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ORIGINAL RESEARCH ARTICLE

# Involvement of *PARP-1* Val762Ala Polymorphism in the Onset of Cervical Cancer in Caucasian Women

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**Abstract**

*Background and Objective* Data on the Val762Ala (rs1136410) polymorphism in the poly(adenosine diphosphate [ADP]-ribose) polymerase 1 (*PARP-1*) gene as a risk factor for various types of cancers in different ethnicities are inconsistent. We studied this association in a Caucasian population.

*Methods* Using high-resolution melting curve analysis (HRM), we studied the distribution of the *PARP-1* Val762Ala polymorphism in patients with cervical cancer ($n = 446$) and in controls ($n = 491$).

*Results* Logistic regression analysis adjusting for age, pregnancy, oral contraceptive use, tobacco smoking, and menopausal status demonstrated that the *PARP-1* Val762Ala polymorphism was associated with an increased risk of cervical cancer. The adjusted odds ratio (OR) for patients with the Ala/Val genotype versus the Val/Val genotype was 1.381 (95 % CI = 1.025–1.859, $p = 0.033$), and the adjusted OR for the Ala/Ala or Ala/Val genotype versus the Val/Val genotype was 1.403 (95 % CI = 1.057–1.863, $p = 0.019$). The $p$ value from the chi-square test of the trend observed for the *PARP-1* Val762Ala polymorphism was statistically significant ($p_{trend} = 0.0123$). Stratified analyses of the *PARP-1* Val762Ala genotype distribution and cervical cancer risk showed that the age-adjusted OR of Ala/Ala or Ala/Val vs Val/Val for pregnancy was 1.388 (95 % CI = 1.027–1.877, $p = 0.0328$), 1.773 (95 % CI = 1.145–2.745, $p = 0.0100$) for contraceptive use, and 1.604 (95 % CI = 1.132–2.272, $p = 0.0077$) for postmenopausal women. The age-adjusted OR of Ala/Val vs Val/Val for contraceptive use was 1.769 (95 % CI = 1.114–2.809, $p = 0.0154$) and for postmenopausal women was 1.577 (95 % CI = 1.094–2.272, $p = 0.0143$).

*Conclusion* Our studies suggest that the *PARP-1* Val762Ala polymorphism may be a genetic risk factor for cervical cancer.

## 1 Introduction

The development of cervical tumors is a multi-step process including infection by the human papillomavirus (HPV) and involvement of the immune system, tumor suppressor genes, and proto-oncogenes [1, 2]. During cervical tumorigenesis, the normal cervical epithelium is transformed into cervical intraepithelial neoplasia (CIN), which may further progress to invasive cervical carcinoma [1, 2]. It is well recognized that the primary etiologic factors of this cancer are some oncogenic HPVs in which E6 and E7 oncoproteins deregulate innate and adaptive immunity and abnormally alter apoptosis, causing the cell cycle to drive normal cervical epithelium cells to immortalization [2–4]. The oncoproteins E6 and E7 may also result in chromosomal instability and increase DNA damage during HPV

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carcinogenesis [3, 5]. Moreover, DNA damage is accumulated during DNA replication as well as through exposure to genotoxic cellular metabolites and environmental insults [6]. There are several canonical pathways for DNA repair, and the predominant pathway for single strand break repair is the base excision repair (BER) pathway [7, 8]. The BER may cooperate with a family of related enzymes termed poly(adenosine diphosphate [ADP]-ribose) polymerases (PARP) [9, 10]. Approximately 90 % of the cellular PARP activity is due to PARP-1, which is an early-activated sensor of DNA strand breakage [6, 11]. PARP-1 conducts extensive polymerization of ADP-ribose from its substrate nicotinamide adenine dinucleotide ($NAD^+$) to nuclear proteins involved in DNA repair, genomic stability, transcription regulation, cell death, and proliferation [12, 13]. The proteins involved in pathways of DNA repair are crucial in the prevention of cancer development, and numerous single nucleotide polymorphisms (SNPs) in genes encoding these proteins may be risk factors for various cancers [14, 15]. At least 60 SNPs have been reported in *PARP-1* (http://snp500cancer.nci.nih.gov), and among them is the most frequently studied functional *PARP-1* polymorphism, which includes a 2446T>C transition leading to Val762Ala variation [16, 17].

