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RESEARCH

# XRCC2 R188H (rs3218536), XRCC3 T241M (rs861539) and R243H (rs77381814) Single Nucleotide Polymorphisms in Cervical Cancer Risk

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**Abstract** Human Papillomavirus (HPV) is the main cause of cervical cancer and its precursor lesions. Transformation may be induced by several mechanisms, including oncogene activation and genome instability. Individual differences in DNA damage recognition and repair have been hypothesized to influence cervical cancer risk. The aim of this study was to evaluate whether the double strand break gene polymorphisms XRCC2 R188H G>A (rs3218536), XRCC3 T241M C>T (rs861539) and R243H G>A (rs77381814) are associated to cervical cancer in Argentine women. A case control study consisting of 322 samples (205 cases and 117 controls) was carried out. HPV DNA detection was performed by PCR and genotyping of positive samples by EIA (enzyme immunoassay). XRCC2 and 3 polymorphisms were determined by pyrosequencing. The HPV-adjusted odds ratio (OR) of XRCC2 188 GG/AG genotypes was OR=2.4 (CI=1.1–4.9, $p$=0.02) for cervical cancer. In contrast, there was no increased risk for cervical cancer with XRCC3 241 TT/CC genotypes (OR=0.48; CI=0.2–1; $p$=0.1) or XRCC3 241 CT/CC (OR=0.87; CI=0.52–1.4; $p$=0.6). Regarding XRCC3 R243H, the G allele was almost fixed in the population studied. In conclusion, although the sample size was modest, the present data indicate a statistical association between cervical cancer and XRCC2 R188H polymorphism. Future studies are needed to confirm these findings.

**Keywords** Cervical cancer · HPV · XRCC2 · XRCC3 · Single Nucleotide Polymorphism

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## Introduction

It is wildly accepted that infection with Human Papillomavirus (HPV) is the leading cause of cervical cancer. However, HPV infection is very common and in most women it clears up naturally in about 8–12 months. It is estimated that less than 1 % of HPV positive women will progress to severe dysplasia or cervical cancer [1]. The combination of factors that predispose to neoplasia in infected tissue is poorly understood. Much effort has been given to HPV and environmental factors, but the role of host susceptibility to cervical carcinogenesis remains largely unknown.

Studies performed on biological and adoptive sisters of cancer patients identified that development of cervical cancer depends, to a significant extent, on inherited genetic factors [2]. Among these, variants of DNA repair genes are frequently correlated with a higher risk of several human solid tumors. We [3] and others [4–6] have explored polymorphisms in excision nucleotide genes that could be involved in cervical cancer susceptibility. Here, we expand our evaluation to DNA double strand break (DBS) repair polymorphisms in XRCC3 and XRCC2 genes. These genes share essential roles in homologous recombination (HR), a key repair pathway by which somatic cells maintain genome integrity following DNA replication [7].

Previous studies have shown that genomic instability is a crucial event in HPV associated cancers, with a significant increase in single and double strand breaks [8, 9]. Experimental data also suggest that chromosomal aberrations may be the result of viral onco-proteins action [10, 11]. In this sense, introduction of HPV E6 and E7 proteins in keratinocytes increased the number of cells with phosphorylated histone H2AX, a marker of DSB damage [12]. Current analyses show that replication of integrated HPV may induce local rearrangements within the integration locus, activating DNA damage checkpoints and recruiting HR proteins [13, 14]. These findings led us to speculate that polymorphisms in HR genes may be directly involved in cervical cancer risk.

Some of the XRCC2 and XRCC3 single nucleotide polymorphisms (SNPs) have been related to human cancers. A G-A substitution at codon 188 of XRCC2, which changes Arg for His (c.563 G>A; rs3218536), may carry a small but significant risk to colorectal [15] and breast cancer [16–18]. While these associations need to be evaluated in larger studies, the substitution is located in a conservative amino acid that does not belong to any known functional motive [16]. Another relevant variant is XRCC3 T241M (exon 7, c.722C>T, rs861539), which several authors have associated with breast cancer [15, 18]. In support of this line, mammalian cells transfected with XRCC3 241M led to a slightly but significance resistance to DSB inducers in relation to the wild type [19]. However, the association between rs861539 and cervical cancer is inconclusive [6, 20–22].

## Material and Methods

A total of 322 cervical samples were collected from women attending public hospitals that were part of an anonymous specimen data bank in La Plata, Argentina. Samples corresponded to 205 normal cytologies and 117 squamous cervical cancers. Cervical exfoliated cells from the ecto-endocervix were collected using a cytobrush or spatula. Samples were eluted in 5 ml of phosphate-buffered saline (PBS), pelleted, and kept frozen at −80 °C. Biopsy specimens were fixed in formalin and paraffin-embedded and kept at room temperature.

