, EXO1, CYBA,* and *XRCC1)* and 2 immune response genes *(IRF3* and *TLR2)* that were statistically significantly associated ($P < .05$) with CIN3 or cervical cancer when compared with the genotype distribution of those polymorphisms in random control subjects (table 2). Specifically, the *IRF3* S427T (rs7251), *EXO1* T439M (rs4149963), *CYBA* 3′UTR (rs7195830), and *FANCA* G501S (rs2239359) polymorphisms demonstrated increased risk for CIN3 or cervical cancer for each additional variant allele with P_{trend} values of .01, .02, .04, and .008, respectively. The *TLR2* S450S (rs3804100) and *XRCC1* Q399R (rs25487) polymorphisms demonstrated decreased risk with each additional variant with P_{trend} values of .02 and .03, respectively. Haplotype analyses of the 3 *FANCA* polymorphisms that were genotyped (*FANCA* G809D [rs7195066], G501S [rs2239359], and T266A [rs7190823]) demonstrated that, consistent with the individual SNP results, the haplotype with only the *FANCA* G501S (A-**G**-G) variant conferred the highest risk for CIN3 or cervical cancer (OR, 1.8 [95% CI, 1.4–2.5]). We note, however, that the haplotype with variants in the 2 other *FANCA* polymorphisms also yielded statistically significant risk elevation (OR for **G**-A-**A**, 1.6 [95% CI, 1.1–2.2]) for CIN3 or cervical cancer, when compared with the most common haplotype (A-A-G). We further evaluated SNPs in these 6 genes to determine whether their effects were more pronounced for HPV persistence or for progression to CIN3 or cervical cancer.

HPV persistence

Polymorphisms in *IRF3* S427T and *XRCC1* Q399R were significantly associated with HPV persistence with P_{trend} values of .04 and .03, respectively, when women with persistent HPV infection were compared with random control subjects (table 3). With the added power of combining the group of women with CIN3 or cervical cancer and the group of women with persistent HPV infection, compared with random control subjects, we observed a 1.3-fold risk increase (95% CI, 1.0–1.7) for *IRF3* and a 1.5-fold risk increase (95% CI, 1.1–2.1) for the CG and CC genotypes, respectively (referent, GG) ($P_{trend} = .009$). For *XRCC1* Q399R, we observed decreased risk for the AG and AA genotypes with odds ratios of 0.81 (95% CI, 0.64–1.0) and 0.61 (95% CI, 0.41–0.91), respectively ($P_{trend} = .009$).

Results for the persistence of infection with *oncogenic* strains of HPV were consistent, although they were statistically significant only for the *XRCC1* Q399R polymorphism (women with persistent HPV infection and women with CIN3 or cervical cancer versus random control subjects, OR for AG, 0.70 [95% CI, 0.49–1.0] and OR for AA, 0.49 [95% CI, 0.26–0.93]; $P_{trend} = .009$). In analyses restricted to women with persistent HPV infection for ≥2 or more years, associations with *IRF3* were pronounced, with odds ratios of 1.8 (95% CI, 1.2–2.7) and 2.0 (95% CI, 1.2–3.2) for the CG and CC genotypes, respectively ($P_{trend} = .$

005); these results were consistent and statistically significant for women with HPV persistence due to oncogenic strains and women with persistent infection due to nononcogenic strains. Results from analyses restricted to women infected with HPV-16 were consistent with the overall results but not statistically significant (data not shown).

Progression

TLR2 S450S, *EXO1* T439M, *CYBA* 3′UTR, and *FANCA* polymorphisms were associated with the risk of progression to CIN3 or cervical cancer. Risk for each additional variant allele was elevated for *EXO1, CYBA,* and all 3 *FANCA* polymorphisms and decreased for *TLR2* S450S when women with CIN3 or cervical cancer were compared to women with HPV persistence only (table 4). Again, with the added power of comparing women with CIN3 or cervical cancer to women with HPV persistence combined with random control subjects, we observed more significant P_{trend} values for *EXO1* (P_{trend} = .007), *CYBA* (P_{trend} = .01), *FANCA* G501S (P_{trend} = .01), and *TLR2* S450S variant allele (P_{trend} = .03). Notably, the *FANCA* haplotype with the *FANCA* G501S variant and the haplotype with both the *FANCA* G809D and T266A variants demonstrated increased risk for CIN3 or cervical cancer (OR for A-G-G, 1.6 [95% CI, 1.2–2.2] and OR for G-A-A, 2.4 [95% CI, 1.6–3.6]), compared with the common A-A-G haplotype.