Data demonstrating that the *PARP-1* Val762Ala (rs1136410) substitution is a risk factor for various types of cancers in different ethnicities are inconsistent [16, 17]. Recently, the contribution of the *PARP-1* Val762Ala polymorphism to cervical cancer was demonstrated in an Asian population [18]. We evaluated the *PARP-1* Val762Ala genotype and allele frequencies in patients with cervical cancer ($n = 446$) and controls ($n = 491$) from a Polish population.

## 2 Patients and Methods

### 2.1 Patients and Controls

The patients were 446 women with histologically recognized cervical carcinoma according to the International Federation of Gynecology and Obstetrics (FIGO). All women were enrolled between April 2007 and Jun 2012 at the Department of Radiotherapy, Greater Poland Cancer Center in Poznan, Poland (Table 1). The controls included 491 unrelated healthy female volunteers who were matched by age to the patients (Table 1). Data on pregnancy, oral contraceptive use, tobacco smoking, and menopausal status were obtained during the clinical interview. All individuals were Caucasian, enrolled from the Wielkopolska (Greater Poland) area of Poland. Patients and controls provided written informed consent. The study was approved by the Local Ethical Committee of Poznan University of Medical Sciences.

**Table 1** Clinical and demographic characteristics of the patients and controls

| Characteristic | Patients ($n = 446$) | Controls ($n = 491$) |
|---|---|---|
| [a]Mean age (years) ± SD | 52.5 ± 9.9 | 51.8 ± 10.1 |
| Tumor stage | | |
| IA | 59 (13.2 %) | |
| IB | 61 (13.7 %) | |
| IIA | 59 (13.2 %) | |
| IIB | 53 (11.9 %) | |
| IIIA | 146 (32.7 %) | |
| IIIB | 52 (11.7 %) | |
| IVA | 9 (2.0 %) | |
| IVB | 7 (1.6 %) | |
| Histological grade | | |
| G1 | 85 (19.1 %) | |
| G2 | 141 (31.6 %) | |
| G3 | 96 (21.5 %) | |
| Gx | 124 (27.8 %) | |
| Histological type | | |
| Squamous cell carcinoma | 376 (84.3 %) | |
| Adenocarcinoma | 54 (12.1 %) | |
| Other | 16 (3.6 %) | |
| Pregnancy | | |
| Never | 47 (10.5 %) | 54 (11.0 %) |
| Ever | 399 (89.5 %) | 437 (89.0 %) |
| Oral contraceptive pill use | | |
| Never | 244 (54.7 %) | 275 (56.0 %) |
| Ever | 202 (45.3 %) | 216 (44.0 %) |
| Tobacco smoking | | |
| Never | 289 (64.8 %) | 328 (66.8 %) |
| Ever | 157 (35.2 %) | 163 (33.2 %) |
| Menopausal status | | |
| Premenopausal | 155 (34.8 %) | 186 (37.9 %) |
| Postmenopausal | 291 (65.2 %) | 305 (62.1 %) |
| HPV genotypes | | |
| 16 and 18 | 307 (68.8 %) | |
| 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68 | 346 (77.6 %) | |

[a] Age at first diagnosis

### 2.2 Genotyping

DNA was isolated from peripheral leucocytes using a salting-out procedure. The *PARP-1* Val762Ala (rs1136410) DNA fragment was amplified using the primers 5′ CTATC ATCAGACCCTCCCCTGA 3′ and 5′ GATACCTAAGTC GGGGGCTTTC 3′. This polymorphism was then genotyped by high-resolution melting curve analysis (HRM) on a LightCycler 480 system (Roche Diagnostics, Mannheim, Germany). The presence of the *PARP-1* Val762Ala polymorphism was verified by commercial sequencing analysis of 15 % randomly selected samples.