## DNA Extraction

Paraffin-embedded samples were washed twice with xylol and finally with 100 % ethanol, re-suspended in 350 ml of proteinase K digestion buffer (250 mg/ml), and incubated for 2 h at 56 °C. Cervical exfoliated cell pellets and frozen biopsies were suspended and washed twice with 1 ml of PBS, and incubated for 24 h at 56 °C in 400 ml of digestion (extraction) buffer (50 mM Tris-ClH pH 8,5; 1 mM EDTA; 1 % Triton 3100 and 0,5 % Tween 20) containing 250 mg/ml of proteinase K (Promega). After proteinase digestion, samples were boiled for 10 min at 100 °C. DNA purification was conducted by the Salting out (direct protein precipitation methodology) procedure [23]. Finally, the DNA was (re)suspended in distillate water and stored at −20 °C.

## HPV Genotyping

HPV DNA was detected by nested PCR using two rounds of amplification, yielding a 150 bp PCR amplicon that includes a conserved sequence of the viral genome. The primers for first round were MY09/11 [24], and for the second round GP 05/06+ [25]. GP06 primers were biotinylated for later PCR enzyme immune assay [26]. Protocol and cycling conditions for DNA amplification were described elsewhere [3]. PCR products were electrophoresed in 2 % agarose gels, stained with SaferGreen™ (Invitrogen) and visualized in blue light by SafeImager™ (Invitrogen).

## PCR EIA

Briefly, 5 uL of the positive amplicons was captured on streptavidin-coated Maxi Sorp wells (Nunc, Thermo Fisher Scientific, Rochester, NY). The biotin labeled Gp was denatured with 0.2N Na(OH) at room temperature for 30′, washed three times (0.25× standard saline citrate, 20 % Tween 20) and hybridized with fluorescein-labeled oligoprobes corresponding to HPV types: 6, −11, −16, −18, −31, −33, −35, −39, −45, −51, −52, −56, −58, and −66. The plate was incubated for 20 min at 60 °C with 5 pmol of each probe per 100 uL hybridization buffer (5× standard saline citrate, 20 % Tween 20). After a washing step, samples were incubated for 30 min with anti-fluorescein monoclonal antibodies (1:1000) (Millipore, Billerica, MA). After two additional washing steps, the reaction was revealed with 1-Step Turbo TMB-ELISA (Pierce Biotechnology, Rockford, IL). Coloring was stopped after 10 min by 1 M sulfuric acid and the optical density of the color reaction was measured by spectrophotometry (BioRad) at 405 nm.

## Amplification and Pyrosequencing of XRCC2 R188H (rs3218536) and XRCC3 T241M (rs861539), R243H (rs77381814) Polymorphisms

The XRCC2 and XRCC3 primers were designed with FastPCR software (Primer Digital ltd, Finland) version 6.1.55. The XRCC2 R188H primers delimited a region of 151 bp (forward, XRCC227370-90 5′-CTG GAT AGA CCG CGT CAA TGG-3′; reverse, BioX2-27501-21, biotin-5′-ATG

AGC TCG AGG CTT TCT GCA-3′). Each PCR mix contained 0.5 uM of forward and reverse primers; 2 mM of each dNTP; 2 mM Cl2Mg; 1× PCR buffer (ClK 500 mM; Tris.ClH 100 mM; pH 9.0; Triton 100 1 %), 1 unit of Taq DNA polymerase (Inbio, Argentina) and 5 uL of DNA sample in a total volume of 50 uL. Cycling program was carried out with an initial denaturing step of 92 °C for 3 min, followed by 35 cycles of 30 s at 92 °C, 30 s at 60 °C, and 45 s at 72 °C, with a final elongation step of 72 °C for 5 min.

The XRCC3 primers delimited a region of 152 bp (forward, XRCC31742-62, 5′-CTC ACC TGG TTG ATG CAC AGC-3′; reverse, X3-241-Piro, biotin-5′-TGG TCA TCG ACT CGG TGG CAG-3′). An additional XRCC3 polymorphism, R243H (rs77381814), was also genotyped due to proximity to T241M (rs861539). Each PCR mix contained 0.5 uM of forward and reverse primers; 2 mM of each dNTP; 1 mM Cl2Mg; 1× PCR buffer (ClK 500 mM; Tris.ClH 100 mM; pH 9.0; Triton 100 1 %), 1 unit of Taq DNA polymerase (Inbio, Argentina), 5 uL of DNA sample in a total volume of 50 uL. Cycling program was carried out with an initial denaturing step of 92 °C for 3 min, followed by 35 cycles of 30 s at 92 °C, 50 s at 59 °C, and 45 s at 72 °C, with a final elongation step of 72 °C for 5 min.

