

Null Results in Brief**Lack of Association between p53 Codon-72 Polymorphism and Squamous Intraepithelial Lesions in Women with, or at Risk for, Human Immunodeficiency Virus and/or Human Papillomavirus Infections¹****Giovanni Rezza,² Massimo Giuliani, Anna Rosa Garbuglia, Diego Serraino, Giuseppina Cappiello, Giovanna Migliore, Margherita Branca, Arrigo Benedetto, Giuseppe Ippolito, and the DIANAIDS Collaborative Study Group³**

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Introduction

It has been suggested that genetic factors play a role in the carcinogenesis of HPV⁴-infected cervix (1), yet this hypothesis continues to be a focus of debate. In particular, there has been interest in a common polymorphism that occurs in the p53 amino acid sequence and results in the presence of either a proline or arginine at position 72 (2). The arginine form of p53 has been found to be significantly more susceptible than the proline form to E6-mediated degradation, and the allelic analysis of persons with HPV-associated cancer has revealed an overrepresentation of homozygous arginine-72 p53, as compared with the normal population. This observation suggests that women homozygous for arginine-72 are approximately seven times more susceptible to HPV-associated tumorigenesis than heterozygous women (3). However, some studies have found no such excess risk (4–6).

Received 9/29/00; revised 12/14/00; accepted 2/9/01.

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¹ Supported by Ricerca Corrente 1998, IRCCS L. Spallanzani, and by Progetto Ricerca AIDS, Ministero della Sanità, Istituto Superiore di Sanità.

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⁴ The abbreviations used are: HPV, human papillomavirus; SIL, squamous intraepithelial lesion, MLR, multiple logistic regression; OR, odds ratio; CI, confidence interval; LSIL, low-grade SIL; HSIL, high-grade SIL.

In the present study, we tested the hypothesis that polymorphism at the codon 72 of the p53 is associated with HPV-related SILs of the cervix, studying both HPV-positive and HPV-negative women with or at risk for HIV infection.

Materials and Methods**Study Population, Cytology, and HPV-typing Procedures.**

The study participants were sexually active women at risk for HIV infection because they injected drugs, were sexual partners of male injecting drug users, or had engaged in at-risk heterosexual intercourse. Details on the methods of recruitment, data and specimen collection, smear examination, and HPV typing have been described in elsewhere (7, 8).

Analysis of Codon-72 Polymorphism. To analyze the codon-72 polymorphism of p53, a 199-bp product from PCR was digested using restriction and separation procedures described by Ara *et al.* (9).

Statistical Analysis. The Fisher's exact test was used to compare the different proportions of p53 genotypes across the cytological diagnoses. The association between the *arginine/arginine* allele and SIL after adjustment for other factors was assessed by means of unconditional MLR analysis to compute ORs and 95% CIs.

Results

Two-hundred and forty three Caucasian women (median age, 30 years; range, 17–45 years) were included in the study. SIL was diagnosed in 71 (29.2%) of these women: 45 (18.5%) had LSIL, and 26 (10.7%) had HSIL.

HPV-DNA was detected in 80 (32.9%) of 243 women; 130 of 243 women (53.5%) were HIV-positive. HPV typing was performed for 45 of the 80 women with HPV-DNA; 33 (73.3%) of them had high-risk HPV types (*i.e.*, 16, 18, and 31).

The Distribution of the p53 genotype according to cytological findings is presented in Table 1. Half of the women were found to be homozygous for the arginine allele (Arg/Arg); 39.5% were heterozygous (Arg/Pro); and 11% were homozygous for the proline allele (Pro/Pro). No statistically significant differences were found in the proportions of the different p53 genotypes when comparing the cytological findings (Table 1).

After adjusting for confounding factors (*i.e.*, HPV and HIV infection, smoking history, and having had three or more sexual partners in lifetime), only the presence of HPV-DNA on cervical samples (MLR-OR, 14.8; 95% CI, 6.9–31.7) and HIV infection (MLR-OR, 5.4; 95% CI, 2.4–11.9) remained significantly associated with the risk of SIL (data not shown in table). Women homozygous for the arginine allele had a 50% higher risk of SIL (MLR-OR, 1.5; 95% CI, 0.7–3.1) compared with women nonhomozygous for arginine, but this increase was not

Table 1 p53 genotype by results of cervical-smear analysis for 243 women^a

Cervical smear	p53 genotype					
	Arg/Arg ^b		Arg/Pro ^b		Pro/Pro ^b	
	No.	%	No.	%	No.	%
No evidence of SIL (<i>n</i> = 172) ^c	86	50.0	71	41.3	15	8.7
Total SIL (<i>n</i> = 71) ^c	35	49.3	25	35.2	11	15.5
LSIL (<i>n</i> = 45)	22	48.9	17	37.8	6	13.3
HSIL (<i>n</i> = 26)	13	50.0	8	30.8	5	19.2
Total (<i>n</i> = 243)	121	49.8	96	39.5	26	10.7

^a Italy, 1994–1995.^b Arg, arginine; Pro, proline.^c Fisher's exact test (normal *versus* total SIL; 2 degrees of freedom) = 2.63; *P* = 0.50.

statistically significant. A similar nonsignificant increase was observed when only HSIL was used as case-definition and women with LSIL were excluded from the analysis.

When the analysis was restricted to the 17 women with high-risk HPV types, the risk of HSIL for women with arginine homozygosis was 2.1 times higher; however, the increase was not statistically significant (95% CI, 0.3–17.6; data not shown in table).

Discussion

The findings of our study show no association between arginine homozygosis and SIL, and thus they do not support the hypothesis that the p53 polymorphism is associated with an increased risk of cervical lesions. In particular, we assessed the role of p53 polymorphism, taking into account HPV and HIV infections, which are well-established determinants of SIL (8), and found that the presence of such infections does not modify the association between p53 polymorphism and the risk of SIL.

Because we did not study women with invasive cervical cancer, we cannot exclude that the p53 polymorphism may act at later stages of carcinogenesis. For this reason, the findings of this study only suggest that the p53 polymorphism has no effect on the development of preinvasive lesions. Interestingly, we found a lack of an association in both HIV-positive and HIV-negative women, stressing that the effect of HIV-induced immunosuppression is not likely to be modified according to p53 polymorphism.

When the analysis was restricted to women for whom it was possible to evaluate the HPV type, the power of the study to detect a statistically significant association was limited. In fact, we based our sample-size calculation on a relative risk of ~7, as suggested by previous studies (3).

In conclusion, our study supports the results of previous investigations indicating that p53 polymorphism does not

greatly affect the risk of preneoplastic lesions of the cervix and shows that this finding is not modified by concurrent HIV infection.

Acknowledgments

We thank Mark Kanieff for editorial assistance.

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