**Table 2** Association of the *PARP-1* Val762Ala (rs1136410) polymorphism with cervical cancer

| Genotype | Patients (frequency) | Controls (frequency) | Odds ratio (95 % CI) | $p^a$ | Adjusted Odds ratio (95 % CI)[b] | $p^a$ | $p_{trend}$ |
|---|---|---|---|---|---|---|---|
| Val/Val | 295 (0.66) | 361 (0.74) | Reference | – | Reference | | |
| Ala/Val | 129 (0.29) | 114 (0.23) | **1.385 (1.031–1.860)** | **0.0304** | **1.381 (1.025–1.859)** | **0.033** | **0.0123** |
| Ala/Ala | 22 (0.05) | 16 (0.03) | 1.683 (0.8677–3.263) | 0.1199 | 1.290 (0.922–1.804) | 0.136 | |
| Ala/Val + Ala/Ala | 151 (0.34) | 130 (0.26) | **1.421 (1.074–1.882)** | **0.0138** | **1.403 (1.057–1.863)** | **0.019** | |
| Minor allele frequency | 0.19 | 0.15 | | | | | |

[a] Chi-square analysis. [b]ORs were adjusted for age, pregnancy, oral contraceptive use, tobacco smoking, and menopausal status. Significant results are highlighted in bold

### 2.3 Statistical Analysis

The differences in genotypic and allelic prevalences between patients and controls and their genotype deviations from Hardy–Weinberg (HW) equilibrium were evaluated via the chi-square test. The polymorphism was tested for association with cervical cancer incidence using the chi-square test for trend ($p_{trend}$). Moreover, the odds ratio (OR) and 95 % confidence intervals (95 % CI) were calculated. Unconditional logistic regression analysis was used to adjust for the effects of confounders such as age, pregnancy, oral contraceptive use, tobacco smoking, and menopausal status. A $p$ value of $<0.05$ was considered statistically significant.

## 3 Results

### 3.1 Prevalence of the *PARP-1* Val762Ala Polymorphism in Women with Cervical Cancer

The distribution of *PARP-1* Val762Ala genotypes did not exhibit significant differences from HW equilibrium in the cases and controls. The prevalence and adjusted analyses of *PARP-1* Val762Ala genotypes in women with cervical cancer are presented in Table 2. The frequency of the *PARP-1* Ala/Ala genotype was approximately 1.7-fold higher in the patients than in the controls. The *PARP-1* Ala/Val heterozygous genotype frequency was also higher in women with cervical cancer than in the controls(0.29 and 0.23, respectively). The *PARP-1* Ala allele frequency was increased in patients compared to controls (0.19 and 0.15, respectively). The $p$ value from the chi-square test of the trend observed for the *PARP-1* Val762Ala polymorphism was statistically significant ($p_{trend} = 0.0123$). Logistic regression analysis demonstrated that the *PARP-1* Val762Ala polymorphism was associated with an increased risk of cervical cancer. The adjusted OR for patients with the Ala/Val genotype versus the Val/Val genotype was 1.381 (95 % CI = 1.025–1.859, $p = 0.033$) and the adjusted OR for the Ala/Ala or Ala/Val genotype versus the Val/Val genotype was 1.403 (95 % CI = 1.057–1.863, $p = 0.019$). However, we did not observe statistical significance for the Ala/Ala genotype versus the Val/Val genotype. In this case, the adjusted OR was 1.290 (95 % CI = 0.922–1.804, $p = 0.136$). Stratification of the patients based on the histological type of the cancer revealed a borderline association of the Ala/Ala or Ala/Val genotype with squamous cell carcinoma, with an adjusted OR of 1.340 (95 % CI = 1.068–1.804, $p = 0.048$). However, we did not find a significant association between the *PARP-1* Val762Ala polymorphism and adenocarcinoma, tumor stage, or histological grade (data not shown).