The obtained PCR products were electrophoresed in agarose gel (2 %), stained with SaferGreen and visualized in blue light by SafeImager (Invitrogen). Twenty five micro-liters of each positive PCR product was transferred to 96-wells microplate and sequenced by Pyrosequencing PSQ96 HS System (Biotage, Uppsala, Sweden) according to manufacturers' instructions. The sequencing primer for XRCC2 was: XR2-188-Int, 5′-TTG TAA ATG ACT ATC-3′, and nucleotide dispensation order was: TAGACTGTC. The internal primer for XRCC3 was XR3-241-Int, 5′-GGC ACT GCT CAG CTC-3′ and could detect both XRCC3 T241M (rs861539)

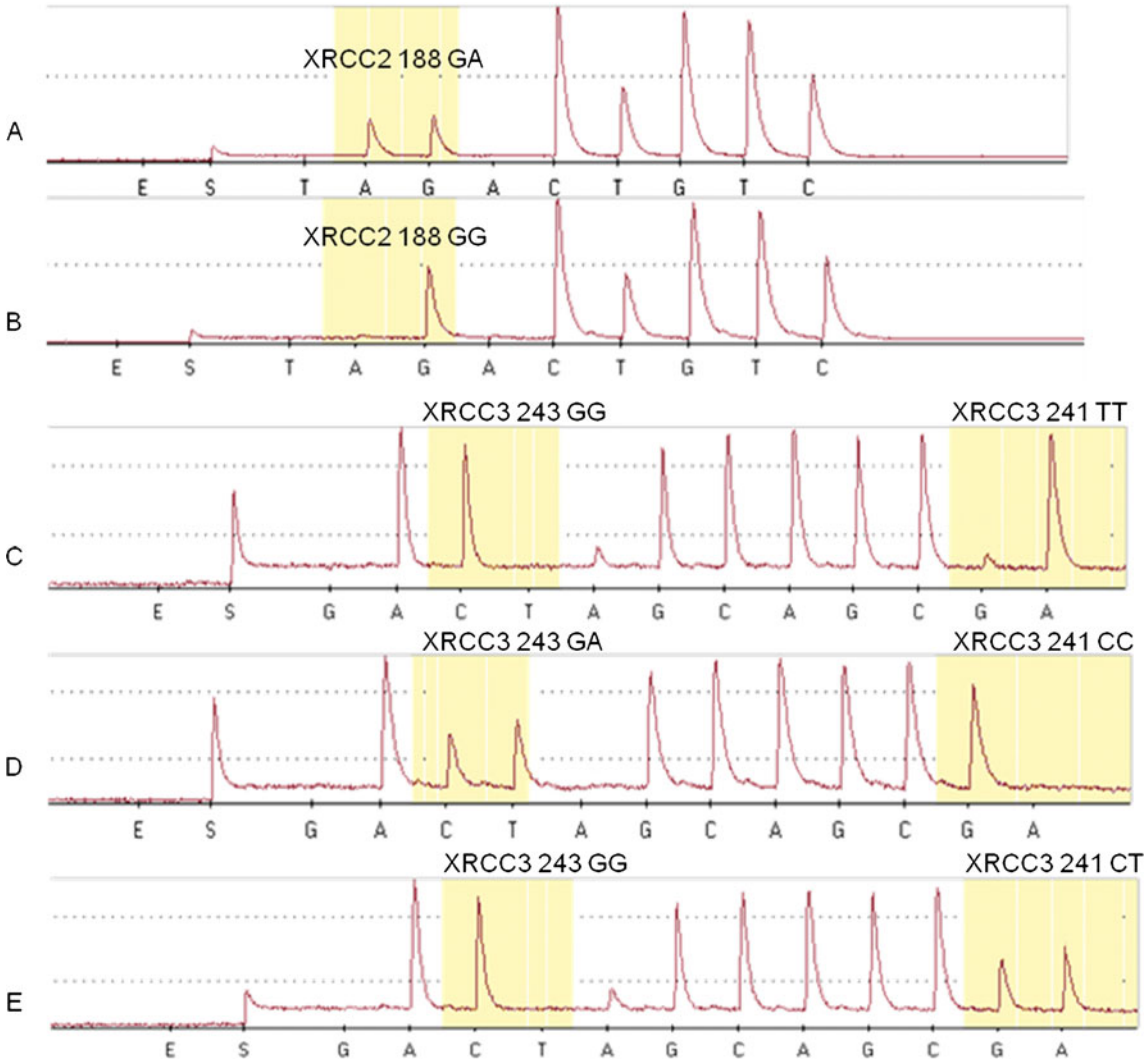


**Fig. 1** Experimental pyrogram patterns for analysis of: **a** XRCC2 188 AA; **b** XRCC2 188 GG; **c** XRCC3 241 TT and 243 GG; **d** XRCC3 241 CC and 243 GA; **e** XRCC3 241 TC and 243 GG (Note that XRCC3 sequence in pyrograms is complementary to consensus)

**Table 1** Genotype distribution of XRCC2 R188H and XRCC3 T241M variants in cases and controls

| | | Cases | Controls | Odds ratio ($IC_{95\%}$)(P) | Odds ratio[a] ($IC_{95\%}$) (P) |
|---|---|---|---|---|---|
| XRCC2 R188H | GG | 106 | 165 | 2.3 (1.1–4.7) (0.019) | 2.4 (1.1–4.9) (0.02) |
| | AG | 11 | 40 | Reference | Reference |
| XRCC3 T241M | TT | 11 | 32 | 0.53 (0.24–1.16) (0.11) | 0.48 (0.2–1) (0.1) |
| | CT | 56 | 95 | 0.92 (0.56–1.49) (0.73) | 0.87 (0.52–1.4) (0.6) |
| | CC | 50 | 78 | Reference | Reference |

[a]HPV-adjusted odds ratio

and R243H (rs77381814) SNPs. The nucleotide dispensation order for this reaction was: GACTAGCAGCGA. Representative pyrograms for XRCC2 and XRCC3 SNPs are shown in Fig. 1.

## Statistical Analysis

Statistical associations were assessed by the chi-square test, $p$ values were two sided, and significance was set at $p<0.05$. For risk estimation, odds ratios and 95 % confidence interval were obtained by binary logistic regression using the SPSS software (SPSS Inc).