In analyses that compared women with CIN3 or cervical cancer to women with persistent infection due to *oncogenic* HPV types, associations for *TLR2* S450S, *EXO1* T439M, *FANCA* G809D and *FANCA* T266A remained statistically significant with P_{trend} values of .02, .04, .02, and .03, respectively. All also remained statistically significant in analyses comparing women with CIN3 or cervical cancer to women persistently infected with oncogenic HPV types ≥2 years (table 5, which is only available in the electronic version). In addition, results were consistent in analyses restricted to women persistently infected with HPV-16 (data not shown).

We note that the all FDR values based on the P_{trend} were above our predefined notable threshold of 0.2 after taking into account all SNPs tested. By the FPRP, we found that the association between *FANCA* G501S and CIN3 or cervical cancer (assigning a prior probability of 0.05) resulted in a FPRP value of 0.17 for an additive model with an OR of 1.5, suggesting a <20% chance of being a false-positive, given our prior probability. No other results were found notable by FPRP.

DISCUSSION

In our evaluation of selected immune response and DNA repair gene variants and their association with HPV persistence and progression to cervical cancer, we report that common variants in genes influencing DNA damage were associated with both HPV persistence and progression to CIN3 or cervical cancer and genes influencing immune response were associated with HPV persistence.

Most notably, polymorphisms within the DNA repair gene *FANCA* were associated with CIN3 or cervical cancer but not with HPV persistence. *FANCA* is 1 of 12 groups of genes within the Fanconi anemia pathway and is thought to play a role in the recognition of DNA damage and the repair of DNA damage by homologous recombination. *FANCA* is the major gene implicated in Fanconi anemia (FA) with *FANCA* mutations accounting for ~70% of all FA cases. FA patients are characterized by increased apoptosis in hematopoietic cells, chromosome instability, sensitivity to DNA cross-linking damage, DNA damage from oxidative stress and/or reactive oxygen species, and telomere shortening [27]. FA patients are susceptible to cancer, including cervical cancer and other HPV-associated tumors [28], and our results, which implicate variants in *FANCA* with disease progression, add to the

current understanding of FA and cervical cancer. Our data suggest that, in addition to FA mutations, FA variants may be an important host event involved in susceptibility to cervical cancer.

We also identified associations for DNA repair genes *EXO1* and *CYBA* with progression to CIN3 or cervical cancer and associations for *XRCC1* with HPV persistence. The association we observed between *EXO1* and *CYBA* and disease progression supports the involvement of DNA repair in cervical pathogenesis and progression to CIN3 or cervical cancer [29, 30]. *XRCC1* plays a role in base-excision repair of spontaneous and induced DNA damage [31–34], and its association with HPV persistence (both overall and of oncogenic HPV strains) was not expected. Although it is possible that the increased susceptibility to DNA damage among women with the *XRCC1* R399Q variant facilitates HPV persistence, our findings require replication and further investigation.

Of the immune response genes evaluated, a variant in the innate immunity gene *IRF3* was associated with HPV persistence, and a *TLR2* variant was associated with progression to CIN3 or cervical cancer. Our results for *IRF3* are consistent with our hypothesis about immune response genes involved in persistent infection and consistent with the growing literature on *IRF3* in viral infections, including herpes simplex virus 1 infection and hepatitis C persistence [35–37]. We note that the association with HPV persistence was further pronounced when persistence was limited to women persistently infected for ≥2 years, but the associations were equally significant for persistence for ≥2 years of infection with either oncogenic or nononcogenic HPV strains, consistent with *IRF3*'s role in innate immunity. Finally, Toll-like receptors are essential for response to bacterial infections and inflammatory response [38, 39], and our observed association between the *TLR2* S450S variant and CIN3 or cervical cancer support the potential role of innate immune response genes and inflammatory response in progression from HPV persistence to CIN3 and cervical cancer.

Study limitations include potential survival bias, as supplemental case patients diagnosed outside the Guanacaste cohort were retrospectively ascertained, and DNA could not be obtained from deceased individuals. However, since half of supplemental case patients had CIN3, survival bias is unlikely to affect our results. Because of our limited number of patients with invasive cancer, the use of CIN3 or cancer as a case group may have obscured associations specific to invasion. Finally, although we targeted predefined genes and intended for our evaluation to be hypothesis generating, we cannot exclude the possibility that some of our results are false-positives (or false-negatives). Although we did not find FDR values above our predefined notable threshold of 0.2 after taking into account all SNPs tested, we note that the association between *FANCA* G501S and CIN3 or cervical cancer (assigning a prior probability of .05) was notable by FPRP (0.17), indicating a <20% chance of being a false-positive, given our prior probability. Finally, study limitations also include our evaluation of a relatively small proportion of these genes, as permitted by our candidate SNP selection process, which was based largely on available biological evidence and validated assays. For example, full coverage of the *FANCA* gene using tag SNPs would require an additional 18 SNPs. Thus, the fact that we did not select tag SNPs or conduct other, more comprehensive analyses within each candidate gene may have decreased our ability to identify significant SNPs related to disease. We therefore cannot discount the possibility that some of the genes evaluated could be associated with disease but are not thus identified in our analyses because of the limited number of SNPs evaluated.