### 3.2 Stratified Analyses of *PARP-1* Val762Ala Genotype and Cervical Cancer Risk

The results of age-adjusted analyses of *PARP-1* Val762Ala genotype and cervical cancer risk stratified by pregnancy, oral contraceptive use, tobacco smoking, and menopausal status are presented in Table 3. An increase in cervical cancer risk was seen among patients with a positive history of pregnancy or oral contraceptive use, and among women of postmenopausal age. The adjusted OR for pregnancy with Ala/Ala or Ala/Val vs Val/Val genotype was 1.388 (95 % CI = 1.027–1.877, $p = 0.0328$). The adjusted OR for contraceptive use with Ala/Val vs Val/Val genotype was 1.769 (95 % CI = 1.114–2.809, $p = 0.0154$) and with Ala/Ala or Ala/Val vs Val/Val genotype it was 1.773 (95 % CI = 1.145–2.745, $p = 0.0100$). The adjusted OR for postmenopausal women with Ala/Val vs Val/Val genotype was 1.577 (95 % CI = 1.094–2.272, $p = 0.0143$) and with Ala/Ala or Ala/Val vs Val/Val genotype it was 1.604 (95 % CI = 1.132–2.272, $p = 0.0077$). However, no significant association was seen between *PARP-1* Val762Ala and patients with a positive history of tobacco smoking.

**Table 3** Stratified analyses of the *PARP-1* Val762Ala genotype distribution and cervical cancer risk: pregnancy, oral contraceptive use, tobacco smoking, and menopausal status

| High risk exposure | Patients | | | Controls | | | Adjusted odds ratio (95 % CI)[b] | $p^d$ |
|---|---|---|---|---|---|---|---|---|
| Genotype | Val/Val | Ala/Val | Ala/Ala | Val/Val | Ala/Val | Ala/Ala | | |
| Pregnancy | | | | | | | | |
| Ever | 268 | 114 | 17 | 324 | 101 | 12 | 1.363 (0.994–1.868)[a] | 0.0538 |
| | | | | | | | 1.277 (0.872–1.868) | 0.2078 |
| | | | | | | | **1.388 (1.027–1.877)[c]** | **0.0328** |
| Never | 27 | 15 | 5 | 37 | 13 | 4 | 1.333 (0.526–3.376)[a] | 0.5392 |
| | | | | | | | 1.332 (0.644–2.757)[b] | 0.4310 |
| | | | | | | | 1.467 (0.638–3.374)[c] | 0.3606 |
| Oral contraceptive use | | | | | | | | |
| Ever | 131 | 60 | 11 | 165 | 44 | 7 | **1.769 (1.114–2.809)[a]** | **0.0154** |
| | | | | | | | 1.454 (0.888–2.383)[b] | 0.1355 |
| | | | | | | | **1.773 (1.145–2.745)[c]** | **0.0100** |
| Never | 164 | 69 | 11 | 196 | 70 | 9 | 1.191 (0.804–1.765)[a] | 0.3808 |
| | | | | | | | 1.171 (0.740–1.853)[b] | 0.5000 |
| | | | | | | | 1.222 (0.840–1.778)[c] | 0.2926 |
| Smoking | | | | | | | | |
| Ever | 101 | 47 | 9 | 119 | 39 | 5 | 1.413 (0.849 –2.351)[a] | 0.1812 |
| | | | | | | | 1.582 (0.890–2.810)[b] | 0.1159 |
| | | | | | | | 1.528 (0.943–2.475)[c] | 0.0836 |
| Never | 194 | 82 | 13 | 242 | 75 | 11 | 1.315 (0.908–1.904)[a] | 0.1463 |
| | | | | | | | 1.176 (0.775–1.785)[b] | 0.4444 |
| | | | | | | | 1.316 (0.925–1.871)[c] | 0.1258 |
| Menopausal status | | | | | | | | |
| Premenopausal | 112 | 36 | 7 | 138 | 42 | 6 | 1.048 (0.622–1.768)[a] | 0.8584 |
| | | | | | | | 1.234 (0.700–2.174)[b] | 0.4649 |
| | | | | | | | 1.080 (0.660–1.769)[c] | 0.7572 |
| Postmenopausal | 183 | 93 | 15 | 223 | 72 | 10 | **1.577 (1.094–2.272)[a]** | **0.0143** |
| | | | | | | | 1.317 (0.869–1.995)[b] | 0.1925 |
| | | | | | | | **1.604 (1.132–2.272)[c]** | **0.0077** |