## Results

Overall HPV DNA was detected in 39 % (80/205) of controls and 67 % (78/117) of cases. According to our methodology, the distribution of HPV types among the positive samples showed that 29 % of detection in controls and 50 % in case subjects belonged to high-risk types. HPV 16 was the prevalent type in control subjects (55 %), followed by HPV 18 (18.9 %), HPV 11 (9.4 %), HPV 6 (5.4 %), HPV 31 (4 %) and HPV 33 (1.3 %) Similar results were obtained for case patients: HPV 16 was the prevalent type (65.7 %), followed by HPV18 (10 %), HPV 31 (5.7 %), HPV 33 (4.2 %), HPV 11 (2.8 %) and HPV 45 (1.4 %). Co-infection frequency was low; among HPV positive samples 15.6 % of controls and 7.8 % of cases had more than one infection.

The allele and genotypes frequencies of XRCC2 R188H (rs3218536) and XRCC3 T241M (rs861539) polymorphisms are shown in Table 1. All genotype distributions of controls were consistent with the Hardy Weinberg equilibrium ($p=0.16$ for rs3218536 and $p=0.4$ for rs861539). For the additional XRCC3 243 polymorphism (rs77381814), the GG genotype was almost fixed in the population, with the exception of one control GA. Figure 1 depicts the obtained pyrograms for the resulting genotypes. The comparison between XRCC genotypes and HPV types revealed no association between infection and polymorphism (Table 2). Viral types were divided in low and high risk groups in order to provide sufficient statistical power.

Binary logistic regression was used to calculate odds ratios for cervical cancer risk. The allele frequency of XRCC2 188 G (rs3218536) was slightly higher in cases (0.95) than controls (0.91), but the difference was statistically significant ($p=0.023$). In this sense, the homozygous 188 GG genotype was associated with an increasing risk for cervical cancer (OR=2.3; CI=1.1–4.7; $p=0.019$) when compared with XRCC2 188 AG. It is noteworthy that we did not find any individual carrying the XRCC2 188 AA genotype. On the other hand, the distribution of XRCC3 241 (rs861539) genotypes remained similar between cases and controls. In this sense, the allele frequency of XRCC3241 C was similar in controls (0.61) and cases (0.66).