Study strengths include our population-based study design, which approximated a case-cohort design because the proportion of women in the cohort with evidence of CIN3 or cancer was small. In our analysis, we have excluded women with a CIN2 diagnosis from

both the case and control groups, because it is frequently misclassified. The final 3 comparison groups (women with CIN3 or cervical cancer, women with HPV persistence, and random control subjects) allowed evaluation of both HPV persistence and disease progression.

In summary, our results require replication but, to our knowledge, we are the first to report potential host genetic variants relevant for HPV persistence and those relevant for progression to CIN3 or cervical cancer. If replicated, functional studies to determine the biological relevance of confirmed variants should be pursued. Improved gene coverage of the implicated genes (e.g., *FANCA* and *IRF3*) and evaluation of additional genes within these DNA repair and immune response pathways can help refine and develop the findings reported here, if real. Finally, future efforts should include evaluating the interplay between viral and host genetics along with HPV cofactors in determining the risk of HPV persistence and of progression to CIN3 or cervical cancer.

Acknowledgments

We are grateful to Sabrina Chen from the Information Management Services for data management and programming support. We are indebted to Robert Welch for his management of this genotyping effort at the National Cancer Institute Core Genotyping Facility and for his scientific contributions to our research efforts. We are also grateful to Jill Koshiol for her careful review of this manuscript.

This work was supported by the National Cancer Institute Intramural Program and National Institutes of Health (contracts CO-12400, CP-21081, and CP-31061 to R.H.; grant CA-78527 to R.D.B.); FUCODOCSA (Costa Rican Foundation for Training in Health Sciences); Caja Costarricense de Seguro Social (Costa Rica).

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Table 1

Immune response and DNA repair gene polymorphisms evaluated in women with cervical intraepithelial neoplasia grade 3 or cervical cancer, women with persistent human papillomavirus infections, and random control subjects from a 10,049-woman cohort in Guanacaste, Costa Rica.

Gene	Alias	Location	SNP500 location	Amino acid change and/or alias	RS number
BRCA1	Breast cancer 1, early onset	17q21	Ex12−1485C→T Ex12−984A→G	P871L E1038G	rs799917 rs16941
BRCA2	Breast cancer 2, early onset	13q12.3	Ex10+321A3C Ex2+14G→A	N372H 5′UTR	rs144848 rs1799943
BRIP1	*BRCA1* interacting protein C-terminal helicase 1	17q22-q24	−1918G→A Ex19−151T→C	S919P	rs2048718 rs4986764
CD80	CD80 molecule	3q13.3-q21	Ex3+35G→A	V45V	rs2228017
CD86	CD86 molecule	3q21 3q21	Ex5−151G→A Ex8+35G→A	V185I A310T	rs2681417 rs1129055
CTLA4	Cytotoxic T-lymphocyte-associated protein 4	2q33	Ex1−61A→G	T17A	rs231775
CYBA	Cytochrome b-245, alpha polypeptide	16q24	Ex4+11T→C Ex6−41G→A Ex6−16T→C	Y72H 3′UTR 3′UTR	rs4673 rs1049255 rs7195830
EXO1	Exonuclease 1	1q42-q43	Ex12+49C→T Ex11+20A→G Ex15+59C→T Ex12+105G→A	T439M H354R P757L V458M	rs4149963 rs735943 rs9350 rs4149965
FANCA	Fanconi anemia, complementation group A	16q24.3	Ex17+31G→A Ex9+4A→G Ex27−79G→A	G501S T266A G809D	rs2239359 rs7190823 rs7195066
FAS	Fas (TNF receptor superfamily, member 6)	10q24.1	−670G→A Ex2+16G→A Ex9−252C→T	A16T 3′UTR	rs1800682 rs3218619 rs1468063
FCGR2A	Fc fragment of IgG, low affinity IIa, receptor (CD32)	1q23	Ex4−120A→G	H166R	rs1801274
GPX1	Glutathione peroxidase 1	3p21.3	Ex1−226C→T	P200L	rs1050450
IFNGR2	Interferon gamma receptor 2 (interferon γ transducer 1)	21q22.11	Ex2−16A→G Ex7−141G→A Ex7−134C→T Ex2−34C→G	Q64R 3′UTR 3′UTR T58R	rs9808753 rs12655 rs1059293 rs4986958
IFNG	Interferon, γ	12q14	−1615C→T		rs2069705
IL10RA	Interleukin 10 receptor, α	11q23	Ex7−109G→A	3′UTR	rs9610
IL10	Interleukin 10	1q31-q32	−853C→T −626A→C −1116A→G Ex5+210T→C −3584A→T	aka -819 aka -592 aka -1082 3′UTR	rs1800871 rs1800872 rs1800896 rs3024496 rs1800890
IL12A	Interleukin 12A (natural killer cell stimulatory factor 1, cytotoxic lymphocyte maturation factor 1, p35)	3q25.33-q26	Ex7+277G→A	3′UTR; aka 8685G→A	rs568408
IL12B	Interleukin 12B (natural killer cell stimulatory factor 2, cytotoxic lymphocyte maturation factor 2, p40)	5q31.1-q33.1	Ex8+159A→C	3′UTR	rs3212227
IL1A	Interleukin 1, α	2q14	Ex5+21G→T Ex1+12C→T	A114S aka -889, 5′UTR	rs17561 rs1800587
IL1B	Interleukin 1, β	2q14	−1060T→C Ex5+14C→T −580C→T	aka -511 F105F aka -31	rs16944 rs1143634 rs1143627
IL1RN	Interleukin 1 receptor antagonist	2q14.2	IVS6+59A→T	aka A9589T	rs454078