[a] (Ala/Val vs Val/Val); [b](Ala/Alal vs Val/Val); [c](Ala/Alal and Ala/Val vs Val/Val), [d]chi-square analysis. All *p*-values were adjusted for age. Significant results are highlighted in bold

## 4 Discussion

The activity of PARP has been implicated in cancer development and anticancer therapy [16, 17, 19–21]. Efficient DNA repair mechanisms are essential for protecting against the accumulation of genetic defects in DNA and subsequent carcinogenesis [14]. It was demonstrated that Epstein–Barr virus-immortalized lymphocytes from centenarians displayed a maximal PARP activity that was significantly higher than that seen in controls aged 20–70 [21]. A large difference between patients with cancer and healthy subjects in the PARP levels of peripheral blood mononuclear cells (PBMC) has also been reported [20–24]. Ranjit et al. [20] found that PBMC from patients with esophageal cancer, breast cancer, and lymphocytic malignancies contained lower levels of PARP than PBMC from healthy individuals. Furthermore, decreased PARP-1 activity in peripheral blood lymphocytes has been observed in patients with tumors of the larynx, lung, colon, and prostate [22–24]. In addition to these findings, skewed PARP-1 levels have been observed in different primary human malignancies, including breast, colorectal and head and neck cancers, and in melanoma [25–27].

The role of the PARP-1 enzyme in tumorigenesis has also been well documented in the murine model [28–30]. *PARP-1* knockout mice (*PARP-1*$^{-/-}$) treated with either alkylating compound or γ-radiation exhibited increased genomic instability, higher numbers of chromosomal aberrations, and reduced telomere length as compared to the wild-type mice [28]. The *PARP-1*$^{-/-}$ mice also displayed an increased risk of chemically induced carcinogenesis of the lung, liver, and colon [29, 30].

Therefore, genetic variants of *PARP-1* that contribute to PARP-1 activity may be risk factors for cancer development and progression. The *PARP-1* 762Ala gene variant seems to play a protective role in the development of some cancers in Caucasian populations [31–35], but the opposite is seen in Chinese populations, where the *PARP-1* 762Ala gene variant seems to be a risk factor for cancer in several studies [36–39].

We found an association of the *PARP-1* Ala/Val genotype together with the Ala/Ala genotype with cervical cancer development in Caucasian women, but this association was not observed solely for the *PARP-1* Ala/Ala genotype. The *PARP-1* Val762Ala polymorphism has also been recognized as a risk factor for cervical tumorigenesis in Chinese women [18]. Ye et al. [18] demonstrated that the *PARP-1* Ala/Ala genotype contributed to cervical carcinoma but not to CIN. The lack of an association of the Ala/Ala genotype with cervical cancer in our studies might due to a lower frequency of the Ala/Ala genotype in Caucasian women as compared to Chinese women.

Many genetic studies have been performed to date to assess the role of the *PARP-1* Val762Ala polymorphism as a risk factor for carcinomas of the brain, head and neck, esophagus, lung, breasts, stomach, bladder, colorectum, prostate, skin, among others; however, those studies provide discordant results [22, 31–43]. Recently, two meta-analyses were conducted to evaluate the contribution of the *PARP-1* Val762Ala polymorphism to overall cancer risk and the risks of different cancer types in distinct ethnicities [16, 17]. In the first meta-analysis, the *PARP-1* Ala variant demonstrated an association with an increased risk of cancer among Asian populations, but a decreased risk of cancer among Caucasian populations, especially for glioma [16]. The second meta-analysis confirmed that the *PARP-1* Ala variant is associated with a significantly increased risk of gastric carcinoma in Chinese populations; in Caucasians, the Ala variant protected significantly from brain tumors in two American subgroups, but not from the development of other cancers [17].

The *PARP-1* Val762Ala substitution is situated in the sixth helix of the C-terminal catalytic domain that binds $NAD^+$ and results in poly(ADP-ribosyl)ation [44]. This C-terminal catalytic domain is currently targeted for the development of effective PARP inhibitors [45]. The *PARP-1* 762Ala gene variant is significantly associated with low poly(ADP-ribosyl) activity [22]. The Val762Ala substitution in the PARP-1 enzyme produces a steric alteration in the catalytic domain leading to reduced activity of the PARP-1 762Ala enzyme variant [46].