**Table 2** Distribution of XRCC genotypes among women infected with low-risk and high-risk HPV types

| HPV | XRCC2 R188H | | | | | | XRCC3 T241M | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Controls | | *P* value | Cases | | P value | Controls | | | *P* value | Cases | | | *P* value |
| | AG | GG | | AG | GG | | CC | CT | TT | | CC | CT | TT | |
| Neg | 25 | 100 | | 2 | 37 | | 51 | 59 | 15 | | 17 | 16 | 6 | |
| Low-risk[a] | 4 | 18 | 0.8 NS | 2 | 18 | 0.9 NS | 6 | 9 | 7 | 0.9 NS | 12 | 8 | 0 | 0.77 NS |
| High-risk[b] | 11 | 47 | 0.8 NS | 7 | 51 | 0.4 NS | 21 | 27 | 10 | 0.9NS | 21 | 32 | 5 | 0.43 NS |

*NS* Non significant

[a] HPV 6, 11, 42

[b] HPV 16, 18, 31, 33, 45

## Discussion

The role of DNA repair genes on the risk of human cancers is being increasingly recognized. Genetic instability is a common feature of human tumors and recent evidence suggests that mutations in DNA repair genes are implicated in both initiation and cancer progression. Whereas mutations in high penetrance genes such as the breast cancer genes BRCA1 and 2 are less frequent, there are low penetrance polymorphisms that may explain the remaining risk. In this sense, single nucleotide polymorphisms of DNA repair genes are extensively studied in breast and ovarian cancer. Here, we present evidence that supports that XRCC2 R188H (rs3218536) polymorphism may be associated with cervical cancer.

The frequency of the XRCC2 188 A allele found in this study was lower than those reported from Europe [16, 27] and the US [28]. To the best of our knowledge, this is the first study examining the XRCC2 188 G>A variant in cervical cancer. A meta-analysis performed by Vineis et al. [8] with data collected from 1985 to 2007 showed that XRCC2 188 A confers a slightly but significantly risk for colorectal cancer. Other authors have associated XRCC2 A with breast and ovarian cancer, but the association remains controversial [16, 27, 29, 30]. Contrary to most cancers studied so far, we found that the risk allele associated with cervical cancer was G, not A. Although there is needed more studies to assess this relation, an intriguing issue is raised as to whether XRCC2 188 G>A has a different role in cervical cancer, probably by identifying HPV induced DNA damage in host genome or by playing a part in viral integration [22].

Despite speculations, few active sites have been demonstrated for the XRCC2 gene and codon 188 (rs3218536) does not lie within any of them. Rafii et al. [16] have shown that XRCC2 is able to form complexes with certain RAD51 paralogs, therefore functional motives remain to be identified. It is also possible that cancer association is not directly linked to codon 188, but to another SNP located inside the Walker motive (ATPase). Similar to this, XRCC3 T241M (rs861539) polymorphism modifies an aminoacid that does not lie in a known functional motive, but unlike XRCC2 188 (rs3218536), it has stronger evidence of differential activity between alleles. In this sense, it was shown that this variant responds differentially to certain DSB inducers in CHO cells which were transfected with human variants of XRCC3 [19].

Population studies have shown that the XRCC3 T241M (rs861539) polymorphism was associated with breast cancer [15, 18], although the conferred risk, as other low penetrance genes confers, is relatively low. We failed at finding a significant association between rs861539 and cervical cancer. These results are in agreement with those found by others [20–22]. In agreement, a large case control study performed in Costa Rica, which analyzed the contribution of DNA repair gene polymorphisms and cervical cancer, did not identify an association between rs861539 and neoplasia. It is noteworthy, however, that in that study HPV persistence was linked to another DNA repair gene variant, XRCC1 codon 399 polymorphism (rs25487) [6].

Despite controversial findings, the link between cervical cancer risk and genetic variants of DNA repair genes remains to be proved. Our results support the view that functional polymorphisms may influence cervical cancer risk. Although the mechanism is unknown, recent data suggest that expression of homologous recombination proteins is actively involved in HPV induced instability. Kazara et al. (2009) demonstrated that chromosomal rearrangements could be triggered by the unscheduled replication of integrated HPV, yielding numerous double strand breaks and exceeding the cellular DNA repair system [12].

In conclusion, our results provide evidence for a statistical association between a genetic polymorphism of XRCC2 and cervical cancer, suggesting that this protein may be specifically involved in repair of HPV related DNA damage. However, larger studies are needed to confirm this hypothesis.

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**Conflict of interest statement** We declare that we have no conflict of interest.

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