Gene	Alias	Location	SNP500 location	Amino acid change and/or alias	RS number
IL6	Interleukin 6 (interferon, β 2)	7p21	−236C→G −660A→G −635C→G	aka -174 aka -598. -597 aka -572	rs1800795 rs1800797 rs1800796
IL8RA	Interleukin 8 receptor, α	2q35	Ex2+860G→C	S276T	rs2234671
IL8RB	Interleukin 8 receptor, β	2q35	Ex3+1235T→C Ex3+811C→T Ex3−1010G→A	3′UTR L262L 3′UTR	rs1126579 rs2230054 rs1126580
IL8	Interleukin 8	4q13-q21 4q13-q21	−351A→T Ex1−65C→T	aka -251 5′UTR	rs4073 rs2227538
IRF1	Interferon regulatory factor 1	5q31.1	Ex7+11A→G Ex10−347G→A	P185P 3′UTR	rs9282762 rs839
IRF3	Interferon regulatory factor 3	19q13.3-q13.4	Ex1+95A→G Ex8−81G→C Ex1−40T2→G	S427T	rs2304204 rs7251 rs2304205
JAK3	Janus kinase 3 (a protein tyrosine kinase, leukocyte)	19p13.1	Ex24+291T→C	3′UTR	rs3008
LTA	Lymphotoxin alpha (TNF superfamily, member 1)	6p21.3	IVS1+90A→G Ex1+49A→C	NcoI, aka A252G 5′UTR, aka -91	rs909253 rs2239704
MSH6	MutS homolog 6 *(E. coli)*	2p16	−556G→T	−556G→T	rs3136228
NOS2A	Nitric oxide synthase 2A (inducible, hepatocytes)	17q11.2-q12	Ex16+14C→T −2892C→T	S608L aka -1173	rs2297518 rs9282799
NOS3	Nitric oxide synthase 3 (endothelial cell)	7q36	Ex8−63T→G IVS1−762C→T	D298E aka -786	rs1799983 rs2070744
NQO1	NAD (P)H dehydrogenase, quinone 1	16q22.1	Ex6+40C→T	P187S	rs1800566
OGG1	8-oxoguanine DNA glycosylase	3p26.2	Ex6−315C→G	3′UTR S326C	rs1052133
PARP1	Poly (ADP-ribose) polymerase family, member 1	1q41-q42	Ex17+8T→C	V762A	rs1136410
PCNA	Proliferating cell nuclear antigen	20pter-p12	IVS2−124C→T	PCNA	rs25406
PMS1	PMS1 postmeiotic segregation increased 1 *(S. cerevisiae)*	2q31.1	Ex1−4G→C	5′UTR	rs5742933
RAD54B	RAD54 homolog B *(S. cerevisiae)*	8q21.3-q22	Ex6−32T→C	N250N	rs2291439
SOD2	Superoxide dismutase 2, mitochondrial	6q25.3	Ex2+24T→C	V16A	rs4880
STAT1	Signal transducer and activator of transcription 1, 91kDa	2q32.2	IVS21−8C→T	splice variant	rs2066804
TERT	Telomerase reverse transcriptase	5p15.33	Ex2−659G→A Ex16+203C→T	A305A 3′UTR	rs2736098 rs2853690
TGFB1	Transforming growth factor, β 1	19q13.1	Ex1−327C→T	P10L	rs1982073
TGFBR1	Transforming growth factor, beta receptor I (activin A receptor type II-like kinase, 53kDa)	9q22	Ex9+195A→G	3′UTR	rs868
TLR2	Toll-like receptor 2	4q32	Ex3+613T→C	N199N S450S	rs3804099 rs3804100
TLR4	Toll-like receptor 4	9q32-q33	Ex4+636A→G Ex4+936C→T	D299G T399I	rs4986790 rs4986791
TNF	Tumor necrosis factor (TNF superfamily, member 2)	6p21.3	−487A→G −417A→G −1036T→C −1042C→A	aka -308 aka -238 aka -857 aka -863	rs1800629 rs361525 rs1799724 rs1800630
TP73	Tumor protein p73	1p36.3	Ex2+4G→A Ex2+14C→T	5′UTR 5′UTR	rs2273953 rs1801173
XRCC1	X-ray repair complementing defective repair in Chinese hamster cells 1	19q13.2	Ex10−4A→G Ex9+16G→A Ex6−22C→T	Q399R R280H R194W	rs25487 rs25489 rs1799782
XRCC3	X-ray repair complementing defective repair	14q32.3	Ex8−53C→T	T241M	rs861539