In our studies, we also observed that *PARP-1* Val762Ala increased the risk of cervical cancer in women with a positive history of pregnancy, oral contraceptive use, and postmenopausal women. This is in agreement with literature indicating possible causative roles in cervical tumorigenesis of contraceptive use, tobacco consumption, age, and environmental exposures [47–49]. These confounding variables, especially exposure to unknown environmental insults, may affect the evaluation of genetic factors, including the *PARP-1* Val762Ala SNP, as risk factors for various cancers [47–49]. The two recent meta-analyses indicate that the *PARP-1* Val762Ala substitution may contribute to not only race-specific but also tissue-specific genetic effects in tumorigenesis [16, 17]. Our findings demonstrate the association of the *PARP-1* 762Ala gene variant with cervical cancer in Caucasians. This may be due to interactions between the reduced activity of the *PARP-1* Ala variant enzyme and individual exposure to some environmental factors. In addition to our findings, the *PARP-1* Ala/Ala and Val/Ala genotypes have been shown to be risk factors for bladder cancer in a large cohort of Caucasian patients [50]. Moreover, in Caucasians, the *PARP-1* Ala/Ala genotype was also significantly associated with an increased risk of prostate cancer [22].

Our genetic assessment is the first to demonstrate that the *PARP-1* 762Ala gene variant can be a risk factor for cervical cancer in a Caucasian cohort; this study should therefore be replicated in other independent cohorts.

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## References

1. Georgieva S, Iordanov V, Sergieva S. Nature of cervical cancer and other HPV-associated cancers. J BUON. 2009;14(3):391–8.
2. Walboomers JM, Jacobs MV, Manos MM, et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. J Pathol. 1999;189(1):12–9.
3. Münger K, Howley PM. Human papillomavirus immortalization and transformation functions. Virus Res. 2002;89(2):213–28.
4. Sasagawa T, Takagi H, Makinoda S. Immune responses against human papillomavirus (HPV) infection and evasion of host defense in cervical cancer. J Infect Chemother. 2012;18(6):807–15.
5. Duensing S, Munger K. The human papillomavirus type 16 E6 and E7 oncoproteins independently induce numerical and structural chromosome instability. Cancer Res. 2002;62(23):7075–82.
6. Hoeijmakers JH. DNA damage, aging, and cancer. N Engl J Med. 2009;361(15):1475–14853.
7. Kim YJ, Wilson DM 3rd. Overview of base excision repair biochemistry. Curr Mol Pharmacol. 2012;5(1):3–13.