Gene	Alias	Location	SNP500 location	Amino acid change and/or alias	RS number
	in Chinese hamster cells 3				

Table 2

Genotype distributions of *IRF3, TLR2, EXO1, CYBA, XRCC1*, and *FANCA* polymorphisms in women with cervical intraepithelial neoplasia grade 3 (CIN3) or cervical cancer, compared with random control subjects, adjusted for age.

Gene, SNP, genotype	Random control	CIN3 or cancer	OR (95% CI)[a]	P_{trend}
	Subjects, no. (%)			
Immune response gene				
IRF3 S427T rs7251				
GG	160 (36)	136 (29)	1.0[b]	.01
CG	200 (45)	217 (47)	1.3 (0.94–1.7)	
CC	82 (19)	109 (24)	1.6 (1.1–2.3)	
CG or CC	282 (64)	326 (71)	1.4 (1.0–1.8)	
TLR2 S450S rs3804100				
TT	380 (86)	424 (91)	1.0[b]	.02
CT	58 (13)	38 (8)	0.61 (0.39–0.95)	
CC	3 (1)	2 (0)	0.56 (0.09–3.5)	
CT or CC	61 (14)	40 (9)	0.61 (0.40–0.93)	
DNA repair gene				
EXO1 T439M rs4149963				
CC	227 (52)	211 (47)	1.0[b]	.02
CT	184 (42)	192 (43)	1.2 (0.87–1.5)	
TT	26 (6)	45 (10)	2.0 (1.2–3.3)	
CT or TT	210 (48)	237 (53)	1.3 (1.0–1.6)	
CYBA 3′UTR rs7195830				

Gene, SNP, genotype	Random control	CIN3 or cancer	OR (95% CI)[a]	P_{trend}
CC	207 (48)	191 (42)	1.0[b]	
CT	184 (43)	217 (47)	1.3 (0.97–1.7)	
TT	38 (9)	51 (11)	1.5 (0.93–2.4)	
CT or TT	222 (52)	268 (58)	1.3 (1.0–1.7)	.04
XRCC1 Q399R rs25487				
GG	195 (44)	225 (49)	1.0[b]	
AG	195 (44)	198 (43)	0.87 (0.66–1.1)	
AA	52 (12)	34 (7)	0.58 (0.36–0.94)	
AG or AA	247 (56)	232 (51)	0.81 (0.62–1.1)	.03
FANCA G809D rs7195066				
AA	174 (40)	165 (36)	1.0[b]	
AG	209 (48)	224 (49)	1.1 (0.85–1.5)	
GG	55 (13)	64 (14)	1.2 (0.76–1.8)	
AG or GG	264 (60)	288 (64)	1.1 (0.86–1.5)	.4
FANCA G501S rs2239359				
AA	160 (38)	135 (31)	1.0[b]	
AG	201 (48)	220 (50)	1.3 (0.95–1.7)	
GG	59 (14)	84 (19)	1.7 (1.1–2.6)	
AG or GG	260 (62)	304 (69)	1.4 (1.0–1.8)	.008
FANCA T266A rs7190823				