8. Fortini P, Pascucci B, Parlatini E, et al. The base excision repair: mechanisms and its relevance for cancer susceptibility. Biochimie. 2003;85(11):1053–71.
9. Masson M, Niedergang C, Schreiber V, et al. XRCC1 is specifically associated with poly(ADP-ribose) polymerase and negatively regulates its activity following DNA damage. Mol Cell Biol. 1998;18(6):3563–71.
10. El-Khamisy SF, Masutani M, Suzuki H, et al. A requirement for PARP-1 for the assembly or stability of XRCC1 nuclear foci at sites of oxidative DNA damage. Nucleic Acids Res. 2003;31:5526–33.
11. Schreiber V, Dantzer F, Ame JC, et al. Poly(ADP-ribose): novel functions for an old molecule. Nat Rev Mol Cell Biol. 2006;7(7):517–28.
12. Kim MY, Zhang T, Kraus WL. Poly(ADP-ribosyl)ation by PARP-1: 'PAR-laying' NAD+ into a nuclear signal. Genes Dev. 2005;19(17):1951–67.
13. Kumari SR, Mendoza-Alvarez H, Alvarez-Gonzalez R. Functional interactions of p53 with poly(ADP-ribose) polymerase (PARP) during apoptosis following DNA damage: covalent poly(ADP-ribosyl)ation of p53 by exogenous PARP and noncovalent binding of p53 to the M(r) 85,000 proteolytic fragment. Cancer Res. 1998;58:5075–8.
14. Heinen CD, Schmutte C, Fishel R. DNA repair and tumorigenesis: lessons from hereditary cancer syndromes. Cancer Biol Ther. 2002;1(5):477–85.
15. Ford BN, Ruttan CC, Kyle VL, et al. Identification of single nucleotide polymorphisms in human DNA repair genes. Carcinogenesis. 2000;21(11):1977–81.
16. Yu H, Ma H, Yin M, et al. Association between PARP-1 V762A polymorphism and cancer susceptibility: a meta-analysis. Genet Epidemiol. 2012;36(1):56–65.
17. Pabalan N, Francisco-Pabalan O, Jarjanazi H, et al. Racial and tissue-specific cancer risk associated with *PARP1* (ADPRT) Val762Ala polymorphism: a meta-analysis. Mol Biol Rep. 2012;39(12):11061–72.
18. Ye F, Cheng Q, Hu Y, et al. *PARP-1* Val762Ala polymorphism is associated with risk of cervical carcinoma. PLoS One. 2012;7(5):e37446.
19. Leonetti C, Biroccio A, Graziani G, et al. Targeted therapy for brain tumours: role of PARP inhibitors. Curr Cancer Drug Targets. 2012;12(3):218–36.
20. Ranjit GB, Cheng MF, Mackay W, et al. Poly(adenosine diphosphoribose) polymerase in peripheral blood leukocytes from normal donors and patients with malignancies. Clin Cancer Res. 1995;1(2):223–34.
21. Muiras ML, Müller M, Schächter F, et al. Increased poly(ADP-ribose) polymerase activity in lymphoblastoid cell lines from centenarians. J Mol Med. 1998;76:346–54.
22. Lockett KL, Hall MC, Xu J, et al. The ADPRT V762A genetic variant contributes to prostate cancer susceptibility and deficient enzyme function. Cancer Res. 2004;64(17):6344–8.
23. Pero RW, Roush GC, Markowitz MM, et al. Oxidative stress, DNA repair, and cancer susceptibility. Cancer Detect Prev. 1990;14(5):555–61.
24. Rajaee-Behbahani N, Schmezer P, Ramroth H, et al. Reduced poly(ADP-ribosyl)ation in lymphocytes of laryngeal cancer patients: results of a case–control study. Int J Cancer. 2002;98(5):780–4.
25. Goncalves A, Finetti P, Sabatier R, et al. Poly(ADP-ribose) polymerase-1 mRNA expression in human breast cancer: a meta-analysis. Breast Cancer Res Treat. 2010;127(1):273–81.
26. Nosho K, Yamamoto H, Mikami M, et al. Overexpression of poly(ADP-ribose) polymerase-1 (PARP-1) in the early stage of colorectal carcinogenesis. Eur J Cancer. 2006;42(14):2374–81.
27. Staibano S, Pepe S, Lo Muzio L, et al. Poly(adenosine diphosphate-ribose) polymerase 1 expression in malignant melanomas from photoexposed areas of the head and neck region. Hum Pathol. 2005;36(7):724–31.
28. d'Adda di Fagagna F, Hande MP, et al. Functions of poly(ADP-ribose) polymerase in controlling telomere length and chromosomal stability. Nat Genet. 1999;23(1):76–80.
29. Nozaki T, Fujihara H, Watanabe M, et al. Parp-1 deficiency implicated in colon and liver tumorigenesis induced by azoxymethane. Cancer Sci. 2003;94(6):497–500.