Gene, SNP, genotype	Random control	CIN3 or cancer	OR (95% CI)[a]	P_{trend}
GG	179 (41)	170 (38)	1.0[b]	.2
AG	214 (49)	216 (48)	1.1 (0.79–1.4)	
AA	47 (11)	64 (14)	1.4 (0.89–2.1)	
AG or AA	261 (59)	280 (62)	1.1 (0.85–1.5)	
	Estimated prevalence[c], %			
FANCA haplotype[d]				
A-A-G	47	38	1.0[b]	
A-**G**-G	15	23	1.8 (1.4–2.5)	
G-A-**A**	13	16	1.6 (1.1–2.2)	
G-G-A	21	20	1.3 (0.98–1.7)	

NOTE. CI, confidence interval; OR, odds ratio; SNP single-nucleotide polymorphism.

[a] Subjects with CIN3 or cancer vs. random control subjects

[b] Reference.

[c] Estimated by use of the expectation-maximization algorithm in HaploStats (CRAN).

[d] Prevalence ≥5% in control group.

Table 3

Genotype distribution of *IRF3, TLR2, EXO1, CYBA, XRCC1* and FANCA polymorphisms in relation to persistence of human papillomavirus (HPV) infection, adjusted for age.

Gene, SNP, genotype	Random control	HPV persistence	HPV persistence and CIN3 or cancer	HPV persistence vs. random control		HPV persistence and CIN3 or cancer vs. random control	
				OR (95% CI)	P_{trend}	OR (95% CI)	P_{trend}
	Subjects, no. (%)						
IRF3 S427T rs7251							
GG	160 (36)	107 (28)	243 (29)	1.0[a]	.04	1.0[a]	.009
CG	200 (45)	192 (51)	409 (49)	1.4 (1.0–1.9)		1.3 (1.0–1.7)	
CC	82 (19)	79 (21)	188 (22)	1.4 (0.97–2.1)		1.5 (1.1–2.1)	
CG or CC	282 (64)	271 (72)	597 (71)	1.4 (1.0–1.9)		1.4 (1.1–1.8)	
TLR2 S450S rs3804100							
TT	380 (86)	334 (89)	758 (90)	1.0[a]	.4	1.0[a]	.05
CT	58 (13)	40 (11)	78 (9)	0.78 (0.51–1.2)		0.68 (0.47–0.98)	
CC	3 (1)	3 (1)	5 (1)	1.2 (0.23–5.8)		0.79 (0.19–3.3)	
CT or CC	61 (14)	43 (11)	83 (10)	0.80 (0.53–1.2)		0.69 (0.48–0.98)	
EXO1 T439M rs4149963							
CC	227 (52)	204 (54)	415 (50)	1.0[a]	.6	1.0[a]	.3
CT	184 (42)	149 (40)	341 (41)	0.90 (0.67–1.2)		1.0 (0.8–1.3)	
TT	26 (6)	22 (6)	67 (8)	0.96 (0.53–1.8)		1.4 (0.86–2.3)	
CT or TT	210 (48)	171 (46)	408 (50)	0.91 (0.69–1.2)		1.1 (0.84–1.3)	
CYBA 3′UTR rs7195830							

Gene, SNP, genotype	Random control	HPV persistence	HPV persistence and CIN3 or cancer	HPV persistence vs. random control		HPV persistence and CIN3 or cancer vs. random control	
				OR (95% CI)	P_{trend}	OR (95% CI)	P_{trend}
CC	207 (48)	178 (48)	369 (44)	1.0[a]		1.0[a]	
CT	184 (43)	162 (44)	379 (46)	1.0 (0.8–1.4)		1.2 (0.91–1.5)	
TT	38 (9)	32 (9)	83 (10)	0.96 (0.58–1.6)		1.2 (0.81–1.9)	
					.9		.2
CT or TT	222 (52)	194 (52)	462 (56)	1.0 (0.77–1.3)		1.2 (0.93–1.5)	
XRCC1 Q399R rs25487							
GG	195 (44)	196 (52)	421 (50)	1.0[a]		1.0[a]	
AG	195 (44)	148 (39)	346 (41)	0.76 (0.57–1.0)		0.81 (0.64–1.0)	
AA	52 (12)	34 (9)	68 (8)	0.65 (0.40–1.0)		0.61 (0.41–0.91)	
					.03		.009
AG or AA	247 (56)	182 (48)	414 (50)	0.74 (0.56–0.97)		0.77 (0.61–0.97)	
FANCA G809D rs7195066							
AA	174 (40)	165 (44)	330 (40)	1.0[a]		1.0[a]	
AG	209 (48)	170 (45)	394 (48)	0.85 (0.63–1.1)		0.99 (0.77–1.3)	
GG	55 (13)	40 (11)	104 (13)	0.76 (0.48–1.2)		0.97 (0.67–1.4)	
					.2		.9
AG or GG	264 (60)	210 (56)	498 (60)	0.83 (0.63–1.1)		0.98 (0.77–1.2)	
FANCA G501S rs2239359							
AA	160 (38)	131 (36)	266 (33)	1.0[a]		1.0[a]	
AG	201 (48)	168 (47)	388 (49)	1.0 (0.74–1.4)		1.2 (0.90–1.5)	
GG	59 (14)	62 (17)	146 (18)	1.3 (0.83–1.9)		1.5 (1.0–2.1)	
					.3		.03
AG or GG	260 (62)	230 (64)	534 (67)	1.1 (0.80–1.4)		1.2 (0.97–1.6)	
FANCA T266A rs7190823							