30. Tsutsumi M, Masutani M, Nozaki T, et al. Increased susceptibility of poly(ADP-ribose) polymerase-1 knockout mice to nitrosamine carcinogenicity. Carcinogenesis. 2001;22(1):1–3.
31. Liu Y, Scheurer ME, El-Zein R, et al. Association and interactions between DNA repair gene polymorphisms and adult glioma. Cancer Epidemiol Biomarkers Prev. 2009;18(1):204–14.
32. Rajaraman P, Hutchinson A, Wichner S, et al. DNA repair gene polymorphisms and risk of adult meningioma, glioma, and acoustic neuroma. Neuro Oncol. 2010;12(1):37–48.
33. Smith TR, Levine EA, Freimanis RI, et al. Polygenic model of DNA repair genetic polymorphisms in human breast cancer risk. Carcinogenesis. 2008;29(11):2132–8.
34. Huang M, Dinney CP, Lin X, et al. High-order interactions among genetic variants in DNA base excision repair pathway genes and smoking in bladder cancer susceptibility. Cancer Epidemiol Biomarkers Prev. 2007;16(1):84–91.
35. Li C, Hu Z, Lu J, et al. Genetic polymorphisms in DNA base-excision repair genes *ADPRT*, *XRCC1*, and *APE1* and the risk of squamous cell carcinoma of the head and neck. Cancer. 2007;110(4):867–75.
36. Zhang Q, Li Y, Li X, et al. *PARP-1* Val762Ala polymorphism, CagA+ *H. pylori* infection and risk for gastric cancer in Han Chinese population. Mol Biol Rep. 2009;36(6):1461–7.
37. Stern MC, Butler LM, Corral R, et al. Polyunsaturated fatty acids, DNA repair single nucleotide polymorphisms and colorectal cancer in the Singapore Chinese Health Study. J Nutrigenet Nutrigenomics. 2009;2(6):273–9.
38. Hao B, Wang H, Zhou K, et al. Identification of genetic variants in base excision repair pathway and their associations with risk of esophageal squamous cell carcinoma. Cancer Res. 2004;64(12):4378–84.
39. Chiang FY, Wu CW, Hsiao PJ, et al. Association between polymorphisms in DNA base excision repair genes *XRCC1*, *APE1*, and *ADPRT* and differentiated thyroid carcinoma. Clin Cancer Res. 2008;14(18):5919–24.
40. Zhang Y, Newcomb PA, Egan KM, et al. Genetic polymorphisms in base-excision repair pathway genes and risk of breast cancer. Cancer Epidemiol Biomarkers Prev. 2006;15(2):353–8.
41. Stern MC, Conti DV, Siegmund KD, et al. DNA repair single-nucleotide polymorphisms in colorectal cancer and their role as modifiers of the effect of cigarette smoking and alcohol in the Singapore Chinese Health Study. Cancer Epidemiol Biomarkers Prev. 2007;16(11):2363–72.
42. Wu X, Gu J, Grossman HB, et al. Bladder cancer predisposition: a multigenic approach to DNA-repair and cell-cycle-control genes. Am J Hum Genet. 2006;78(3):464–79.
43. Choi JE, Park SH, Jeon HS, et al. No association between haplotypes of three variants (codon 81, 284, and 762) in poly(ADP-ribose) polymerase gene and risk of primary lung cancer. Cancer Epidemiol Biomarkers Prev. 2003;12(9):947–9.
44. Cottet F, Blanche H, Verasdonck P, et al. New polymorphisms in the human poly(ADP-ribose) polymerase-1 coding sequence: lack of association with longevity or with increased cellular poly(ADPribosyl)ation capacity. J Mol Med. 2000;78(8):431–40.
45. Karlberg T, Thorsell AG, Kallas Å, et al. Crystal structure of human ADP-ribose transferase ARTD15/PARP16 reveals a novel putative regulatory domain. J Biol Chem. 2012;287(29):24077–81.

46. Wang XG, Wang ZQ, Tong WM, et al. *PARP1* Val762Ala polymorphism reduces enzymatic activity. Biochem Biophys Res Commun. 2007;354(1):122–6.
47. Castellsague X, Munoz N. Chapter 3: Cofactors in human papillomavirus carcinogenesis—role of parity, oral contraceptives, and tobacco smoking. J Natl Cancer Inst Monogr. 2003;31:20–8.
48. Magnusson PK, Lichtenstein P, Gyllensten UB. Heritability of cervical tumours. Int J Cancer. 2000;88:698–701.
49. Moreno V, Bosch FX, Muñoz N, et al. Effect of oral contraceptives on risk of cervical cancer in women with human papillomavirus infection: the IARC multicentric case-control study. Lancet. 2002;359:1085–92.
50. Figueroa JD, Malats N, Real FX, et al. Genetic variation in the base excision repair pathway and bladder cancer risk. Hum Genet. 2007;121(2):233–42.