Gene, SNP, genotype	Random control	HPV persistence	HPV persistence and CIN3 or cancer	HPV persistence vs. random control		HPV persistence and CIN3 or cancer vs. random control	
				OR (95% CI)	P_{trend}	OR (95% CI)	P_{trend}
GG	179 (41)	171 (46)	341 (41)	1.0[a]	.3	1.0[a]	.8
AG	214 (49)	160 (43)	376 (46)	0.78 (0.58–1.0)		0.91 (0.71–1.2)	
AA	47 (11)	41 (11)	105 (13)	0.92 (0.57–1.5)		1.1 (0.78–1.7)	
AG or AA	261 (59)	201 (54)	481 (59)	0.80 (0.61–1.1)		0.95 (0.75–1.2)	
	Estimated prevalence[b], %						
FANCA haplotype[c]							
A-A-G	47	47	42	1.0[a]		1.0[a]	
A-**G**-G	15	18	20	1.1 (0.83–1.5)		1.4 (1.1–1.9)	
G-A-**A**	13	9	13	0.66 (0.44–0.99)		1.1 (0.80–1.5)	
G-G-A	21	21	21	1.0 (0.78–1.3)		1.1 (0.91–1.4)	

NOTE. CI, confidence interval; CIN3, cervical intraepithelial neoplasia grade 3; OR, odds ratio.

[a] Reference.

[b] Estimated by use of the expectation-maximization algorithm in HaploStats (CRAN).

[c] Prevalence ≥5% in control group.

Table 4

Genotype distribution of *IRF3, TLR2, EXO1, CYBA, XRCC1* and *FANCA* polymorphisms in relation to progression to cervical intraepithelial neoplasia grade 3 (CIN3) or greater, adjusted for age.

Gene, SNP, genotype	HPV persistence	HPV persistence and random control	CIN3 or cancer	CIN3 or cancer vs. HPV persistence		CIN3 or cancer vs. HPV persistence and random control	
				OR (95% CI)	P_{trend}	OR (95% CI)	P_{trend}
	Subjects, no. (%)						
IRF3 S427T rs7251							
GG	107 (28)	267 (33)	136 (29)	1.0[a]		1.0[a]	
CG	192 (51)	392 (48)	217 (47)	0.86 (0.62–1.2)		1.1 (0.83–1.4)	
CC	79 (21)	161 (20)	109 (24)	1.1 (0.70–1.6)		1.3 (0.96–1.8)	
CG or CC	271 (72)	553 (67)	326 (71)	0.92 (0.67–1.2)	.9	1.2 (0.90–1.5)	.09
TLR2 S450S rs3804100							
TT	334 (89)	714 (87)	424 (91)	1.0[a]		1.0[a]	
CT	40 (11)	98 (12)	38 (8)	0.71 (0.44–1.2)		0.66 (0.44–0.98)	
CC	3 (1)	6 (1)	2 (0)	0.37 (0.06–2.3)		0.48 (0.09–2.4)	
CT or CC	43 (11)	104 (13)	40 (9)	0.69 (0.43–1.1)	.09	0.65 (0.44–0.95)	.03
EXO1 T439M rs4149963							

Gene, SNP, genotype	HPV persistence	HPV persistence and random control	CIN3 or cancer	CIN3 or cancer vs. HPV persistence		CIN3 or cancer vs. HPV persistence and random control	
				OR (95% CI)	P_{trend}	OR (95% CI)	P_{trend}
CC	204 (54)	431 (53)	211 (47)	1.0[a]		1.0[a]	
CT	149 (40)	333 (41)	192 (43)	1.2 (0.91–1.6)		1.2 (0.93–1.5)	
TT	22 (6)	48 (6)	45 (10)	1.8 (1.1–3.2)		1.9 (1.2–3.0)	
CT or TT	171 (46)	381 (47)	237 (53)	1.3 (1.0–1.7)	.02	1.3 (1.0–1.6)	.007
CYBA 3′UTR rs7195830							
CC	178 (48)	385 (48)	191 (42)	1.0[a]		1.0[a]	
CT	162 (44)	346 (43)	217 (47)	1.3 (0.98–1.8)		1.3 (1.0–1.7)	
TT	32 (9)	70 (9)	51 (11)	1.5 (0.89–2.4)			
CT or TT	194 (52)	416 (52)	268 (58)	1.3 (1.0–1.8)	.04	1.3 (1.1–1.7)	.01
XRCC1 Q399R rs25487							
GG	196 (52)	391 (48)	142 (31)	1.0[a]		1.0[a]	
AG	148 (39)	343 (42)	210 (46)	1.0 (0.83–1.5)		0.97 (0.76–1.2)	
AA	34 (9)	86 (10)	104 (23)	1.1 (0.31–1.5)		0.69 (0.45–1.1)	
AG or AA	182 (48)	429 (52)	314 (69)	0.87 (0.51–1.5)	.3	0.92 (0.73–1.2)	.2
FANCA G809D rs7195066							

Gene, SNP, genotype	HPV persistence	HPV persistence and random control	CIN3 or cancer	CIN3 or cancer vs. HPV persistence		CIN3 or cancer vs. HPV persistence and random control	
				OR (95% CI)	P_{trend}	OR (95% CI)	P_{trend}
AA	165 (44)	339 (42)	165 (36)	1.0[a]		1.0[a]	
AG	180 (45)	379 (47)	224 (49)	1.3 (0.97–1.7)		1.2 (0.94–1.6)	
GG	40 (11)	95 (12)	64 (14)	1.6 (1.0–2.5)	.02	1.3 (0.92–1.9)	.08
AG or GG	210 (56)	474 (58)	288 (64)	1.4 (1.0–1.8)		1.2 (0.97–1.6)	
FANCA G501S rs2239359							
AA	131 (36)	291 (37)	135 (31)	1.0[a]		1.0[a]	
AG	168 (46)	369 (47)	220 (50)	1.2 (0.90–1.7)		1.3 (0.99–1.7)	
GG	62 (17)	121 (15)	84 (19)	1.3 (0.85–1.9)	.02	1.5 (2.1–2.1)	.01
AG or GG	230 (64)	490 (63)	304 (69)	1.3 (0.93–1.7)		1.3 (1.0–1.7)	
FANCA T266A rs7190823							
GG	171 (46)	350 (43)	170 (38)	1.0[a]		1.0[a]	
AG	160 (43)	374 (46)	216 (48)	1.3 (0.99–1.8)		1.2 (0.91–1.5)	
AA	41 (11)	88 (11)	64 (14)	1.5 (0.98–2.4)	.02	1.4 (0.99–2.1)	.05
AG or AA	201 (54)	462 (57)	280 (62)	1.4 (1.0–1.8)		1.2 (0.96–1.6)	
	Estimated prevalence[b], %						

Gene, SNP, genotype	HPV persistence	HPV persistence and random control	CIN3 or cancer	CIN3 or cancer vs. HPV persistence		CIN3 or cancer vs. HPV persistence and random control	
				OR (95% CI)	P_{trend}	OR (95% CI)	P_{trend}
FANCA haplotype[c]							
A-A-G	47	47	38	1.0[a]		1.0[a]	
A-**G**-G	18	23	23	1.6 (1.2–2.2)		1.7 (1.3–2.2)	
G-A-**A**	9	17	16	2.4 (1.6–3.6)		1.9 (1.4–2.6)	
G-G-A	21	20	20	1.2 (0.93–1.6)		1.2 (0.99–1.6)	

NOTE. CI, confidence interval; CIN3, cervical intraepithelial neoplasia grade 3; OR, odds ratio.

[a]Reference.

[b]Estimated by use of the expectation-maximization algorithm in HaploStats (CRAN).

[c]Prevalence ≥5% in control group.

Table 5

Genotype distribution of all evaluated polymorphisms across all 3 study groups and risk comparisons among groups, adjusted for age.

The table is available in its entirety in the online edition of *The Journal of Infectious Diseases*.